DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

Twenty-Fourth Meeting
Volume II

Friday, August 27, 2004

8:35 a.m.

Hyatt Regency Washington
400 New Jersey Avenue, N.W.
Washington, D.C. 20001

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

Mark Brecher, M.D., Chairman
Jerry A. Holmberg, Ph.D., Executive Secretary

Larry Allen
Judy Angelbeck, Ph.D.
Celso Bianco, M.D.
Edward D. Gomperts, M.D.
Paul Haas, Ph.D.
Christopher Healey, J.D.
William A. Heaton, M.D.
Jeanne Linden, M.D.
Karen Shoos Lipton, J.D.
Lola Lopes, Ph.D.
Gargi Pahuja
John Penner, M.D.
S. Gerald Sandler, M.D.
Merlyn Sayers, M.D., Ph.D.
Mark Skinner, J.D.
John Walsh
Wing-Yen Wong, M.D.

Non-voting Government Representatives

Jay Epstein, M.D.
Harvey Klein, M.D.
James S. Bowman III, M.D.
Matthew Kuehnert, M.D.
CDR Mike Libby

C O N T E N T S

P R O C E E D I N G S

DR. BRECHER: Okay. Everybody take your seats. We're going to begin.

The committee members have in front of them the revised resolution that was put forward about rare blood disorders, and I suggest you take a minute to read that. We're going to put it up on the screen. Maybe, Mark, since it's basically a resolution, if maybe you could read it?

MR. SKINNER: Thank you, Mr. Chairman.

Based on a few comments during our brief discussion yesterday, plus comments from some of you afterwards, I've tried to anticipate and incorporate some changes. So what you have is a modified draft in a few instances. I've renamed the draft "Rare Blood Disorders" as opposed "Bleeding Disorders," and I'll read it now.

"Whereas, the HHS Advisory Committee on Blood Safety and Availability recognizes the lack of licensed treatments for individuals with rare blood disorders (for example, Factor V, Factor VII, Factor XI, Factor XIII, and Protein C deficiencies)

present a significant health risk and a discrepant therapeutic standard from that for persons with hemophilia;

"And whereas, the committee notes importation for personal use and off-label use are not adequate long-term solutions or acceptable alternatives;

"And whereas, the committee concurs that there is a need to enhance the development and licensure of treatment products for these individuals;

"And whereas, it may be appropriate to apply less stringent standards for therapies for rare blood disorders,

"The committee recommends that the Department of Health and Human Services encourage the development of products to treat individuals with rare blood disorders, including facilitating:

"1. Obtaining additional licensed indications for an already licensed product;

"2. Approval of a licensed indication in the US for European licensed products;

"3. Developing new products.

"The committee also recognizes the importance of industry and investigator collaboration with regulators both pre and post market approval in the licensure of potential new therapies.

"The committee encourages the government to invest in research to optimize treatment for rare blood disorders."

So just to call your attention to the changes, it now references "blood" as opposed to "bleeding" disorders. I added the example of Protein C deficiency. The "whereas" as it relates to the less stringent standards might provide some additional clarification, so that was suggested. The third "whereas" I was more specific in looking at products licensed elsewhere just to specifically reference Europe. I added the reference to collaboration with investigators in addition to industry. And the inclusion of regulators in the last sentence on funding had indicated that wasn't quite appropriate, so I deleted that reference

there. It wasn't meaning that they don't need money to do this. It was it just didn't fit in that sentence.

DR. BRECHER: Thank you, Mark. I realized I was a little out of order. Before we proceed, we do need to have the roll call. Jerry?

DR. HOLMBERG: Let's get back on track here before we can vote on this recommendation. Dr. Brecher?

DR. BRECHER: Present.

DR. HOLMBERG: Larry Allen?

[No response.]

DR. HOLMBERG: Judy Angelbeck?

DR. ANGELBECK: Here.

DR. HOLMBERG: Dr. Bianco?

DR. BIANCO: Yes.

DR. HOLMBERG: And I'm pleased to see that we have Gargi Pahuja present with us. Dr. Penner?

DR. PENNER: here.

DR. HOLMBERG: Dr. Sandler?

DR. SANDLER: Here.

