UNITED STATES OF AMERICA

+ + + + +

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

+ + + 7891 '02 APR -8 P1:41

BLOOD PRODUCTS ADVISORY COMMITTEE

72ND MEETING

+ + + + +

FRIDAY
MARCH 15, 2002

+ + + + +

The Committee met at 8:00 a.m. in the Grand Ballroom, the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Kenrad E. Nelson, Chairman, presiding.

PRESENT:

KENRAD E. NELSON, M.D.	Chairman
JAMES R. ALLEN, M.D.	Member
MARY E. CHAMBERLAND, M.D.	Member
KENNETH DAVIS, JR., M.D.	Member
DONNA D. DiMICHELE, M.D.	Member
SAMUEL H. DOPPELT, M.D.	Member
ROBERT J. FALLAT, M.D.	Consumer Representative
LIANA HARVATH, PhD	Temporary Voting Member
F. BLAINE HOLLINGER, M.D.	Temporary Voting Member
JEANNE V. LINDEN, M.D.	Temporary Voting Member
RAYMOND S. KOFF, M.D.	Member
JUDY F. LEW, M.R.	Member
TERRY V. RICE	Member
PAUL J. SCHMIDT, M.D.	Member
DAVID F. STRONCEK, M.D.	Temporary Voting Member
SHERRI O. STUVER, ScD	Member
LORI A. STYLES, M.D.	Member
LINDA A. SMALLWOOD, PhD	Executive Secretary

3839T2

I-N-D-E-X

Page

III. Review of Data Supporting Extension of Dating Period for Platelets

A. Introduction and Background 12
Jaro Vostal, M.D., Ph.D.

B. Extension of Platelet Storage 16
Sherrill Slichter, M.D.

C. Safer, Cheaper and Just as Good 56
James AuBuchon, M.D.

OPEN PUBLIC HEARING

D. Committee Discussion 112

IV. Bacterial and Fungal Contamination of Human Tissue Intended for Transplantation

A. Introduction and Background 140
Ruth Solomon, M.D.

B. Microbial Contamination and Cross Contamination Concerns During Processing 147
Mary Malarkey

C. Preliminary Findings From Investigation of Allograft-Associated Infections 168
Marion A. Kainer

D. Reducing the Risk of Tissue Transplant-Transmitted Infections 203
D. Ted Eastlund, M.D.

E. Adverse Reactions After Corneal Transplantation 241
Michael A. Lemp, M.D.

OPEN PUBLIC HEARING 265

F. Committee Discussion

ADJOURNMENT 273

P-R-O-C-E-E-D-I-N-G-S

(8:07 a.m.)

DR. SMALLWOOD: May I ask the Committee members to please be seated.

Good morning. Welcome to the second day's session of the 72nd meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary.

On yesterday I read the conflict of interest statement that pertained to the proceedings of this meeting. If there are any questions concerning that, you may see me at the break, and I will be happy to share that statement with you.

For today's meeting, we will have Dr. Jeanne Linden, who is a consultant and who will be participating with us today. Also, two of our members will be -- that were present yesterday are absent, Dr. Fitzpatrick and Dr. Klein.

I would just like to ask the Committee members, if you need to have arrangements made for taxis, to please see the young ladies at the desk outside during the break.

There will be one deviation from our agenda this morning. We will start out with a presentation from Dr. Richard Lewis who will provide you with a summary of a workshop on medical errors. Other than that, we will proceed with our agenda as printed, and hope to keep on time. Thank you.

DR. LEWIS: Thank you, Dr. Smallwood.

I have a 15 minute summary of the workshop, and Dr. Smallwood told me that I had to do it in seven minutes. That was one of the conditions of being on. So she is serious about keeping on time today, and I'll try to do my best to do that.

In the month of February we helped sponsor a workshop on best practices to reduce transfusion errors, and I think this is a very important subject, and it was a worthwhile workshop, which was sponsored both by FDA and the Agency for Health Care Research and Quality, both HHS agencies.

If I could have the next slide, please.

We looked at various areas of errors that could occur in transfusion services and blood banks. We summarized some of the current safety initiatives within Health and Human Services, looked at what some of the sources are for errors, looked at some systematic errors and how to address them, how reporting could figure in on errors in transfusion, and looked at some of the technology that could address some of those problems, both current technology and future technologies. Next slide.

Within HHS, to summarize some of the Patient Safety Task Force initiatives: The Patient Safety Task Force is an HHS-wide task force which includes members from FDA, CMS, CDC, and AHRQ.

The ARHQ also has some independent work on patient safety. They are funding grants and contracts to address medical errors, and also lead the Patient Safety Network, which is an effort to device a large computer analysis method, not a single database but a method to look at all of the different types of information relating to errors that might be contained within HHS.

We also heard from CMS and discussed their Quality Improvement Organization, which also is an error reporting emphasis. Next slide.

Some of the sources of transfusion error: We heard that there are roughly -- this is data from Kathleen Sazama as well as Jeanne Linden. Roughly, over the last ten years 37 deaths per year occur as a result of transfusion errors. Estimates are that about five percent of -- this represents about five percent reporting.

The majority of those errors are ABO incompatibility, roughly 56-59 percent of fatalities, and these errors generally occur either at sample collection or at the actual transfusion. Twenty-five to 29 percent of those errors occur at the blood bank. Next slide.

So it was confirmed by presentation from Hal Kaplan that the human/system interface is where most of these particular errors occur, and some of the contributing factors are wrist band removal, incorrect labels, and confusion over the name of the patient. Next slide.

We heard form Dr. Michael Busch about infectious disease testing, and he had looked at a large database of discordant results between NAT testing and serology in both HIV and HCV studies. He commented that investigating these particular discrepancies offered an opportunity to see where errors might occur in testing.

He put forth a rather large number. If you consider the errors in testing as well as prevalence, the chances of getting an infectious disease from a unit of blood were about one in one billion. Next slide.

We discussed systematic errors, and errors in a particular system and how one operates come from both the organizational level, physical contact with the patient, the environment that the individual -- in which they work, as well as the social attitudes in the particular establishment. It was pointed out that it is important to identify points in a process where errors are most likely to occur. Next.

One presentation addressed some of the inexpensive devices that are used in other areas. That was referred to as Poka-Yoke. It's a Japanese system, and some of the examples that they gave were, as you enter a parking garage, for instance, there is a wooden bar that hangs down that stops vehicles that are too large from going in. We saw how doors would have a handle on it to pull and a plate to push, and we were encouraged to look at some simple, inexpensive devices that prompt us technically to do the right thing and void errors. Next slide.

In evaluating the donor history questionnaire, Susan Wilkinson presented some work that she and some of her collaborators have done using an objective structured clinical examination. They had trained donors and tested the interviewers for their competency, and used this as a system of evaluating the actual donor history, the individuals taking the history as well as their interpretation of the responses. Next.

We looked at a number of reporting systems which changes the focus from identification -- In a hospital setting, it encourages changing the focus from identification of a liability situation to one in which you are constantly self-examining your system to determine where there might be particular errors. Next.

We heard form Sharon O'Callaghan, who discussed the FDA Biological Product Deviation Reporting in manufacturing. Most of those reports come in the areas of quality control, labeling or routine testing.

This particular system also includes a root cause analysis, and some of the major identification of causes for errors were that the individuals were too busy, that there were clerical errors or handwritten, as well as additional needs in the particular environment. Next slide.

MERS-TM is a system that I would hope that everyone has at least heard of, a reporting system that focuses on systems and training rather than individual liabilities, again. We heard an example of its implementation at a large facility and their event recognition and system correction methods. Next slide.

Barcoding today has a focus of HHS, and the Secretary Thompson has encouraged the development of a regulation that would require all drugs and biologics to have barcoding. The overall scope of that rule is yet to be decided, but look for this spring a large workshop to discuss both the scope as well as the type of barcoding.

We should all be familiar with ISBT 128, and we heard about the regulations and implementation of new rules to remove barriers to implementation of ISBT 128. Next slide.

We heard other technology trends. The automated donor interview was presented, and some information on how that facilitates the donor history. Dr. AuBuchon presented patient identification system, the blood lock, and his estimates were that it saved, in his facility roughly $200,000 quality adjusted life years, and he pointed out that, although this is very high for other implementation of medical procedures, however, in the context of some of the things that we do to reduce the incidence of infectious diseases in blood, this was rather small.

We also looked at laboratory instrumentation and some of the testing equipment, and how that particular equipment incorporates systems so to reduce interactions with humans and automate the process as much as possible to reduce errors in testing, as well as some patient identification systems, barcoding on wrist bands as well as on blood banks, and how that could reduce numbers of errors. Next slide.

In terms of future technologies, we heard some interesting presentations from the International Biometrics Association. They talked about identifying the actual biological unit through things such as voice scans, facial scans, and fingerprint analysis.

I thought it was very interesting, in terms of fingerprint analysis, that there were devices as small as an inch in diameter that one could place their thumbprint on and read the individual immediately. It seemed to me that that could be very applicable to the patient setting where you could find an individual's fingerprint, whether they are conscious or unconscious, and identify the appropriate unit.

Software to identify an individual is available, and rapid -- Actually, it's faster to verify that an individual is who you think that it is than it is faster to identify an individual. I think this verification would be something that would be applicable in the hospital setting.

Thank you very much. I don't know how I did for time. I hope that I stayed within my boundaries. I appreciate the opportunity to present this. I thought it was an important topic and, hopefully, we will address it again at the AABB convention this fall. Thank you

CHAIRMAN NELSON: Any questions or comments? Yes, James?

DR. ALLEN: In one of your early slides where you showed 37 deaths per year and estimated that was about five percent reporting, given that the event is a death, I'm surprised at the degree of underreporting. Is there any explanation for that or ways to correct that?

DR. LEWIS: These were data from Dr. Sazama from M.D. Anderson, and she didn't cite, and I didn't follow up, what her actual sources were. She said that it had been reported. I was surprised, too, and it isn't in our regulations that it is mandatory reporting for all deaths that are associated with transfusion.

CHAIRMAN NELSON: Thank you.

DR. LEWIS: Thank you.

CHAIRMAN NELSON: The first topic today on the agenda is review of data supporting extension of dating period for platelets, and this will be introduced by Dr. Vostal from the FDA.

DR. VOSTAL: Good morning, and thank you for the opportunity to introduce this session. Today we are going to talk about the extension of platelet shelf life from five days to seven days and about the quality of platelets that have been stored out to seven days.

Just as an introduction, I would like to direct your attention to the slide over here that covers the platelet storage milestones that we have had over the history of. Starting in 1981, back then platelets were stored out to three days, but improved plastics and bags allowed random donor platelet storage to increase from the three days to five days.

Things were going pretty well. So in 1984 this was further increased to seven days. However, about a year and a half later, in 1986, there was a BPAC Committee meeting very similar to this one. That discussed the incidence -- an increased incidence of bacterial contamination associated -- or bacterial contamination and substance -- transfusion substance reactions associated with platelet transfusions.

Based on this data, the dating period for platelet storage was moved back to five days. Now we fast forward to 2002, and we are coming to a point where we think we may have methods of controlling bacterial contamination of the platelet. This could be either by detection or decontamination.

So the question comes up again: When we have the bacterial contamination problem under control, whether we can extend the shelf life of platelets back out to seven days.

Could I have the next slide, please?

We have some reservations about directly extending the shelf life, and that is because there are major differences between platelets that were stored out to seven days in 1984 and the platelets that we are using today.

For example, if you look at the differences in the products that were used, in 1984 it was only random donor platelets that were stored out to seven days, but today we like to do random donor platelets as well as single donor apheresis platelets.

Leukoreduction wasn't carried out back then. So there are plenty of leukocytes in these products. However, today leukoreduction is almost universal. So there is a big difference in terms of number of white cells present in these platelet products.

The storage conditions themselves have changed. The plastic bags that were used in 1984 have been improved with different plastics, and some of the apheresis instruments also have different plasma to platelet ratios. So all these things put together make for a different condition for storing platelets out to seven days.

If I could have the next slide. Now this slide -- This is a cartoon modified from Scott Murphy's review in Transfusion Medicine Reviews in 1999. It kind of focuses on the different factors that play a role in storing platelets.

Of course, there is the plastic bag that's gas permeable to oxygen and carbon dioxide. The platelets are themselves stored at room temperature in plasma, and they have the presence of leukocytes. The biochemical events that take place in these cells is that free fatty acids are metabolized by oxidative metabolism to ATP, and glucose is metabolized by glyçolysis to lactate and lactic acid.

Now the ratio of these -- or the predominance of these pathways is determined by the availability of oxygen that is diffusing through the outside -- through the bag.

In the lack of oxygen, the predominant pathway is glycolysis and produces lactic acid, leads to generation of acid in plasma. This is usually buffered by bicarbonate that can convert -- that can combine with the acid and generate CO_2 which can then diffuse out of the bag.

If there is -- So in cases where there is low oxygen present, you can have a lot of acid generation. And if it overcomes the bicarbonate present in plasma, you can have a drop in acid or drop in pH. You can also have a rise in pH if the number of platelets present is decreased or if the number of leukocytes that also contribute to the cycle is decreased.

So the pH at the end of storage of the platelet product sort of indicates the conditions that the platelet went through when it was stored out.

Just to show you that we think these conditions are changes, I would like to show you the next slide. This is data that is collected by the FDA from platelet products that are submitted to FDA for licensure, and we measure pH at outdate of these platelet products.

You can see that in 1995 pH was close to 7. By '96-97 and up to '99, there is a rise in pH.

This may not seem that much, but if you look at the next slide, here we show the percent of the products tested that have a pH greater than 7.4.

As you are going from '95 to '99, you can see that by 1999 more than 40 percent of the products have a pH greater than 7.4.

Now it's not clear whether this has any detrimental effects on platelets when they are transfused, but I think it demonstrates that the conditions for platelet storage are changing over time. That is why we are actually interested to see whether the platelets that are stored out to seven days under the current conditions will still work when transfused today.

So with that brief introduction, I would like to welcome Dr. Slichter, who is the Executive Vice President of Research at Puget Sound Blood Center. She is going to continue with the clinical aspects of seven-day platelet storage.

DR. SLICHTER: Thank you. Could I have the first slide, please. As Dr. Vostal has mentioned, in 1986 over 15 years ago now, the dating time of platelets was shortened from seven days to five days, because of bacterial concerns, you know, as this - let's see, have we got a pointer? There.

Because of this difference in growth rate of bacterial in platelets, which as everyone knows, are stored at room temperature, versus growth rate in red cells which are stored at four degrees Centigrade. So that's why the dating period of platelets was, in fact, reduced.

If you look at the data -- and this is a literature review done by Mo Blajchman, reported in 2000 -- bacterial contamination of a platelet component is not insignificant, .3 to 1.6 percent. Transfusion associated sepsis is one in 50,000 transfusions with a 20 percent fatality rate, and would suggest that there are 50 to 100 deaths per year associated with bacterial contamination.

Now the causes of bacterial contamination are pretty well understood. Probably the biggest reason for bacterial contamination is inadequate skin preparation prior to the venipuncture. One way to potentially avoid this complication is to remove the first aliquot of blood, which is considered to reduce the risk by taking either the skin plug out of the system and diverting it prior to drawing the rest of the blood into a bag.

The real advance, I think, in terms of whether there is a possibility for extending platelet storage is in the last two areas. There are -- and Dr. AuBuchon who follows me will discuss this. There are a variety of systems now that may be able to be used to detect the presence of bacteria prior to release of the product from the blood center that will allow us to prevent bacterial transfusion, and extend platelet storage.

The other process that is moving along is a decontamination process. So that there are techniques now available for pathogen inactivation of platelets prior to their storage.

Now what I am going to talk to you about today, because I have a limited amount of time, is I am going to concentrate on the *in vivo* transfusion aspects of platelets. As many of you in this room know, there are a variety of methods of *in vitro* testing of platelets to determine the quality of the platelets.

It is at least my opinion that those *in vitro* assays can tell you whether it's a go or no go, meaning that if the *in vitro* assays look very abnormal, you probably don't have a product that will survive *in vivo*.

If the *in vitro* assays, however, look reasonable, you really, in my opinion, don't know whether that is going to give a very high recovery and a good survival or something much more modest. So what I am going to concentrate with you on today is *in vivo* evaluation of platelets during storage.

There are really two major techniques that we use. One is to store autologous platelets in normal volunteers. We radiolabel the autologous platelets and reinfuse them.

Because we have two different isotopes that we can use, either chromium or indium, we actually have the opportunity to store two different products under differing conditions and simultaneously or sequentially transfuse those products into the same normal volunteer.

Now the reason why that is a distinct advantage is because, for reasons that we really don't understand, there are substantial differences in how well each individual platelet stores. So that the ability to compare in the same individual labeled platelets and simultaneous reinfusion is a big advantage.

Now once the data suggests that radiolabeled viability measurements in normal volunteers are reasonable, then we go to transfusion experiments in thrombocytopenic patients where viability is measured by platelet increments, corrected count increments which I'll describe, days to next transfusion, and also, importantly, to measure hemostasis; because, after all, platelets are supposed to prevent or control bleeding.

Now I am going to talk about two different aspects of how to determine the quality of the platelets. Both of them have to do with looking at the platelet increment, which is the post-transfusion minus the pre-transfusion count, and then making a correction for the volume of distribution.

So the platelet recovery does it by blood volume divided by number of platelets transfused. The corrected count increment makes a similar adjustment based on body surface area, again divided by number of platelets transfused.

Now this is a very important slide that I am going to spend a little bit of time on, because one of the issues is that we know that, on average, about 60 percent of the platelets that we transfuse circulate. The other third are pooled in the spleen, and the normal platelet survival is somewhere around eight to ten days.

So the issue becomes, if we only have a cell which has an intrinsic life span of eight to ten days, how long can we really expect to extend storage *in vitro* and get a product that is worth transfusing?

Well, the very interesting study that Stein Holme did with Andy Heaton in 1995 looked at five-day stored platelets, which is the green line here, compared to fresh, and you can clearly see that both the recovery and the survival is reduced. But interestingly, they, simultaneously with the five-day stored platelets, harvested platelets from the same normal individual and radiolabeled them fresh at the time that this was infused.

What this data shows is that the viability of the platelets after two days *in vivo* is the same as after five days *in vitro*, suggesting in fact that the platelet does not have an intrinsic lifespan, but rather the lifespan is influenced by the conditions under which it is maintained, and that you are worse off to be *in vivo* than *in vitro*.

What he then did is do a calculation which he called mean residual platelet lifespan, which looks at the area below the survival curve divided by the initial platelet recovery, and basically showed that if you make that calculation, this is *in vitro* mean residual lifespans and *in vivo*. So that the platelet aging *in vitro* was only .44 percent of the -- was only

44 percent of that *in vivo*.

So that what this suggests is that, in fact, if we do store *in vitro*, we may be able to get a useful product that's been stored for eight, ten or even somewhat longer because of the difference. He attributed the difference between how platelets survive *in vivo* and *in vitro* to the differences in storage temperature.

So *in vitro*, we store at 22. *In vivo*, as you know, that's 37. So the metabolic activity of platelets *in vivo* is substantially higher than it is *in vitro*.

Now the next set of data that I am going to show you looks at the issue which Dr. Vostal alluded to, that there are a variety of platelet products now available for storage.

So since it's been 15 years since we have been able to store platelets for seven days, a lot of the data that I am going to show you is at five days of storage. But the first thing I wanted to address with the audience is: Is there a difference in five-day storage of platelets based on the method of preparation of the platelets, because we know that platelets can suffer a collection injury.

In other words, if you centrifuge the

platelets too hard during their preparation, that produces an injury, and in addition, there is a storage injury.

So we, as everybody, I think, in this room knows, make platelet concentrates by what's called the PRP system where we take whole blood. WE do a soft spin. We remove the supernatant PRP, which has a high leukocyte count. We do a hard spin, and then we re-suspend the platelets in a small volume of residual plasma.

In contrast, in Europe they make so called buffy coat platelets. Here what happens is you take the whole blood and, instead of doing a soft spin, you do a very hard spin, which then concentrates the platelets as well as the white cells on top of the red cells. You then remove the buffy coat layer. You pool the buffy coats and do a soft spin.

So that the issue here became the hard spin to make a platelet concentrate in the U.S. is done at the end, and the platelets are hard spun against the walls of the bag.

In this system the hard spin is done against the red cell layer, which theoretically means that the buffy coat platelets, in fact, may be a better quality platelet, because at no point are the platelets hard spun against the walls of the bag.

Now this is starting to show the data on storage time in plasma on post-transfusion platelet viability. These are paired, radiolabeled, autologous platelet storage studies in normal volunteers.

In this study there were nine volunteers who participated. Their platelets were stored in PRP platelet concentrates, and this is recovery and survival data at zero recovery and survival at five days.

Now in some of these studies they didn't provide in the manuscript the p-values. So anything that had a statistically significant p-value I will have listed on the slide. So there is some decrease both in recovery and survival here.

These are buffy coat platelets, again some decrease in recovery and survival, but you will note that the recoveries and survivals at both time zero and five days are basically the same.

This is now apheresis platelets stored for one day or five days, and absolutely no difference in this data.

This is now five-day versus seven-day, nine individuals in two separate studies. What you can see here is basically there is no difference between five-day and seven-day stored platelets, autologous platelets in plasma in normal volunteers in this one study.

Now this is five-day storage of different types of radiolabeled autologous platelets in plasma. This is PRP-PC, buffy coat PC, nine individuals. This is platelet recovery, no difference. This is buffy coat versus apheresis C, which is Cobe. This is PRP apheresis F, which is Fenwal. This is PRP apheresis H which is Haemonetics. No difference in any of this data between the different types of products when stored for five days.