DR. HOLMBERG: Dr. Gomperts?

[No response.]

DR. HOLMBERG: Dr. Haas?

DR. HAAS: Here.

DR. HOLMBERG: Chris Healey?

MR. HEALEY: Here.

DR. HOLMBERG: Dr. Heaton?

DR. HEATON: Here.

DR. HOLMBERG: Dr. Linden?

DR. LINDEN: Here.

DR. HOLMBERG: Dr. Sayers?

DR. SAYERS: Here.

DR. HOLMBERG: Mark Skinner?

MR. SKINNER: Here.

DR. HOLMBERG: John Walsh?

MR. WALSH: Here.

DR. HOLMBERG: Dr. Wong?

DR. WONG: Here.

DR. HOLMBERG: Karen Lipton?

MS. LIPTON: Here.

DR. HOLMBERG: Dr. Lopes?

DR. LOPES: Here.

DR. HOLMBERG: Dr. Epstein?

DR. EPSTEIN: Here.

DR. HOLMBERG: Dr. Klein?

DR. KLEIN: Here.

DR. HOLMBERG: Dr. Bowman?

DR. BOWMAN: Here.

DR. HOLMBERG: Dr. Kuehnert?

[No response.]

DR. HOLMBERG: Commander Libby?

COMMANDER LIBBY: Here.

DR. HOLMBERG: Okay. Also, just some housekeeping.

Dr. Klein, if you would like to move over here, it's up to you. I just noticed yesterday you were a little--

DR. KLEIN: I want to see.

DR. HOLMBERG: If you want to see, and I apologize for that yesterday. I meant to get over there to make this available to you. And, Dr. Heaton, if you want to--if that's going to be a problem, we probably could squeeze in over here somewhere.

DR. HEATON: I'm okay.

DR. HOLMBERG: Okay. The other thing, too, is that--and I just violated what I was going to say. We've been asked by the audio-visual staff member to be very careful with these mikes, and if you noticed, I just incorrectly handled it. Please don't handle it with the top or at the very bottom try to move it. Yesterday it was noticed that several people were moving the device at the bottom portion. This is not very secure, and down here if they fall apart, we lose the communication among the rest of the speakers. So we have to be very careful with the goose neck.

DR. BIANCO: We should ask for licensed devices on the next one.

[Laughter.]

DR. HOLMBERG: Celso, I think what we need to do is have an SOP on this and go through the appropriate training and validate that SOP.

DR. BRECHER: Thank you, Jerry.

All right. This possible resolution is open for comment. Jeanne?

DR. LINDEN: I suggest that numbers 1 and

2 be made plural so we're not talking about a single licensed product or a single licensed indication, but multiple products, multiple indications.

DR. BRECHER: We can make that change.

Dr. Sayer?

DR. SAYERS: I realize we could nitpick this to death, but paragraph 3, I think somebody yesterday didn't like "enhance," "enhancing development," and neither do I. So that could be there's a need for "development and licensure of treatment products" instead of "enhancement."

And then, 4, I'm afraid that if we say "less stringent," it implies some sort of dereliction of our duty towards ensuring high standards for patients. So maybe we could just say "to apply different standards" instead of "less stringent standards."

DR. BRECHER: We can make those changes.

Jay?

DR. EPSTEIN: Yes, on that same paragraph, I think another way of approaching that would be to

call for flexible approaches to validation. It's not the standard we're changing. The standard is in the statute, safe and effective. The product has to be safe, pure, potent, and the regulatory standard, safe and effective for a drug. So that's not what we're changing. It's a flexible approach to validation.

DR. BRECHER: I think we can make that change.

MR. SKINNER: Can I just go back to the suggested change for deleting "enhance." I think part of the reason "enhance was there is for the last sentence on funding, and maybe it doesn't fit there. But providing funding is going to enhance opportunities, I mean, I guess encourage. There's kind of an economic stimulus reference there, and "enhance" was maybe misplaced. But we do think there's a need to promote this area of science.

DR. LINDEN: I was going to suggest the word "promote" perhaps as an alternative.

MR. SKINNER: That helps. There's one other grammatical error that Karen pointed out.

There's an "s" missing on present in the first sentence--I mean "presents." It should be "presents a significant health risk in the first paragraph.