Now this is survival data from the same studies. Again no difference in the survival or recovery of different types of products when direct comparisons are made in the same normal individuals.

Now the other thing that is of interest, I think, when we consider extending platelet storage is whether or not the use of additive solutions would provide a benefit.

As you know, we now store platelets in plasma. Many of the buffy coat preparations done in Europe are pooled and re-suspended in a platelet additive solution. Use of a platelet additive solution may provide benefit, because it may improve the quality of the platelets during storage, and also allow us to salvage more plasma for other uses.

So this just lists the kind of platelet additive solutions that have been used and are available. They have a variety of different kinds of things in them. What they all contain is either acetate, gluconate or citrate as sources of metabolic energy, because one of the problems you will notice is that none of these solutions contain glucose, because glucose tends to caramelize under sterilization conditions, and so there needs to be provided alternate sources of nutrients to support oxidative metabolism.

Most of the studies have used a residual plasma concentration of somewhere around 35 to 3[illegible] percent to provide some glucose. So that none of these studies are stored in 100 percent of the additive solution.

Now this is a study again done by Ste[illegible] Home, published in 1994. The reason to show you this data, I think, is because it quite nicely shows the storage lesion. So that over time -- This is plasma stored platelets. You can see that over time, and he stored platelets up to 15 days where the platelet recovery is less than ten percent.

You can see that there is loss of viability over time. He then looked at PAS-2 stored platelets, starting at five days, showed that they were the same at five days as plasma, but some improvement actually in the quality of the platelets when stored in PAS versus plasma over time, starting at seven days of storage.

This is the same study, but now instead of looking at platelet recovery, looking at platelet survival, again showing the loss of survival of platelets in circulation. Same data at five days, but an improvement at seven days in PAS compared to plasma.

This is studies that we have recently been doing in Seattle looking at Plasmalyte. The only storage solution that is commercially available for us to use is Plasmalyte. We have used Plasmalyte concentrations of 50 to 82 percent and, in fact, think that the recovery is better with the higher Plasmalyte concentrations than the lower.

So our current standard is to use about 80 percent Plasmalyte. Here is our -- We did six normal volunteers, paired observations. This is five-day storage in Plasmalyte versus plasma. As you can see, the data is exactly the same.

This is now ten normal volunteers stored for seven days, Plasmalyte versus plasma, and as suggested in the prior slide from Dr. Holme, at seven days we are getting better recovery, statistically significant difference in Plasmalyte compared to plasma, and a bit better survival compared to plasma, but does not reach statistical significance.

Now the other thing I would like to share with you, kind of again in regard to Dr. Vostal's statement that we are now storing platelets under conditions that are truly different than they were 15 years ago. What I would like to point out to you is that these recoveries of 80 and 64 percent in Plasmalyte are extremely high, and much higher than we would have predicted.

The old data would have been somewhere around 40 to 50 percent recoveries at five and seven days, and I don't have a good explanation for this except to say that I've got the same technician who is using the same radiolabeling techniques, and we can't identify that it is a difference in how we are processing the platelets that have led to this difference.

Now what we next did is do paired studies in normal volunteers, did five normal volunteers, where each bag of their apheresis collected platelets -- one was stored for five days, one for seven days, but both were stored in Plasmalyte.

What you can see here is that the recoveries are exactly the same, some decrease in survival, but not a statistically significant difference. So that going from five-day Plasmalyte to seven-day did not produce a change.

The only clue we have about why the recovery may be better in our current studies is because, in order to do the Plasmalyte storage studies, we needed to have donors with high platelet counts.

So what you can see here is this is our five versus seven-day Plasmalyte data that I just showed you. This is then the platelet count of the donor, and you will notice that the donor whose platelet count is around 200,000 has, in fact, a recovery in the fifties, which is what we would anticipate, but there seems to be a higher recovery in people who have higher platelet counts.

This may be very interesting, because this may be a physiologic thing, that one of the reasons potentially why people have high platelet counts is because they have less storage of their platelets in the spleen, and again you notice how close the recoveries are for an individual donor, always higher for the five-day than for the seven-day, but very close data when the same normal individual is used for paired observations.

Now the last part of the talk I am going to talk about what we are really interested in, which is ow well the platelets do when they are transfused into thrombocytopenic patients.

This is very old data which we collected that basically shows that the normal platelet recovery is around 60 to 65 percent. Normal platelet survival is somewhere between eight and ten days. But if you get a thrombocytopenic patient who actually needs transfused platelets, although their recovery is similar to what's found in normal, their survival, in fact, is reduced, and it is around five days under optimum conditions.

Now platelets are lost by two mechanisms. One is senescence with a maximum platelet lifespan of ten days. But interestingly, there is a random platelet loss in hemostasis. So about 7,000 platelets per microliter per day are lost in what we consider to be an endothelial supportive function, and this loss is irregardless of the age of the platelets and is to prevent us from leaking through our vascular system.

Now there's a direct relationship -- Once you get to less than about 100,000 platelets, there is a direct relationship between platelet count and platelet survival. So that the lower your platelet count is at the time you are transfused, the more reduced is your platelet survival.

So that when you are talking about transfusing platelets into people whose baseline platelet count is somewhere around 10-20,000, you are talking about a survival of about two to three days.

So the point of this discussion is that, in terms of storing platelets, we would like to have platelets which have basically a normal recovery, and then as long as the survival of platelets is at least two or three days, if not more like five or six days, because you don't want the survival of the product to be shorter than the intrinsic survival of the cell in the patient.

So I think, since the average platelet lifespan under optimum conditions -- I think most clinicians would think, if they get a five-day survival out of transfused platelets, they are doing very well. So I think that's the target that we conceivably ought to use.

Now I picked again out of the literature the best studies that I could find which made good comparisons. This is now fresh versus five-day plasma stored PRP platelet concentrates into the same -- from the same donor into 12 thrombocytopenic patients. So the donor came back on different occasions and transfused the same thrombocytopenic patient.

You can see here that five-day storage, recoveries are about 47 percent less than fresh, survival 8 1/2 days versus 6 1/5. So less, but obviously very good data.

This is now transfusion of one, three and seven-day plasma stored PRP into the same 16 patients. So they were given three transfusions of either one, three or seven-day stored platelets. This is looking at corrected count increments at an hour and 24 hours. No difference between three-day and seven-day stored for either one hour or 24 hour CCI, but a statistically significant difference between one hour in either three or seven at both time periods.

This is now looking at 18, 17, 13 patients, all of whose platelets were either PRP, buffy coat or apheresis. This is the number of each type of transfusion that these 18 patients got. So they got all PRP-PC, 162 transfusions.

Storage time averaged about three days with all of the preparations, and none of these are statistically significant differences in terms of one hour or 24 hour CCIs.

This is the patients transfused with platelets stored for three to five days in plasma, PAS or Plasmalyte, and the type of product. So this is buffy coat. This is apheresis, buffy coat, apheresis.

The only statistically significant difference, interestingly, was for buffy coat platelets stored in plasma versus PAS-2. CCIs at both one hour and 24 hours were better for plasma than for PAS-2, but none of these other differences are statistically significantly different, again suggesting that all of the products that we have available do basically the same thing under the same storage conditions.

Now I am going to end up the talk with a discussion about the pathogen inactivation system that is currently farthest along in its development. It is a system that has been proposed by a Cerus-Baxter consortium.

It involves using basically a PAS-3 solution. They call it InterSol. So 65 percent PAS, 35 percent plasma. They add a psoralen called amatosolin as 59 to the collected platelets. They then expose this platelets to UV-A light, and then they transfer the UV-A exposed light platelets to another container that has an absorption device that removes any residual breakdown products of the amatosolin or any remaining whole product. Then it is finally transferred to a storage container.

Now it is important that this product, in fact, be in a storage solution, because UV-A light has very poor penetrance. So reducing the amount of residual plasma allows better penetrance and, therefore, an inactivation process to proceed.

Now using this inactivation process, this is the data that was obtained in 16 normal volunteers who had apheresis collection done. Half of the product was treated. Half was not treated, and this is the platelet recovery and survival data after five days of storage.

Although there is a statistically significant decrease in platelet both recovery and survival, the quality of the product is still within clearly an acceptable range.

Now there have been two transfusion trials, one done in the U.S., the so called SPRINT trial, one done in Europe, the so called euroSPRITE trial, that have actually looked at pathogen inactivated platelets transfused into thrombocytopenic patients.

In the U.S. trial the platelets were collected by Amicus apheresis machine. In the SPRINT trial buffy coat platelets were used. This now looks at the platelet increment at one, 24 hours, platelet transfusion interval, and platelet transfusion events.

What you can see, again as would have been predicted by the normal volunteer radiolabeled studies, the recoveries and survivals of the treated platelets are statistically significantly less for both the Amicus as well as the buffy coat treated platelets.

Here the differences are not statistically significant, but there is clearly a trend for the treated platelets to provide less quality platelets than the control. Here you see again that the transfusion interval is the two to three days that I discussed with you is what we usually see in thrombocytopenic patients.

Now these products were stored for up to five days. So I think the issue is this is a pathogen inactivation process which introduces some loss of viability of the platelets following treatment, and then the issue becomes, if we take these five-day stored platelets and extend them to seven days, what is the data going to look like, since we have a somewhat compromised product even at five days that is statistically significantly less quality product than similarly transfused control platelets.

So I think that's an issue that needs to be addressed. Finally, the last slide just looks at the primary endpoint, interestingly, for the U.S. SPRINT trial was not does the platelet count go up, do the platelets survive, but rather are the platelets hemostatically effective.

So I think the FDA rightly wanted to make sure that the treated platelets, in fact, were still able to provide hemostasis. So this is the treated platelets. This is the control platelets.

Patients who have WHO Grade 2 bleeding, percent in each arm, was exactly the same. WHO Grade 2 bleeding is more than petechiae and ecchymosis, but a bleeding that does not require a red cell transfusion. Grade 3 bleeding requires a red cell transfusion. Grade 4 bleeding means that it's a life threatening type of bleed, and again bleeding events were the same. Days of bleeding -- we are looking at mean a bit more in the treated than the control, but the median was the same. Duration of platelet support was the same.

So with that, I will conclude. Thank you.

CHAIRMAN NELSON: Thank you, Dr. Slichter. Any questions or comments?

DR. LEW: Yes. On a slide before, you showed events, and I didn't know what those events meant, but it looked like there was more in the treated group than the nontreated.

DR. SLICHTER: Yes. This is -- Events means the number of times that you were transfused with platelets. So in both the SPRINT trial and the euroSPRITE trial, in order to support you through your thrombocytopenic period, you needed about 25 percent more platelets. Yes, Toby?

DR. SIMON: One fact that I kind of wanted to probe that isn't directly in your presentation but harkens back to the discussions of 15 years ago when we shifted back from seven to five days: As I recall, the bacterial growth in the platelets was generally between three and five days.