DR. BRECHER: Is that about what you wanted, Jay, in that particular sentence?

DR. EPSTEIN: I prefer the word "adopt" to "apply," but that's okay, "...may be appropriate to adopt flexible approaches."

MR. SKINNER: In the first paragraph, after end of the parentheses, it should be "presents a significant health risk." That should be plural.

DR. BRECHER: Dr. Sandler?

DR. SANDLER: The sentence, "The committee recognizes the importance of industry and investigator collaboration with regulators," isn't it more specific if we said "the importance of industry and investigator initiation of the regulatory process"? Wasn't that Jay's point? It's not their collaboration. It's their initiation. I thought that was a central point.

MR. SKINNER: That's not the point that I intended. In fact, I disagree with that point.

DR. SANDLER: Okay. I'll back away from that.

MR. SKINNER: This point really was trying to go to the importance of participation in Phase IV trials. The post-market trials are important if you're going to have lower standards or different standards. At least we tend to believe that the situation is so difficult now, the companies aren't even incented to come to them. So if we simply say if you bring it, then we will help you, it isn't going to work unless we do the other parts.

DR. BRECHER: Dr. Penner?

DR. PENNER: In the area for "encourage the development" in that paragraph, "The committee recommends...encourage." Would it be stronger to say "promote"? I don't know if this was already mentioned, "promote the development of products" rather than just "encourage." In the first sentence after HHS.

DR. LINDEN: Replace "encourage" by

"promote."

DR. BRECHER: Further suggestions? Jay?

DR. EPSTEIN: It's perhaps a very subtle point, but "collaboration with regulators post-market approval in licensure" is an awkward construct because licensure antecedes post-approval.

DR. BRECHER: I think that they are referring to post-market data from Europe.

DR. EPSTEIN: No. I thought that was speaking to post-market commitments.

MR. SKINNER: Jay is correct. The intended reference there was to Phase IV work that's going to be critical if we're going to make some of these others changes to bring the products to market.

DR. BRECHER: I see.

MR. SKINNER: And maybe we want to just reference space for--

DR. EPSTEIN: I mean, it can be fixed, instead of saying "in the licensure," say "in the validation." Then, you know, it's not limited to

the licensure process. It's calling for collaboration post-licensure. Also, if I had my way--

MR. SKINNER: Take out "licensure" and put "validation."

DR. EPSTEIN: Right. It wouldn't be the word "collaboration." Perhaps it's "cooperation."

MR. SKINNER: Okay. That word "licensure"--

DR. EPSTEIN: I suggest changing "licensure" to "validation" and "monitoring," really. Or you could say "licensure and monitoring." But the point is that it's two different things in two different stages.

MR. SKINNER: I like "licensure and monitoring."

MS. LIPTON: My only comment is to replace "collaborate" with "cooperate" makes it sound like it's a one-way thing with the industry and investigators, and I think what we're trying to signal is let's solve a common problem together, not...

DR. EPSTEIN: You don't think cooperation does that?

MS. LIPTON: I think that the way it's written, the cooperation goes just from the industry and investigator to regulators.

DR. EPSTEIN: Well, we can fix that by saying "the importance that industry, investigators, and regulators cooperate."

DR. HOLMBERG: "Collaboration" to "cooperation"?

DR. EPSTEIN: Yes, but also change the word order. "The committee also recognizes the importance for industry, investigators, and regulators to cooperate in the pre and post market approval of potential new therapies."

DR. BRECHER: I think it will be "industry, investigators, and regulators cooperation."

DR. EPSTEIN: For industry, investigators, and regulators to cooperate.

DR. BRECHER: Oh, okay.

DR. EPSTEIN: "...both pre and post market

approval of potential new therapies."

DR. BRECHER: "...for industry, investigators"--"investigators" after the word "industry." Does that leave out academic investigators?

DR. EPSTEIN: No. They're investigators.

DR. BRECHER: If we put a comma after "industry," then it's all investigators. So a comma after "industry."

DR. EPSTEIN: Take it--it says "with regulators both pre and post market..." Take out the "with regulators" now, "to cooperate both pre and post market approval," and then strike the words "in the licensure and monitoring." Strike the words "in the licensure and monitoring."