So a seven-day platelet was not necessarily more likely to be bacterially contaminated than a five-day platelet, but the thrust was that, as platelets -- that the longer the interval you allowed, the more longer storage you would have. So that pushing it back might potentially reduce. Is that the right recollection?

DR. SLICHTER: I think that's the right -- You know, what they are doing in Europe now, interestingly, is they are storing their buffy coat platelets for five days, and in some blood centers they are then using a pathogen inactivation system to then determine if the product at five days is bacterially contaminated. If it's not, then they are now storing them for seven days.

In specific answer to your question, Toby, I think that's right. I mean, I think -- and I think Dr. AuBuchon will talk about that most people feel that a pathogen inactivation system -- you can't use it on day zero, because there is not enough time for the bacteria to have grown to allow their detection. But if you start the detections process at three or four days, then probably you are going to have enough bacteria to see them, if they are there.

I think, Toby, that the reason why -- You know, you probably know this better than I, because I think you were at the FDA or in the blood products -- in the government anyway at the time that this decision was made. But I think the reporting did show that there was more evidence of bacterial contamination.

Probably, as the first slide I showed, there has to be a certain log growth of platelets in order for it to be clinically relevant to a transfused patient.

DR. SIMON: The major reason I'm bringing this up is just so people understand what I think is correct, that it's not so much that more growth occurs between five and seven days, but rather that the longer the storage, the more likely. So the feeling is, if you go to seven days, you would get more contamination than if you had five days.

DR. SLICHTER: Oh, yes.

DR. SIMON: The other issue: I think that there was a feeling pragmatically that, if you had five days, it took care of most of the clinical problems, because you got -- It used to be three days, and then your Friday platelets expired on Monday, and it was terrible if you were a patient who needed platelets early in the week, and that five days allowed that you get through that, and holiday weekends. But when you dealt with a lot of smaller hospitals and rural, seven versus five really did make a difference in helping with supply, whereas in the most urban metropolitan areas, it wasn't such a key issue.

CHAIRMAN NELSON: You know, but given the variety of organisms, I wonder if between five and seven you might get a higher burden and more clinical events. Is that --

DR. SIMON: It would certainly be possible, but I think most of the problem occurred, as I recall -- I guess Jim will talk about it in a little more detail between the three and five days.

DR. SLICHTER: The other issue, I think, is that I have been told that there's some data that the storage solutions are bacteriostatic. So that we may get some additional benefit, not only on the quality of the platelets by putting them in a storage solution, but potentially also on the rate of growth of bacteria.

DR. HOLLINGER: Is the issue with wanting to store from five to seven days one that a lot of platelets are outdated in that time, and what percentage are they, or is there some other issue of being able to more effectively use the platelets for patients and so on? What's the major issue of wanting to extend it?

DR. SLICHTER: Yes. The major issue, I

think, is shelf life and outdating. The outdating rate depends a lot on how good your blood center is about managing your inventory. I think our outdate rate for platelets is maybe around 10-15 percent. Is that right, Mike? Okay. Mike Strong is here from our blood center, and he knows the numbers.

So that's part of the issue, but for, as Toby said, a lot of small centers, they don't have an inventory that allows them to be as flexible as a large major metropolitan transfusion service such as we are happens to be.

So I think, as long as we can document that we have a good quality product -- You know, it's kind of like when we went from 35 day stored red cells to 42. You know, people said, well, you know, what do you need that extra seven days for? Can't you manage your inventory? And it made a very big difference in terms of outdating, once we eventually got the extended red cell storage.

So I think that anything we can do to extend platelet storage will be a welcome addition for blood centers.

DR. DOPPELT: Do you have any idea by how much this will increase your inventory on shelves? I mean, how many more platelets. If you keep platelets for seven days, by how much will this increase the number of platelets you have available?

DR. SLICHTER: I don't know. Mike, do you have any answer to that?

DR. STRONG: Strong, Seattle. As Sherrill mentioned, for red cells we made a conversion to the additive solutions a few years ago, and it clearly dropped our outdate on red cells from about -- We were running about four to five percent, and we are now less than one percent.

For platelets, the extra couple of days -- The big difference there is considering the time frame of the week and when you are drying the platelets, and as Sherrill mentioned, the weekend -- and as Toby has also mentioned, the weekend is where you suffer, because you can't get as much collections over the weekend either for apheresis or for whole blood platelets.

So the extra two days really makes a big difference in how that inventory is managed over the course of the week. So my guess is it could drop it as much as 50 percent by having that extra couple of days.

DR. DOPPELT: Can I ask a second question?

DR. SLICHTER: Please.

DR. DOPPELT: How effective are these platelets from a hemostatic standpoint, if they are extended for seven days? I couldn't get a clear understanding of that.

DR. SLICHTER: There's really very, very little in the literature about even fresh platelets, five-day platelets, in terms of their hemostatic efficacy. What I would say to you is that I am not aware of a situation in which the platelets are viable and not functional.

So that in our experience, if the viability, meaning the recovery and survival of the platelets, is good,I'm not aware of a discrepant situation between function. So for example, when we stored platelets at four degrees Centigrade, they had a good recovery and extremely short survival and did not correct bleeding time.

So I think it is important that, when we get to seven-day stored platelets similar to what the FDA required for the pathogen inactivated platelets, that we in fact look at hemostasis and make sure that with extended platelet storage, hemostasis is still there. But I don't know of any real data, even when seven-day stored platelets were approved and licensed, that really looked at -- specifically at hemostasis.

But most clinicians would tell you that, you know, once you put platelets in, you ordinarily expect to see bleeding controlled and didn't.

I mean, there was not a hue and cry from the clinician saying, my god, everybody is bleeding to death now that you have seven-day platelets, but I think it's important not to forget that we are transfusing platelets to provide hemostasis. So we need to make sure that that is, in fact, evaluated.

DR. STRONCEK: I guess a couple of things. Managing platelet inventories is much more difficult than red cells. I agree with what Sherrill and Mike have said, that red cells most places, I think, have a one percent outdating, but platelets it's ten to 15 percent.

On transfusion services even in big hospitals, there tends to be a handful of users that can use a lot of platelets. So there are times when it's slow. You know, the business is slow, and having an extra seven days helps. Then long weekends, it makes a big difference.

Then as far as -- You know, the effectiveness of platelets -- Maybe, Sherrill, you can comment on this, but my impression of platelets is when they get old, they tend to get cleared, but they still are probably somewhat effective with hemostasis.

There were those platelet -- what were they? -- freeze dried platelets that people were trying to market about five years ago where it ended up they were platelet membranes which had very -- just minutes as far as half-life, but at least in animal models they showed that they were able to go to lesions and cause some hemostatic effect.

So I would guess that, even if these platelets don't have as long a half-life, when they are there they probably help in some way.

DR. SLICHTER: Yes. The other thing, I think, just information for the committee, we did a study looking at the platelet transfusion trigger and looked at 5,000, 10,000 and 20,000 as a trigger, and looked at radiochromium labeled stool blood loss as a quantitative measure of how much bleeding you do, depending on the level you are transfused at.

I would tell you -- and there's data in the literature from transfusion trials -- that if you look at 20 versus ten, it's the same. When we looked at 20, ten and five for a quantitative blood loss in the stool, it was the same.

So I think the number of platelets that you need -- I mean, I mentioned that there are 7,000 platelets per microliter per day that are involved in an endothelial supportive function.

So I think, as long as you have at least 7,000 platelets circulating and they are of some quality, probably hemostasis is effective. So I think the number of platelets you need to provide hemostasis is relatively small.

DR. SCHMIDT: We used to transfuse platelets that had been collected in the EDTA, because as we looked at the platelets under EDTA, they looked nice and round and, therefore, they must be good.

I think we stopped doing that because of data out of Seattle which was post-cardiac surgery in which the message was kind of, if the platelet count went up significantly after transfusion, that was bad, because the platelets weren't doing their job. They're not hemostatically effective.

Was that Laurie Harker's data or --

DR. SLICHTER: I don't think Laurie ever--

DR. SCHMIDT: It was very old.

DR. SLICHTER: Well, it was very old data, and I think it was really Frank Gardner who -- and Dick Aster who really documented that EDTA spheres the platelets so that they are irreversibly sphered and compared to citrate collected platelets, they had very poor recovery and very poor survival.

So I'm not sure that there was ever functional data on EDTA compared to citrate collected platelets. I think that the viability of the platelets was substantially compromised in EDTA compared to citrate, but those were studies that were done by Aster and Gardner.

DR. SCHMIDT: But the studies of post-cardiac surgery -- I can remember that message, that if the platelet count goes up, that's bad, because they are not going to the walls of the vessels.

DR. SLICHTER: I don't think that's --

DR. STYLES: I think you make a very good point, which is that we could probably increase the platelet supply just by educating the clinician about the proper level at which to transfuse patients. We could probably make a much greater impact than anything we would do with dating.

I think, to me, the issue -- What seems to me you have said is that these platelets are probably effective or what is going to constitute effective enough and that they are probably going to result in an increased exposure of thrombocytopenic patients at the current level of clinical practice.

I don't think that people are going to

radically change, though I wish they would, the level at which they transfuse patients, but given the level of current practice, I would say that your data show pretty consistently that they are going to get more transfusions.

Now the issue of whether you can give them a better product -- But I'm a bit concerned about that, given the problems of infection currently. Now pathogen inactivation may eliminate that concern, but the other problems, especially in the multiple transfused patients with resistance to platelets, which I see all of the time and is a real problem.

DR. SLICHTER: Yes. I think that is a problem, and I think the other issue that I've tried to address a little bit is the issue that, once you take one hit like if you have a collection injury and then you -- so that you hard spin the platelets against the walls of the bag initially to make a platelet concentrate by the PRP method, and then you store them, then that collection injury is magnified.

So one of the concerns that at least I have is whether the pathogen inactivated platelets which have a processing injury from the pathogen inactivation, whether when we extend the storage of those, is that going to be a problem? I don't know the answer.

I don't think any studies have been done. I mean, they have done *in vitro* studies with the pathogen inactivated platelets for seven days and have shown that they have good quality, but as I've mentioned, I think *in vitro* and *in vivo* may not necessarily be the same.

I also agree that we could substantially reduce the number of platelets transfused if we did, in my opinion, two things, which is reduce the trigger and also reduce the dose, because we don't need a 60,000 post-transfusion platelet count. I mean, that makes the doctor feel good, but the patient doesn't need it.

DR. STYLES: I have one last question. Were both these trials blinded?

DR. SLICHTER: Yes, they were both blinded trials. Absolutely. That was very important, particularly for the U.S. trial which looked hemostasis. So the bags were covered. The people who were doing the bleeding assessment had no idea which arm of the study the patients were in.

DR. KOFF: Can I ask you about the temperature issues that you've raised?

DR. SLICHTER: Yes.

DR. KOFF: David mentioned cryopreserved. You've talked about the differences between 22 and 37, and now I see the reference to the Aster work that, I guess, looked at -- I'm not that familiar with it -- looked at -- must have looked at a curve at different temperatures in storage.

DR. SLICHTER: Yes. Right.

DR. KOFF: Are there sufficient data -- Have those studies been repeated? Have they looked not just at survival but hemostasis? It just seems, without completely being ignorant of this, that if 22 is better than 37 and maybe there is a role for cryopreservation, is there some wiggle room for lower temperatures which would still maintain platelet function, survival, reduce bacterial contamination, growth at least?

DR. SLICHTER: Yes. That's a very good question, because the issue is, if 37 is worse than 22, why don't you just keep going down? We did look very early on at 4, which was the same temperature that we store red cells. That was no good. And Aster did do a very careful set of experiments going down from 22 to 20 to 18 to 15 to the dah-dah-dah.

As soon as you got to something less than 20, you started to show substantial decreases in viability. There were no function measurements made. So I can't talk about function, but I can talk about viability.

So I think we are not going to be able to push that particular envelope, which is a great idea, but I think is not going to get us where we want to be.

DR. SAYERS: Thanks. Sayers, Dallas.

Just a cautionary note. Some would view that physician education is an oxymoron, but with that aside, just a question, Sherrill, of clarification.

You made mention about what some centers in Europe were doing looking at five-day platelets. Now were they then subjecting some of those platelets to bacterial detection or bacterial inactivation? If it was detection, were they just throwing out ones where they had --

DR. SLICHTER: The latter, Merlyn.

DR. SAYERS: It was inactivation?

DR. SLICHTER: So they looked at detection, not inactivation. The inactivation procedures are going to be done up front. So you prepare the platelets. You pathogen inactivate, and then you store.

So in Europe what they are doing is they are taking five-day platelets which are going to outdate. They are then subjecting them to a pathogen detection process.

DR. SAYERS: I see.

DR. SLICHTER: And then the ones that are positive -- they are not transfusing the ones that are negative. They are transfusing and allowing them to then better manage their inventory.

DR. SAYERS: Thanks.

DR. LEW: Just to follow up on Dr. Styles' comments, has anyone looked in the patients who need them continuously, assuming that they are going to get some that are earlier platelets and some that are later platelets, how much extra transfusion they will get, and then balance that to the other risks for platelet transfusion, as well as for people who may need it acutely for trauma, what it may entail in terms of extra platelets?

Twenty percent or 25 percent that you mentioned seems awfully high in terms of the extra needs for someone who needs it chronically. Has someone done those type of analyses at FDA or someplace else?

DR. SLICHTER: Not that I know of. But, you know, one of the advantages of pathogen inactivation is that you inactivate the pathogens. So that, even though you may have to give more platelets, they are in fact pathogen inactivated. So the issue for the clinician becomes, as often with advances in science, there are tradeoffs.

So the tradeoff that you as the clinician have to recognize is you get a produce which is going to be pathogen inactivated for both bacterial, viruses and protozoa -- okay? -- and a broad range of viruses, bacteria and protozoa, and is that worth the fact that you may have to then increase the number of platelets that the patient requires.

You know, one of the issues then becomes whether they are alloimmunized, but in this trial they did look -- At the U.S. trial they did look for the development of lymphocytotoxic antibodies in both arms. There were over 300 patients per arm, a wide variety of patients, and the incidence of lymphocytotoxic antibodies in both arms was about five to six percent, and these are leukoreduced apheresis platelets that were transfused in both arms.

DR. HOLLINGER: I guess maybe we should in many cases promote single donor apheresis, just in terms of bacterial contamination, and just using a single donor sometime when you would have to use multiple units or bags which would compound the issue, I guess, of contamination.

What percentage right now -- I have a couple of questions, but what percentage of the platelets that are currently used are from single donor versus random donor? Do you know? For patients?

DR. SLICHTER: Speak up, Jim. Two-thirds apheresis, Jim says.

DR. HOLLINGER: Two-thirds are apheresis?

The other question is just a technical one. I was just curious. Most of these studies are done with chromium labeled cells or indium. Most cells -- I don't know about the platelets. Red cells are usually negatively charged, and you put chromium on and they become positively charged.

We used to use that actually to add antigens to the cells for doing serologic tests. But what happens to cells? Do we know, when you do a chromium labeling, does it alter the cells in some way -- the platelets in some ways that it -- where they might be more uptaken, the spleen or other places, endothelium and so on? Do we have an idea about that, because that's what a lot of these studies are based on in recovery and survival?

DR. SLICHTER: Yes. Well, we were concerned about that very issue. So in the early days Scott Murphy was doing radiolabeling studies and doing them after storage. So one of the issues was, was he getting that great data, because the dead cells wouldn't take up the label?

So we actually did labeling studies pre-storage and, in addition, did some studies comparing fresh versus -- well, stored versus labeled in the same thrombocytopenic patient to try and look at the issue.

As best I know, our data, nor am I aware of any data in the literature that suggests that the labeling process *per se* is somehow damaging to the cells or giving a different answer, but that's a very good question.

Everybody now does post-labeling. We do it, because we had a secretary who was ordering our chromium and found something cheaper in the book than what we were ordering. So she ordered that for us, and lo and behold, it was cheaper because it wasn't sterile.

So I had some septic normal volunteers, because I stored their platelets for three days with nonsterile chromium, and I was one very nervous

Nellie.

CHAIRMAN NELSON: Okay. Thank you.

DR. SMALLWOOD: Excuse me. May I ask that everyone that has a statement to make or responding to a question please come to a mike and announce your name. I know we know one another, but for the record we need to have it recorded, and our transcriber does not know everyone. Thank you.

CHAIRMAN NELSON: Dr. AuBuchon.

DR. AuBUCHON: Fresh from my Olympic performance. Thank you very much for the invitation to appear before the Blood Products Advisory Committee today. I would like to extend some of the remarks that Sherrill has begun about using seven-day-old platelets and the clinical conditions which surround the situations in which they may be useful.

I will warn you at the outset that I will be proselytizing you, because I think there is an opportunity in using seven-day-old platelets with a bacterial detection system in order to improve the safety of transfusion recipients. Next slide, please.

Today essentially I will be talking about two things: First, briefly, why we are interested in this subject; and then whether it is really feasible in a hospital setting, practically, to use seven-day-old platelets. Next slide, please.

We are all aware of the increased safety over the last several decades that has been achieved through more stringent donor screening and augmented test procedures. This is a success story of which we all should be proud. Next slide, please.

However, imposed on top of this are the residual problems that really have not changed over the last two decades in terms of bacterial contamination, particularly of platelets. The risk of a unit of platelets having detectable bacteria is approximately one in 3,000.

The probability of a septic death, as you will see, displayed from a number of different studies exceeds the risk of HCV or HIV transmission. Next slide, please.

Indeed, looking at FDA data gleaned from reports from hospitals of transfusion fatalities -- next slide, please -- the two top reasons for deaths are hemolysis, as was discussed earlier by Dr. Lewis from the Error conference, and bacterial contamination. Next slide, please.

So when we transfuse a unit of red cells or a unit of platelets, we think we know what we are putting into the patient. Next slide.

However, we may be putting something in that we do not anticipate and we do not wish to transfuse, namely, bacterial in the case of red cells or occasionally, as some platelets will have some gram negative contamination, also endotoxin. Next slide, please.

Bacterial contamination is very frequent. It is initially at very low concentration, as Dr. Slichter referred to. We are talking about the initial inoculum in a unit of whole blood as being somewhere on the order of one organism per milliliter or possibly even less.

Therefore, if we were going to apply some type of detection system that depends on a sensitivity on the order of 10, 100, 1000 or more organisms per mil, we will have to let some time elapse before there is a sufficient concentration to detect these organisms.

These bugs in blood are very difficult to detect. They are difficult to detect in the unit. They are also very difficult to detect in the patient, because particularly for platelet recipients, these individuals, at the same time that they are thrombocytopenic, are often neutropenic. They are susceptible to fevers and to sepsis.

So when a patient becomes septic after a transfusion, the clinician or even the blood banker may not suspect that the origin of the organisms was the bag of blood as opposed to the patient's GI tract or some other intrinsic source. Next slide, please.

There are numerous reports in the literature documenting just how frequent contamination is. A number of reports from around the world place this risk in the order of hundreds, if not thousands, of cases per million units of platelets transfused.

I've chosen to represent the rate as per million, because now we are often talking about the risk of HCV or HIV in terms of number of cases per million units, often less than one unit per million units. Here we are talking about hundreds or thousands of units per million units transfused. Next slide, please.

Data from the United States from the CDC's bacterial contamination study recently published in Transfusion and previously presented at AABB meetings indicate that there are several hundred clinical cases of post-transfusion sepsis annually in this country, and on the order of one to two dozen deaths.

Now this is a case report study and, undoubtedly, is an underrepresentation of the risk in the United States. Next slide, please.

Looking at longitudinal data gathered in very careful study from Johns Hopkins shows that the risk of post-transfusion sepsis to be on the order of 100 to several hundred per million, whether you are talking about platelet concentrates or apheresis platelets, single donor platelets, and the fatality rate, 14 to 62 per million. Again, contrast that to the HIV rate of now less than one per million. Next slide, please.

Probably the largest study that has been conducted and reported to date comes from France, their ongoing hemovigilance surveillance system. Here they noted that the fatality rate, not just the rate of sepsis now but the fatality rate, due to bacterially contaminated platelet products was approximately seven per million. Next slide.

Dividing that out, that's one per 140,000, again orders of magnitude greater than the risk of HIV transmission. Next slide, please.

There are some changes that can be associated with bacterial contamination of platelets, such as formation of clots in the bag, discoloration, presence of gas bubbles. These are not always reliable, not always present, not always detectable.

Next slide, please.

Some individuals, some institutions have attempted to use gram staining or acridine orange staining to detect bacterial by visual examination of the slide of the unit before releasing it for transfusion. These techniques will pick up some units that are contaminated. However, their sensitivity is in the range of 10^5 to 10^6 organisms per milliliter, obviously beyond what we would like to transfuse instead of a, hopefully, sterile product. Next slide, please.

There is also a concern about false positive rate. When you are looking for small bacteria amongst a sea of small platelets, you can frequently end up with a false positive result from that kind of screening. Next slide, please.

As Sherrill indicated, there are, obviously -- and Jaro indicated -- there are obviously biochemical processes going on in platelets, production of acid in CO_2, and it is theoretically possible to detect the formation of these components in platelets, also the same thing that is going on in bacteria.

So as bacteria are growing, they are producing acid and producing CO_2, and you could theoretically detect bacteria presence by looking for these output. Next slide, please.

There are a number of proposals that have been brought forth and a number of detection devices that are attempting to use this. We don't have anything that is reliable at this point to detect these metabolic end products as an indicator of bacterial contamination. Next slide, please.

One problem is illustrated here from a paper from Dr. Mark Brecher's lab at the University of North Carolina, noting that it is possible to find a drop in glucose in bacterially contaminated units and differentiate that from a sterile control unit. The glucose is, obviously, consumed by the bacterial. Next slide, please.