DR. BRECHER: I imagine it's just not new therapies. Sometimes it's new indications for old therapies.

DR. EPSTEIN: So it would be "potential new therapies and indications."

DR. BRECHER: Right.

DR. EPSTEIN: You need an "in" after

"cooperate."

DR. BRECHER: Further suggestions?

[No response.]

DR. BRECHER: Okay. Why don't we read this into the record before we vote on it so we know what we're voting on in the transcript. Go to the top.

"Whereas, the HHS ACBSA recognizes the lack of licensed treatments for individuals with rare disorders (e.g., Factor V, VII, XI, VIII, and Protein C deficiencies) presents a significant health risk and a discrepant therapeutic standard from that for persons with hemophilia;

"And whereas, the committee notes importation for personal use and off-label use are not adequate long-term solutions or acceptable alternatives;

"And whereas, the committee concurs that there is a need for the development and licensure of treatment products for these individuals;

"And whereas, it may be appropriate to adopt flexible approaches to validating therapies

for rare blood disorders"--

DR. LINDEN: Excuse me. We're going to put the word "promote" in there?

DR. BRECHER: The "promote" is in the next sentence.

DR. LINDEN: Oh, okay. I apologize.

DR. BRECHER: "The committee recommends that DHHS promote the development of products to treat individuals with rare blood disorders, including facilitating, one, obtaining additional licensed indications for already licensed products; two, approval of licensed indications in the U.S. for European licensed products; three, developing new products.

"The committee also recognizes the importance for industry, investigators, and regulators to cooperate in both pre and post market approval of potential new therapies and indications.

"The committee encourages the government to invest in research to optimize treatment for rare blood disorders."

Mark?

MR. SKINNER: There were two comments. First of all, when you were reading your example list, and it may just be the Roman numerals, but you said Factor VIII and it's Factor XIII, and I think that's important.

DR. BRECHER: I'm Roman numeral challenged.

[Laughter.]

MR. SKINNER: I am, too. But I thought it was important, since we're reading it into the record.

The other one is in the second "whereas," "And whereas, the committee concurs that there is a need for the development," I thought we were going to change that "need" to "promote the development and licensure of..." And I think maybe that was the comment Jeanne was going to make.

DR. LINDEN: Yes, we were going to put "to promote" because it said "enhance" before, and we were changing "enhance" to "promote." Because the other one said "encourage," and we changed

"encourage" to "promote," which is really a trivial semantic change. We weren't just taking out "enhance." We were changing it to "promote."

DR. BRECHER: Yes, you're correct, Jeanne.

On the first sentence, do we want to end with "for persons with hemophilia"? It seems like we're just talking about blood disorders, and I can imagine that there are some other blood deficiencies that may not be classified as a hemophilia--

MR. SKINNER: You mean that the standard is--yes, I was comparing the standard, and maybe that was because the original reference was bleeding disorders. So I was comparing these bleeding disorders to hemophilia, which is a bleeding disorder. Now maybe we need to compare blood disorders to other blood disorders. So if there's another reference--you could just say it generically then.

DR. BRECHER: Yes, I would just use blood disorders rather than hemophilia.

DR. EPSTEIN: It should say then "some

other blood disorders." "...a discrepant therapeutic standard from that for persons with some other blood disorders."

DR. BIANCO: "...such as hemophilia."

MR. SKINNER: That would work, "...some other blood disorders such as hemophilia."

MR. HEALEY: Mark, I had a comment. Just in line with the comments that I made yesterday, I wonder if where there are the iterated points 1, 2, and 3, whether it makes sense to add a fourth, something to the extent of "assuring adequate reimbursement for these"--you know, "for the development of such therapies," so that companies have an incentive to explore bringing them to market.

Again, I think the reimbursement piece is missing here. Maybe that's by design, but it's worth noting.

MR. SKINNER: How about we put that in the last--when we're talking about funding the research, and then also funding the use--I mean, funding--paying for the treatment once they're

approved. "...encourage the government to invest in research and to reimburse"--

DR. EPSTEIN: Well, "and to ensure adequate reimbursement for a novel therapy."