The problem in terms of setting this up as an ongoing detection device is that there is a broad range of glucose consumption that can be found in platelet units, and one would theoretically have run the risk of releasing a product that was severely contaminated with bacteria and yet still falling within the "normal range" for glucose in a platelet unit. Next slide, please.

Swirling has also been advocated as a means of detecting the presence of bacteria. Swirling can be thought of -- or maintenance swirling can be thought of as a poor man's pH meter.

Platelets in their normal discoid form will align with the flow of plasma. So if one takes a unit of plasma, rocks it back and forth, you can get a shimmering seen through the unit because of the diffraction grading that is caused by the alignment of the platelets.

If the pH drops for whatever reason, including bacterial contamination and production of acid, the platelets will sphere and blow a pH of about 6.2 and will no longer swirl. So this might be one way of trying to detect contamination. Next slide, please.

We have attempted to look at this, and the sensitivity varies by the organism, depending on the pH drop that is seen. There is not 100 percent sensitivity. It will work sometimes. It won't work all the time. Next slide, please.

Indeed, one could measure pH or measure glucose on a laboratory instrument, and whenever we take one of our contaminated units into our chemistry laboratory to run it through the pH meter, the chemistry techs form a phalanx guard around the blood gas instrument. They don't like to see us coming and have us contaminate their instrument, but you can detect changes in pH that way. However, there is false positivity to deal with again there. Next slide, please.

There are a number of companies that are currently developing simple, quick, fast, cheap techniques to detect byproducts of bacterial growth or to affect bacteria themselves, in order to document that a unit does not have platelet -- bacterial contamination or does not have at least a number of platelets above a certain threshold. These are not yet available on the market, but we look forward to seeing some of them in the future. Next slide, please.

Now what about culturing? We haven't talked about that yet, and that is usually regarded as the gold standard for detecting bacteria. One takes a culture and, if nothing grows, you call the source sterile.

The traditional concept for testing that a blood center would do would require that the result of the test be negative before the unit is labeled and released. That's obviously what we do for viral testing. However, with bacterial testing that will not work very well, because first of all, you have to allow the unit to sit for at least one or two days before a small aliquot from that unit can reliably be used to detect bacteria.

You could do destructive culturing and culture the entire unit on day zero and see if there are any bacteria present, but that, obviously, does not yield a transfusable product.

So the techniques that are being used in European centers, particularly Belgium and the Netherlands, involve culturing on Day One, allowing the bugs to grow up for at least a day, taking a small culture, and seeing whether that turns positive. However, it's not really possible -- next slide, please -- to hold the unit until the culture is verifiably negative, which may take several days before a microbiology lab will stamp negative on the report.

One will have to have a system whereby the unit can be released for transfusion prior to the final result being known as negative. Now there is a possibility that the unit will be in the hands of the hospital before the culture turns positive. In that case, there has to be a system for recalling that unit.

It is also possible the unit could even be transfused before the culture turns positive. However, in that case it's likely that the storage time has been very short, and the bacteria will not have grown up to a level that is dangerous or that the inoculum is clinically dangerous to the patient in that time period.

Essentially, you have a race between growth at 22 degrees in the bag versus growth at 37 degrees in the culture bottle -- in an instrument, for example, automated culture instrument, and the bacteria are going to grow faster at 37, and you are more likely to find the growth in the instrument before it becomes a problem for a recipient of that unit. Next slide, please.

I would like to share with you today our experience in using a slightly different concept from the traditional one, and that is applying a hospital based system to verify the sterility of platelet units. Next slide, please.

The technique we have been using now for almost three years in our institution is applied to apheresis platelets. All of our platelet units are apheresis platelets, and they are cultured on Day Two -- that is, the second day after collection -- by taking a 5 milliliter aliquot obtained by sterile connecting device and placing it in an automated culture system, the BacT/Alert system.

The unit is then put on the usual rotator for release for transfusion and is used as needed. Next slide, please.

What organisms might we have to detect? Well, based on the CDC's BaCon report, you see here a listing of the organisms that were found in blood contamination, and this shows both red cells and platelets. The isolates which are found in red cells are shown with the asterisks.

It's a wide group of organisms. However, these are the same organisms that the BacT/Alert system detects day in and day out, and has for well over a decade, in hospital microbiology laboratories, starting with very low inoculums from patients who have substance or some other bacterial infection.

So we are using this system in this matter. Although it is not approved for detection of bacteria in platelets for the purpose of releasing for transfusion, BacT/Alert has recently been approved by the FDA for quality control testing of platelets, which in my mind essentially amounts to the same function in terms of what we are expecting it to do in the laboratory. Next slide, please.

When should the culture be drawn? As I said, in Europe the culture is usually drawn on Day One. We opted for a Day Two culture in order just to make absolutely sure that any bacteria that were in that bag would be detected with a small aliquot for culture.

For example, in a preliminary study where we inoculated sterile units with 1 CFU per ml., we found actually all of our units growing on Day One, and Day Two even had a higher inoculum in the bag. So we feel that Day Two was safe, but the European experience indicates that Day One may be just as safe. Next slide, please.

How long will it take before the cultures turn positive, if there are bugs in the bag? These data, again from our Brecher's lab at UNC, indicate that on average we are looking at between ten and 20 hours. There are some slow growing organisms, anabacterium, for example, which could be found. It's not a major contaminate in platelets, but far and away most of the organisms that we would be concerned about would be detectable beginning at a relatively low inoculum within a day. Next slide, please.

So after we take our culture on Day Two, we go ahead and release those units whenever they are needed. We will interdict their release if the microbiology laboratory informs us that a culture is positive. Next slide, please.

We would hope that this would not only provide assurance of sterility, but as I'll talk later, I think this will allow us to extend storage to seven days, allow us to store after pooling platelet concentrates, which is not currently allowed in this country, although it is done in Europe, and also allow for reduced cost of leucocyte reduction; because one could pool five or six units of platelet concentrates and then use only one filter rather than multiple filters. Next slide, please.

In our first two years of using this approach, we have cultured about 2600 units of single donor apheresis platelets. We had 16 initial positives, 0.6 percent. Eleven of these could be recultured and were not confirmed. We had been saving additional aliquots where we could retest the unit, and in all those 11 that we could retest, we did not get growth of any organism. Five, we were not able to reculture.

One of those latter five cases, it occurred that the unit was transfused before we got the report of growth from the microbiology laboratory.

The patient had done well on the transfusion. We cultured the patient and did not grow anything. So again, we believe that all of these 16 were indeed false positives. It's a relatively low false positive rate, which is encouraging. Next slide, please.

That was our first two years of experience that we reported recently at the AABB meeting. Shortly after we closed the data for those first two years, we had an interesting report.

We received a unit from an outside supplier. About five percent of our units do come from an outside blood center. The remainder we collect ourselves. We cultured it on Day Two, the day that it arrived.

It was actually a split unit. So we had two different bags, but we knew it had come from the same donor by the numbering system. The next morning we got a report from the microbiology laboratory that one of the two splits was growing bugs.

We were surprised that the other one had not also alarmed, and we thought maybe this is a false positive, that we contaminated the culture somehow. However, the afternoon the other one also grew.

So we had then interdicted two units that were bacterially contaminated from the same collection process. It was the same *staph epi.* organism in each half of the bag.

We were pleased that the system had indeed worked the way it was supposed to work and prevented two patients ultimately from receiving contaminated platelets. Next slide, please.

Now I know this committee is charged not to be concerned about cost, but I can assure you that hospital transfusionists are concerned about cost. I would like to talk a little bit about cost in order to document how this technique can be made not only cost effective but even cost saving, so that hospitals will implement it.

We have been able to identify the costs involved in this technique, and I have tried to capture all of the costs except the amortization of the BacT/Alert incubation cabinet. It amounts to $16.50 per unit cultured. Next slide, please.

If you scale that up for 100 units, you're looking then at $1600. Our outdate rate and the national outdate rate for platelets is 15 percent. So 15 percent -- If we could avoid that 15 percent at $500 per unit, as the approximate cost of single donor platelets, you can see that that is several times greater than the cost of doing the culture.

Would we entirely eliminate all outdating if we were able to extend storage because we are doing bacterial detection? No, but back in the mid-eighties when we did have seven-day platelets, the outdate rate dropped from around 15 percent to three to four percent nationally for platelets.

So I think we would be able to recover the cost of culture, if we were able to extend the storage time. Next slide, please.

Indeed, in our experience, we always have more units being required for transfusion than what we outdate the previous day. I would hope so. Otherwise, we wouldn't be very good inventory managers of our platelets.

So I think that, if we were able to extend storage because of a bacterial detection technique, it would be able to be brought in without an increase in cost. Next slide, please.

But do seven-day-old platelets survive and function as well? As Dr. Slichter very nicely showed, there are changes during storage, and fresh platelets are not the same as five-day-old platelets, are not the same as seven-day-old platelets.

Some institutions have shown that giving older platelets does not provide as much support for patients and results in them needing additional platelet transfusions. In our hands we have not been able to document that in that the corrected count increments are not different using five-day-old platelets versus younger platelets.

There is some difference of opinion on that, but clinically five-day-old platelets seem to work just fine, although one can look very closely and possibly define some differences with increased storage age. Next slide, please.

We were involved in a study, again recently reported at the AABB, funded by Gambro and in collaboration with our colleagues at Red Cross in Norfolk, looking at the effect of storing apheresis platelets that were collected on the Gambro Spectra instrument for five or seven days -- or collected on the team instrument also, and collected and then stored for five or seven days.

This was both an *in vitro* study and *in vivo* study with chromium, indium radiolabeled recovery and.survivals. Next slide, please.

The platelet units were standard leukoreduced plasma suspended single donor platelet units. Next slide, please. Again, these were leukoreduced at the time of collection.

If one looks at the changes in pO_2 and pCO_2 or pH between Day One and Day Five and then on to Day Seven, one can certainly see some differences with increased storage time.

Day Seven is not exactly the same as Day Five. However, I would note that the pH remained above 6.2 and did not indicate any likelihood of going upward. These pH were falling, although remained above the 6.2 threshold throughout seven days. Next slide, please.

Glucose continued to be consumed, and lactate continued to be produced throughout that period, and the rate of glucose consumption and lactate production was no different in that additional two-day period. Next slide, please.

The platelets, of course, showed some evidence of loss of function and increased activation during storage. That is what is normally seen as part of the storage lesion. The changes were not great. They were small, as has been noted by others.

There was a difference between five and seven days, but they are in the approximate same area. As you will see when we get to actual human data, the increase in activation of these platelets did not prevent them from being hemostatically -- apparently hemostatically effective by virtue of them continuing to circulate. Next slide, please.

Looking at the recovery and survival at five days versus seven days, there were statistically significant differences. There were declines in both recovery and survival. Next slide, please.

Shown here in tabular form, these numbers are very similar to those that Dr. Slichter showed from a number of other laboratories in which one can see a decrement in both recovery and survival with the additional two days. However, these numbers still look quite acceptable in comparison to other reported studies.

In particular -- next slide, please -- I'd like to contrast these numbers to data that were submitted to the FDA in support of licensure of seven-day platelets, now almost 20 years ago. Next slide, please.

If you look at this study in comparison to the data of Archer et al., we have better results at seven days than were accepted previously for both recovery and survival. Next slide, please.

If you look at the difference between five days and seven days, there is less of a reduction in both recovery and survival than was seen in data from

20 years ago.

Therefore, based on clinical trial data in normal subjects, it would appear that the seven-day platelets that we have available to us today, stored in different kinds of plastic, stored with different amounts of possibly different anticoagulants than were used 20 years ago and stored in leukoreduced fashion, are at least as good, if not better, than the platelets that were judged acceptable 20 years ago for seven-day storage. Next slide, please.

Now we've been taking some of this work to a practical point in the transfusion service laboratory. Our platelet units, of course, outdate on Day Five, but we keep them on the rotator until the morning of Day Eight -- so in other words, the morning right after the outdate at midnight on Day Seven -- for pH and swirling checks. Next slide, please.

Looking at 91 Cobe Spectra units, 96 percent of them showed swirling on Day Eight, and the pH, average pH, was 6.86. 97 percent were about 6.2 for pH, and the maximum pH was 7.3. So we did not appear to have high pH problems, and very few of the units did not maintain their pH out to Day Eight. Next slide, please.

Now we are an academic medical center, but we are not in a city setting. We are three hours away from our blood supplier who could supply us back-up platelets in case of unusual need. There are certainly times when we have unusual need, and we cannot get platelets fast enough.

In that case, we have to do something. We exhaust our supply, and we need more platelets. Because we have cultured units that have not grown bacteria on our platelet incubator, we have by medical necessity, medical emergency, occasionally had to use units beyond five days of storage in order to support patients who needed platelet transfusion.

So I would now like to share with you some of our experience of transfusing platelets that are in Day Six or Day Seven of storage for patients who needed transfusion, and we have assessed the clinical outcome here by corrected count increments taken one hour after transfusion. Next slide, please.

We have conducted 40 such transfusions over the last three years on Day Six or Day Seven. All.of them appeared to yield the expected clinical results. That is, we never have to transfuse another unit because the patient did not stop bleeding.

In those patients who were stable and in whom we were able to measure corrected count increment within an hour, we had 21 instances where we could evaluate what the outcome was. Next slide, please.

Shown here are these 21 corrected count increments. 7500 is usually used as the CCI indicating a successful transfusion. The mean CCI of these older platelets was 14,000, and only one was at 5,000 or below. Next slide, please.

Shown here on a probability curve, you can see that 90 percent were above 7500. In any clinical trial of platelet transfusions, these would be regarded as excellent clinical outcomes. Next slide, please.

Therefore, we feel that these data support the concept that, although there is a storage lesion and that one can indeed detect differences between platelets that have been stored for five days versus seven days, that clinically seven-day platelets worked quite well.

Now the question was raised by the Committee a few minutes ago, well, what if we have to transfuse more platelets? Is that going to be more of a risk for the recipient? If we are transfusing leukoreduced platelets, transfusing additional platelets should not induce any additional alloimmunization.

What about the other risks involved? What if, if we went to seven-day platelets, we had to transfuse ten percent more platelets? So let's compare not culturing our units and storing them only for five days versus culturing the units, extending the storage time to seven days but maybe have to transfuse ten percent more platelets or one additional platelet for every ten that would otherwise be transfused?

I'm not saying that this will necessary. I'm looking at this sort of a worst case scenario. Next slide, please.

One calculates out the HIV risk. There would, of course, be an increase in the HIV risk, because one would be exposed to more units. Next slide, please.

However, the septic mortality would be greatly reduced, and in this case I am showing that essentially to be zero, because I believe this culturing technique is, if not 100 percent sensitive, very close to that.

So if one looks at the total risk -- I've just used HIV here, but HIV and bacterial contamination risk -- you can see that the total risk is actually lower for the patient, even with the extension of the storage time, providing you are detecting the bacteria.

Well, to return to cost, this is an extra unit that is going to cost the hospital something more. How is the hospital going to deal with that? Next slide, please.

There would, obviously, be an increased cost for this additional unit. There would also be the culturing cost involved. So the total cost would be $720 greater with this worst case scenario adding culturing. Next slide, please.

That is an average of $65 a unit. Next slide, please. However, if we are able to reduce or eliminate the outdating by extending the storage period, this $65 per unit will entirely disappear, and the hospital would not have any increased cost. It might actually see even decreased cost by using this approach.

I have not attempted to figure into the scenario of taking care of those occasional cases where there is septic transfusion. Next slide, please.

Now if we were able to apply a bacterial detection system such as culturing and go to seven-day dating, I think this would potentially allow us to pool units of platelets shortly after their production in a blood center, in other words, give prestorage pooling.

This would be very advantageous for a transfusion service who wouldn't have to worry about trying to pool platelets at the last minute as a surgeon is wanting to transfuse platelets during an operative procedure. It would allow for prestorage leukocyte reduction with a single filter for an entire pool, obviously reducing filtration cost.

It would, of course, allow us to assess sterility in this highest risk component that we are now transfusing, and reduce outdating. Next slide, please.

So, therefore, I would conclude that by applying these techniques, platelet storage for seven days is indeed feasible. It's practical. There is adequate maintenance of function. One sees the expected recovery and survival that is associated with adequate clinical efficacy, and indeed this efficacy is indistinguishable from that achieved with shorter periods of storage.

We would be able to use bacterial culturing, for example, as we've been shown to reduce septic shown risk and reduce overall risk for patients, making transfusions safer, and to do this without any increase in cost, and this is extremely important for hospitals.

I think, therefore, this indicates this is a practical method that can be applied. Next slide, please.

I would like to just close with a few commentaries on the next steps that we should, I hope, proceed along. The first relates to recognition of the clinical significance of bacterial contamination in platelets, and then I think the importance of us, quote, "thinking outside the box," applying some nontraditional approaches to get to the bottom of this problem, which has been around a long time. Next slide, please.

I would pose the rhetorical question: What I weren't up here talking about bacterial contamination, but we were talking about HIV? if the risk of HIV today were recognized at one in 140,000, bells would be ringing an alarm. We would be throwing our hands up and saying we have to do something about this, and we have to do something now. This would be the lead story on the nightly news. It would be the headline in the Washington Post tomorrow, and the public would be demanding that we take some reasonable action to reduce this risk.

I frankly don't see the difference between dying of HIV and dying of bacterial contamination. In fact, today one could make the argument that you are worse off if you die of bacterially contaminated platelet unit, because you are dead within an hour or two as opposed to HIV infection where there is now often effective antiretroviral therapy, and you may live for decades or longer.

Therefore, I think it's appropriate that this Committee look at this situation, and also that we take a step forward and do something different to address this problem.

I applaud Dr. Vostal and the agency for bringing this to the Committee's attention, and I hope that we can use the innovation that is available from our common thought process to provide some leadership for the field to move in a production direction. Next slide.

Part of that leadership, I think, is working outside the box and doing something a little bit different. Now I'm not standing up here presenting a device for a 510(k) approval or licensure. I'm not representing a commercial concern.

There are techniques available today.

There will be some commercially sponsored ones in the future, but there are some today that can be applied.

Almost every hospital that transfuses platelets today has an automated culture system in its microbiology laboratory. This culturing approach can be used practically to improve the safety of platelet transfusions.

It is also important that we gather data from multiple sources. We are not likely to have a single clinical trial that is going to document that, by doing culturing or some other technique, we are absolutely certain that we will eliminate bacterial contamination. That's just not going to happen.

We are going to have to look at all of the data available in the transfusion literature and the microbiology literature to say does it make sense that we apply this approach to make platelet transfusion safer.

Finally, I think it's important that we not relax our standards but take a different endpoint as our decision point for determining whether or not this is the appropriate thing to do. Usually, the agency is looking for proof of safety and efficacy before approving a new approach.

To prove that a bacterial detection system such as culturing will detect all contaminated units or even will absolutely reduce the frequency of sepsis would require the culturing on two different occasions of over 13,000 units before one had a statistically significant sample to document the safety of the technique.

That's just not a practical trial that can be performed. In other words, we might culture on Day Two and then culture at a later time period, say at outdate, to document that the Day Two culture was indeed accurate in showing no bacterial growth.

13,000 cultures times two is a very large study, which I am not aware any company is willing to undertake and, clearly, we as a hospital that transfuses 1500 units of platelets a year is not about to undertake that study. However, based on data from a number of sources, I think we can reasonably conclude that these culturing techniques will detect bacteria reliably and at least reduce the risk of bacterial contamination, even if we can't, with statistical competence, say that it will absolutely eliminate the chance of bacterial contamination.

Final slide, please. So I think we can apply all of the data that are out there and are continuing to be gathered to make platelet transfusions safer, and that is really the onus that is on the blood bankers in this country as well as the agency that guides and regulates us.

Thank you very much.

CHAIRMAN NELSON: Thank you. Yes, Dr. Lew?

DR. LEW: Actually, I had a question. You mentioned that when you looked at 2500 units cultured over two years, that you got 16 positives, but you thought they were false positives. Yet that would imply, if you really think that's true, that then your rate of contamination is obviously substantially lower than anybody else's.

I think there were another slide earlier suggesting that the range of contamination was around your lower .6 to 1.6 or something.

It would also be interesting to know what bugs grew from those 16.

DR. AuBUCHON: The usual rate of bacterial contamination of platelets is quoted in the literature. It's about one in 3,000, and if yo look at our experience in terms of documented repeatedly positive cultures, we are right in the same ballpark.

It's interesting to look at those 16 initial positivity cases and note when they occurred.

We have a relatively small transfusion service laboratory, 15 technologists who are very highly motivated, very skilled and relatively senior. They did not all begin culturing at the same point.

We started with the supervisor working out the technique with my research techs, and then one by one introducing the bench techs to the technique. All of the cultures that were initially positive and could not be confirmed occurred within two weeks of a new technologist learning the culturing system.

On finding one of these cultures, we would go back to the technologist, retrain the technologist to make sure that they really understood what they were doing, and then we would not see additional positives.

So it appears that these initial cases of growth were due to contamination at the time of culturing. It did not truly represent the units being positive. As I said, in the 11 cases we were able to reculture, they were indeed negative.

So this is something that is very much technique related. Why do we have a lower rate than has been reported elsewhere? I would say that many of the studies that have been reported in the literature did not have the capability of going back and reculturing the unit to document that the bugs that were growing in the microbiology laboratory had really come from the unit as opposed to coming from the culturing process.

CHAIRMAN NELSON: You actually really raise two issues, I guess. One is the issue of routine culture monitoring of platelets, and the other is of extending the life or the usefulness of the platelets to seven days. They are both related.