MR. SKINNER: "...support adequate reimbursement."

DR. BRECHER: Okay. Can we go up to the first sentence? I'd like to look at that one again for a second.

It just seems a little awkward to end that sentence, "for persons with some other blood disorders such as hemophilia." I think it just--"persons with blood disorders," "with rare blood disorders."

MR. SKINNER: Then it really becomes redundant.

DR. BRECHER: Oh, okay.

MR. SKINNER: All of these are rare blood disorders. What we're talking about is very rare versus rare, but we don't have a legal definition for "very rare."

DR. BRECHER: Okay. Right, there's rare

and there's very rare--as opposed to well done, yes.

DR. EPSTEIN: Can we look at the last sentence again to just see what you wrote?

[Pause.]

DR. BRECHER: Jay?

DR. EPSTEIN: This is unbelievably minor, but we say "HHS" and we say "DHHS." I'm never sure which we prefer, incidentally.

DR. BRECHER: I think next year it may be different, anyway.

DR. HOLMBERG: I think "DHHS" would be best. Very often it's dropped, the "D" is dropped because of the confusion with Homeland Security.

DR. BRECHER: Matt?

DR. KUEHNERT: Under the category of very minor points, I think it should be "long-term solutions," not "long terms."

DR. BRECHER: Dr. Sandler?

DR. SANDLER: Same category, it's August 27th today when we're doing it.

DR. BRECHER: A stickler for details.

[Laughter.]

DR. BRECHER: All right. Let's take a vote. All in favor, please indicate by raising your hands.

[A show of hands.]

DR. BRECHER: All opposed?

[No response.]

DR. BRECHER: No opposition. It carries unanimously. Oh, and one abstention. I'm sorry.

All right. It is now almost 9 o'clock. What I would like to do now is move on to the regular schedule. I know there are additional resolutions to be made, but we'll come back to that later in the day. So we're now going to move into the section on hepatitis B and the--no, I'm sorry. We're going to move into bacterial contamination of platelet products. The first speaker is Jaro Vostal talking on the FDA's current thinking on future bacterial detection field study design.

I just want to remind speakers that we need to adhere to the time given.

DR. HOLMBERG: I would just also recognize

for the record that we had two people join us during that discussion, and since I did the roll call, one voting member, Larry Allen, and non-voting, Dr. Kuehnert.

DR. VOSTAL: Good morning, and thank you very much for this opportunity to present some of the FDA's current thinking on bacterial detection in platelets and platelet products.

I'd like to start off with just going over where the current status of bacterial detection in platelet products is, and currently there are two culture-based automatic bacterial detection systems cleared by the FDA for quality control testing. There's also in place the AABB Standard 5.1.5.1, which requires bacterial detection on every platelet unit, which essentially amounts to 100-percent quality control.

The culture-based automatic bacterial detection system's use is limited to the apheresis products, and whole blood platelets are being tested for pH and glucose levels by a dipstick. So whole blood platelets are being tested by surrogate

markers of bacterial detection.

FDA has a number of concerns with this approach. First of all, the test performance characteristics of these devices as applied to bacterial detection are unknown. The use of non-validated tests, specifically the glucose and pH measurements by dipstick and methods such as swirling estimations, have not been validated. There is non-standardized methodology being applied even with the culture-based devices across the country, so it's not clear if results in one end of the country would be comparable to results in the other end.

There is potential for excessive false positives because some of these surrogate tests produce a number of false positives due to their low sensitivity.

Less reliable methods are used on whole blood derived platelets created a two-tiered safety system for apheresis and whole blood derived platelets, and this is one of our major concerns because this approach will tend to drive whole

blood derived platelets from clinical use.

So we have several desired improvements to the current state of bacterial detection and storage. First of all, we'd like to see standardized methodology for automatic culture systems, and this would apply to timing of the sample collection, the volume of the sample that's collected, and the duration of the culture that the samples are kept.

We would also like to see application of automatic culture systems to whole blood derived platelets, and this would eliminate the use of non-validated methods for these products. And a way to get there would be to institute pre-storage pooling of platelets or bacterial testing sample pooling. So the application of the culture-based methods to whole blood derived platelets would be more cost-effective.

And, finally, we'd like to see a validation of the automatic culture system for a release test claim.

Another major improvement that we'd like

to see would be an extension of platelet dating from five days to seven days. As you already know, platelet storage was reduced from seven to five days back in 1986 by FDA on the advice of the Blood Products Advisory Committee, and this was done over concerns of increased bacterial contamination at the day seven storage. Return to seven-day storage will require that:

One, platelet storage containers are validated to preserve platelet efficacy out to seven days based on current standards, and the good news in this area is that there are two bags already cleared.

And the other point that has to be met is that bacterial detection method is validated as a release test for seven-day platelets.

Now, a release test has several criteria that we'd like to see demonstrated for these types of devices. First of all, we would like to see sensitivity, and this means a demonstration of the accuracy of the device in detection of contaminated units, then would be specificity, and that is, the

accuracy and detection of non-contaminated units. Next would be the positive predictive value of these tests, and this means how many units with a positive test, positive test results are actually contaminated with a bacteria. And then, finally, what is really useful for clinical application is the negative predictive value of these tests. This answers how many units with a negative test result are actually free of bacteria.

So I'm going to go over ways that we evaluate bacterial detection devices, and we look at two major areas. The first would be performance of the device in analytical testing, and then performance of the device in field studies where it's applied under actual clinical use.

In analytic testing of the bacterial detection devices, we use an artificial system where we look at the sensitivity in detecting a certain level of contamination in intentionally contaminated units. These are referred to as spiking studies. Units of platelets are actually spiked with certain levels of bacteria, either one

colony forming units per mL, 10, or 100 colony forming units per mL. These type of studies define the optimum volume for detection. That's the sample volume for the culture-based devices. They also define optimal medium conditions for detection of bacteria in these products. For example, this could be leukoreduced or non-leukoreduced.

This is a schematic of what these types of designed like. Here you can see--this would be the storage of the products out to five days. You would spike in a certain load early on, and then take a sample, either at day one, day two, and determine through the sampling whether your device was able to detect the inoculated contamination. So it's a relatively straightforward experiment.

Now, when we move towards looking at field studies and designing field studies, things get a little more complicated, and that's because the level of contamination at the time of collection is unknown. In our analytical studies, we're spiking one or 10 CFUs per mL, but it's really known whether this reflects the actual situation and

whether the contamination could be a lot lower than what we're using in these artificial systems.

The level of contamination changes as bacteria proliferate. This is one of the unique features of bacterial contamination of platelet products since they're stored at room temperature. The contamination will start off very low at donation, then proliferate to very high levels within three to four days.

Now, the rate of growth can differ for some slow-growing organisms. One example is Staph epidermidis. Certain organisms grow very fast, peak in a day or two. Some take three, four, five days to peak.

Timing of sampling can significantly affect the success in detecting the contaminated units. If you sample too early and there may not be enough bacteria to detect, you will get--you will miss the window where the device is sensitive enough to detect contaminated units. And, also, the volume of sampling will affect sensitivity, and this is relevant mostly when you have strategies

when you pool samples of multiple products together. So a number of these things have to be considered when designing these types of field trials.

I'd like to share with you a published study that was done by Dr. C.K. Lee of the Hong Kong Red Cross, and this was published in 2003 in Transfusion, and the title is "Estimation of bacterial risk in extending the shelf life of platelet concentrates from 5 to 7 days."

This is a study where they looked at the efficacy of the BacT/Alert device to detect contaminated units, and they started out with 6,000 platelet units, and they sampled them on day two of storage. Now, they had a unique sampling system where they pooled the samples, and they collected 1.5 mL from five units and pooled those together to put into the device. Then they stored these units out to either five days or seven days.

At the end of these days, they took a second culture. This time it was 7 mL. They tested it with the BacT/Alert culture device, and

this second culture was to confirm the results they got on these first cultures.

Now, I also forgot to mention that any positive units that were detected over here were discarded from the studies, so that only unit that were found to be negative with this reading moved on to the second stage.

So looking at the results of the second-day culture, they found that at five days there were four units contaminated; three of these were P. acnes, one was a coagulase negative Staph. On day seven, they had similar results. They had four units contaminated, two with P. acnes and two with coagulase negative Staph. So the total residual risk, if you include all bacterial contaminants, was four out of 3,000 for both five and seven day.