I wonder how many blood banks now do platelet culturing. I know some other than yours do, but how common is it?

DR. AuBUCHON: The quality control culturing of platelets, of course, is done routinely by all collecting agencies, but at this low rate of contamination QC cultures are really useless. As I said, we've been doing this routine culturing technique for now almost three years.

Two months ago the University of North Carolina, Dr. Brecher's laboratory, began using it routinely. They are the second hospital to be doing it in the country.

With discussions with colleagues last night, I am aware of a couple of other blood centers in the country that are now considering doing it, all arising from situations where they had contamination cases. They had fatalities, and now they realize that it really is a problem and they need to address it.

So it is very limited in scope at the present time. In Europe I believe all of the Flemish Red Cross centers are using this technique and all of the blood centers in the Netherlands are using this technique.

CHAIRMAN NELSON: Well, perhaps sometime we are not asked to vote or render an opinion, but it seems like a useful technique that maybe should be standard practice, and the Committee is not asked to give an opinion on this today in a vote or anything like that, but maybe the FDA maybe sometime in the future might consider more formal consideration of all the pluses and minuses.

The other thing that I was quite concerned about is the false positive rate. That seems to be quite high, you know, given the -- That could present some problems, but nonetheless, it does look useful.

DR. AuBUCHON: Well, I understand .6 percent looks high. Of course, that is lower than what is usually quoted in the literature for the positivity rate in taking bug cultures from a normal person, but I can tell you, for example, right now the last time that we had a positive culture on a platelet, initial positive -- it's been over six months, because we haven't had any turnover in our technologist staff. They are all now well trained. They are all used to doing it.

So we had clusters of these positivities when we brought in new technologists into the process.

DR. KATZ: I'm very interested in hearing thoughts from the FDA about how they would approach, for example, the multiplicity of automated culture systems and the whole approach to regulation of extending to seven days, under what circumstances, what instruments.

CHAIRMAN NELSON: Dr. Vostal, you want to represent the VDA? You can be Jay Epstein.

DR. VOSTAL: Well, we are really thinking about this quite hard, and it is a difficult question. We have seen devices that have come to us and presented data that's been collected by spiking experiments *in vitro*.

We have -- It's a major step to accept that data and go and say it's okay for use in clinical situations. However, as Dr. AuBuchon pointed out, doing a clinical trial as we are used to doing would require an enormous amount of resources, because it would be a very big trial.

We are considering alternate ways of looking at this, but so far we haven't really come up with a good solution yet. But we would welcome any input and comments from manufacturers or academicians that could help us in dealing with this problem.

I mean, I think, as Jim pointed out, it's something that should be done. It looks like it's the right thing to do, and we certainly want to do that.

DR. STYLES: Just to clarify some of the data you presented, what was the n on your controlled trial of five versus seven days of platelet storage?

DR. AuBUCHON: The total n between the two centers was 24.

DR. STYLES: Twenty-four? Okay. It seems like sort of -- Something I'm always struck -- I know the difficulty of these studies is that the n's are quite small to say there is no statistical difference in that your power is extremely low. So your chance of making type 2 error is very high.

The second thing is: Do you have any information on the age of the platelets that were associated with the septic events? You seem to have a pretty good handle on the data of the patients -- of not only the reported sepsis patients but the reported fatalities.

DR. AuBUCHON: The best illustration of the effect of storage age and sepsis, I think, comes from the paper published from Johns Hopkins, Morrow the first author, JAMA from almost ten years ago now.

They noted that, although most of their platelets were transfused on Day Two or Day Three, most of their -- almost all of their septic cases came from platelets that had been stored for four or five days.

There clearly is a time period through which the bacteria have to grow up so that they can become a clinically important inoculum.

DR. STYLES: I agree with that. I mean, it makes sense that that is obviously going to be associated with it, but my understanding of the issue is that in '84 we went back to five days, because we saw an increase in infections. So in essence, we made a mistake. We went form five to seven, and then we went back to five very quickly, because we saw that that didn't make a difference.

Then now the opinions that are being put forth is, well, the platelets today are not what they were in 1984. There's been some good data demonstrating, I think, that probably the function, the viability, whether measured *in vitro* or *in vivo*, is probably better.

Outside of your culturing techniques, though, I haven't seen a lot of data which indicates that they are less likely to be infected, whether they are functional or not. I'm not sure if you are aware of any data. I don't know if the FDA has any data on maybe just surveillance of outdated units.

I'm really concerned, however, that we are just going -- while the platelets may function just as well or nearly as well, probably not as well, that they are still at the same risk of causing bacterial or are bacterially contaminated. So the very reason that we made the change hasn't really changed.

DR. AuBUCHON: I think that relates to what Dr. Simon was talking about earlier, and that is by Day Three or Day Four for the most of the organisms that are in platelets, one would expect to find somewhere between 10,000 and a million organisms per milliliter.

Now if you let the units sit for another two days, you can probably get it up to a billion organisms per milliliter. But, frankly, I wouldn't want to be transfused with a million per milliliter.

So if one extends the shelf life of

platelets from five to seven days, the effect with respect to bacterial growth doesn't really come from the additional two days from day five to day seven. It comes from the mean time for which platelet units are held.

In my experience -- I was working in a blood center when we went from five days to seven days -- the average age at transfusion increased by one day. So there is that additional day, and that day really comes in the middle of the current five-day storage period where bacteria could grow to an important inoculum.

DR. STYLES: I understand his point, but at the same time, we did this experiment. We went from five to seven days, and I wasn't around, but it was a mistake, at least by the FDA's opinion, and that we went back to a five-day period.

What data is there to support that the situation -- I understand all about the inoculation issue and the bacterial burden, but I'm just asking for some data which would indicate that the situation has changed from what it was in '84.

DR. AuBUCHON: Well, I would --

CHAIRMAN NELSON: If it is linked to a culture, a negative culture, that's a change.

DR. STYLES: Oh, I absolutely agree. There's a culturing -- I agree with your system. I think this is the way we should be going. I think this is a very important problem. Hence, my reluctance to want to go back and subject people to potentially contaminated units.

I think the culturing or some other detection system is definitely the way to go. But if FDA asks us, can we now have the platelets go from five to seven, there isn't any system in place that gives us additional monitoring.

So then you -- Well, so why do we do that? The argument that seems to be being proposed is that, well, platelets are actually better today than before. I'm just asking -- Maybe I've missed it, but where is that data?

DR. SLICHTER: Can I make a comment, because I think you have a very -- I'm glad that the Committee or at least you are of the opinion that the quality of the platelets are seven days now is probably better than it was before.

So I think we have a good quality product. But I don't think either Dr. AuBuchon or myself or probably anybody else in the room is suggesting that we just license now to go from five days to seven days, because we still have the bacterial contamination problem.

So I think what we are saying to the Committee and to you is that there are two methods that we may now be able to solve the bacterial problem. That will then allow us to extend storage to seven days, because the quality of the product will allow us to do that.

So I think we are saying that you have to combine the seven-day viability function of the platelets with either a pathogen inactivation system or a pathogen detection system, and that what I think we are trying to say is that at least -- I mean, I think Dr. Vostal asked me to present on seven-day stored platelets at the AABB, because I had been saying for years that the FDA, in my opinion, reduced the storage time of platelets form seven days back to five days not only because of the bacterial contamination problem, but because of the quality of the platelets.

As Dr. AuBuchon presented, the data that was used for seven-day licensing in terms of quality -- those are very poor quality platelets. So I think he challenged me to say, well, you know, put your money where your mouth is and get up and review the data.

Having reviewed the data and having done some studies of our own which I presented to you today, I personally am very comfortable that a seven-day stored platelet, particularly if it's stored in an additive solution, is a good quality platelet, is worthy of being licensed, but that has to be combined, in my opinion and I think in yours, with a system to ensure by either detection or inactivation that we don't have bacterial contamination, because that issue has not gone away.

DR. STYLES: I agree with you.

CHAIRMAN NELSON: And also another two days storage might improve, at least by culture, the likelihood that we would detect bacterial contamination before the platelet unit was given.

DR. SIMON: Yes. I think -- I was hoping that maybe we could make some recommendations to Dr. Vostal of how it might be proceeded. But I guess we have to say first that there are really -- in some respects, these are two separate problems, because as Dr. AuBuchon showed, the amount of bacterial contamination did not really go down, although I don't know that things were monitored that well back then.

At the same time as there was a concern

about going to seven days, it's not clear that that problem has been adequately dealt with. So one could propose that we need to proceed with some kind of either bacterial detection or bacterial inactivation, regardless of whether we go to five or seven days.

If we focus on the seven-day issue, isn't it possible in a regulatory framework for the FDA to accept company submissions for seven-day platelets based on quality and function and viability, and to allow their licensure, but only allow their use if there is a bacterial detection system put in similar to Dr. AuBuchon's or if -- Of course, if it's going to be inactivation, it would all be submitted as a package.

So if company X submitted their seven-day platelets and they looked very good, FDA, I would think, could approve conditional that anyone who wanted to use it would have to submit a protocol first showing that they had adequate bacterial detection.

That would allow places that are proceeding, as Dr. AuBuchon, Dr. Brecher and others are, to begin to go to seven days. But it would require submission of data. That seems to me to be one paradigm that might allow us to move ahead.

DR. DOPPELT: I just have one question on the culturing. I'm not familiar with exactly what physically -- how physically you do this culture, but you had some false positives.

What is the possibility that in the process of taking the cultures, you actually take a negative unit and introduce an infection?

DR. AuBUCHON: Well, any manipulation of a unit could always introduce bacteria. The manner in which we obtain the aliquot involves sterility -- a docking sterile connection device of a small transfer pack and running an aliquot out the entire unit in a unidirectional manner into that other bag, and then sealing it off.

So the only way in which the collection process could potentially contaminate the unit would be through the sterile connection deice. Now the FDA has approved the use of the SCD for splitting samples and going into platelet units.

We performed a validation study of the SCD that at that time was marked by Turumo, the SCD-312, about a decade ago, because we were surprised there was nothing in the literature on that. We cultured over 400 weld.

These welds were not conducted in standard conditions. They were conducted after painting the outside of the tube with a high concentration of bacterial suspensions and performing the welds in some cases on a wet piece of tubing, as the external portion was wet, and that's not the way one would normally conduct a weld.

Of those 447-some welds, the only ones that resulted in any contamination of the product on the inside were in those cases where the weld was obviously faulty, and there was reason to have a faulty weld because of the tubing being wet.

So when we had a good weld, which, of course, we always have to check for when we use the sterile connection device, it appears that we have a high confidence that the interior of the tubing will remain sterile.

I believe, in the cases where it looks like we contaminated the aliquot, that probably occurred at the time that the needle was being placed to recept them into that small sample bag. That's probably where we picked up the organisms.

DR. CHAMBERLAND: Jim, that was a nice presentation.

My question has to do with your comments about practicality. I wondered about the generalizability of your approach for institutions