Now, people have argued that P. acnes is not a clinically relevant bacteria, so if you just look at Staph contamination, the risk at day five is one per 3,000, and at day seven it's 2 per 3,000.

Now, if you compare this to day two cultures, they detected over 120--in their continuous monitoring of the platelet products, their contamination rate is one in 2,800. So this study, although it's relatively small, demonstrates that the application of a device--and this is a good detection device. But the way it's applied can lead to missed contaminated units.

So these are some of the lessons from the study by C.K. Lee that I just described to you. I would say the first important lesson is that these type of field studies are feasible, and this demonstrates that, you know, studies such as this can be done.

In addition, it demonstrates how a field study identifies a weak spot in the bacterial testing process. Now, it's the process really that we're testing in the field study. It's not necessarily the device itself. The device itself can be tested by analytical testing, but the process as it's applied to clinical products will not be tested unless there is a field study similar

to this one performed.

The study also demonstrates that a second culture, either at day five or day seven, is necessary to confirm the early culture. So the only way to confirm whether you got an accurate reading early on is to have some kind of a standard method. And since the bacteria grow up to a higher level by day five and day seven and it's easier to detect their contamination, the second culture is considered to be the standard.

As this study demonstrates, sample pooling can decrease sensitivity of the early culture, and, again, a relatively small study will detect only a few contaminated units. Therefore, if you really want to know what the true residual risk is, it will have to be a larger study than this done by Dr. Lee.

So FDA has requested this type of study to be done on the bacterial detection devices, and we proposed our original study design back in December 2002 at the Blood Products Advisory Committee. Now, the design of the study has several key

features. We wanted to compare the bacterial contamination rates on day one and day five to validate the day one test, similar to what was done in the previous study. We would then take an additional culture on day seven to support the extension of dating, set criteria for an acceptance difference between day five and day seven contamination rates to permit extension of dating. So we would decide on what would be acceptable rates at day five and day seven, and based on that, we will be able to prove the concept of seven-day storage. And the study size depended on a goal to establish a minimum of 80-percent sensitivity of the day one culture.

So this was the study that we proposed. Initially, it was approved by the Blood Products Advisory Committee or endorsed by the committee. However, in the two years since, we have not had any manufacturers step forward and perform a study such as this. We've gotten several--a lot of feedback in terms of the design of the study and the potential cost of these studies. So we've been

working hard to modify this.

This slide shows you a schematic of what we proposed in 2002. So we proposed that we were going to use outdated units. We would sample them early on, as was done in the other study, store them out to day five, and if they were not used by day five, we would keep them up to day seven, the outdated units, and test them again to compare the results of the three cultures.

As I mentioned already, we've been working hard to try to modify this study design so it would be more streamlined and more cost-effective. And the major change that we've done is develop a new endpoint. The new endpoint will estimate the residual bacterial risk for a seven-day-old platelet unit tested for bacteria on day one. So if you have a negative reading on day one, we'd like to know what the residual risk is by day seven.

We would be willing to approve a seven-day platelet storage if the bacterial risk at day seven is lower than the current bacterial risk of

untested platelet products. So we would be looking at what the current risk is without application of testing and what will be the risk of the seven-day-old platelet that has been tested by a detection device.

Now, the current estimation risk is estimated to be somewhere between one per 2,000 units to one per 4,000 units contaminated with a bacteria. So the goal of the study would be to demonstrate a point estimate of risk at day seven to be one per 10,000 units, with a 95-percent upper confidence limits that the risk is less than one per 5,000. And applying statistics to this goal, the study size would be approximately 50,000 platelet units.

So the study schematic would look something like this. To limit the cost of the study, we've decided that it would be appropriate to use off-line units, and that means units that are produced specifically for the study. This would be whole blood derived platelets, so that it will be less expensive than buying apheresis

products for the study. And the design would be similar to what was done in Hong Kong. They would be sampled early on and stored, day one or day two. They would then be retested again at day seven, and there would be a comparison of the results to see what the residual risk is, remains at day seven.

Now, here are several cost-saving advantages of the new study design. First of all, we've eliminated one of the cultures at day five, which would limit the cost of supplying those bottles for the study. Our next step would be that day seven samples could be pooled to limit the number of bottles that would have to be used to validate the day one culture.

Now, we think that day seven pooling would be appropriate because the bacterial load by day seven is high, so dilution that would come through the pooling process would not decrease the sensitivity. And these loads can be quite high, 10^{10} or higher CFUs per mL of bacteria. So even pooling ten samples into one bottle could reduce the total number of bottles to approximately 5,000,

which we think would be a significant cost-saving step.

As I already mentioned, we've agreed that whole blood derived platelets would be tested. Units will be produced specifically for this study as a byproduct of the whole blood collection, so they won't have to be purchased specifically for this study. And we've agreed that the data obtained on whole blood derived platelets could be extrapolated to apheresis platelets. And we've also taken out pre-storage pooling away from the study to be done--to be validated separately.

So we feel that these changes have simplified the study, have made it more efficient and more cost-effective, so it could be done a lot easier.

Now, besides modifying the field study that we like to see for validation of a release test, we've also been working on applying bacterial testing to whole blood derived platelets. Whole blood derived platelets are slightly different than single apheresis units. The final transfusion

product is actually a pool of four to six units collected from individual donors. The pooling step is made up to four hours prior to transfusion. So once you make the pool, you only have four hours before you can transfuse it--you have only four hours to transfuse it.

Pooling at the beginning of storage for five days has not been cleared due to concerns over bacteria proliferation in the pool to higher levels than in individual units. This has been our thinking in the past. However, we've reconsidered, and we've looked at the risk of pre-storage pooled platelets and single-unit platelets that have been contaminated with bacteria and made a determination that the risk would be equivalent.

The additional step that needs to be taken into account before pre-storage pooling can be applied is that there are no FDA-cleared storage containers for storing platelet pools out to five days or longer.

This is a schematic of how whole blood derived platelets are handled. Currently you have

individual units that are stored separately, and they have to be tested individually for bacterial contamination and then pooled right before transfusion. Therefore, it's not cost-effective since if you apply the culture-based devices to these products, you have to utilize five in this schematic to determine whether this pool is free of bacteria.

So the other way of doing it would be to pool these before you store, sample the pool, and then wait to see if your pool is negative, and then you can transfuse that.

So there are two approaches to testing whole blood derives platelets, and that's either pre-storage pooling or sample pooling, as we saw was done in that previous study. So the pool of whole blood derived platelets could most economically be tested by either a single test of the pool early in storage or a single test on a pooled sample prepared from the individual unpooled units.

This is a schematic of the analytical type

testing that would be done to demonstrate that the bacteria are--that the bacterial detection devices are sensitive enough to detect either a contaminated pool or the pool of samples taken from individual units. So in this case you have five units. One of these would be contaminated with a certain level of bacteria. There is then a dilution factor because you're pooling several different units, and that dilution factor decreases the sensitivity of most of the devices. So that's why analytical testing would be appropriate for defining how many pools can be made and what volume should be taken from these pools.

So for pre-storage pooling, bacterial detection devices applied to pools will need to be validated by analytical testing to demonstrate sufficient sensitivity to account for the dilution of the bacterial inoculum by the pooling process, and this could be done in pre-storage pooled or pooled samples.

FDA has taken the position that pre-storage pooling systems should not be cleared

unless linked to the use of validated bacterial detection release test. This was our thinking in the past. Based on data that was published that contamination of pools grows up to a higher level of bacteria, bacterial load, we wanted to see a release test in place before those products were used. However, as I mentioned, we reconsidered our thinking in this respect in terms of the clinical risk, and we've come up with a new FDA current thinking, and that is, such systems can be cleared if culture monitoring and quality control is performed by tests with analytical sensitivity similar to that cleared for single units. So this is actually a major step for us, and I think it eliminated a big hurdle for applying the culture-based bacterial detection systems to whole blood derived platelets.

Now, the other step to pre-storage pooling is the approval of a pre-storage--well, approval of pre-storage pooling will require validation of a platelet storage container to preserve platelet efficacy in a pool for five days or longer. And

this validation approach was discussed by us in the March 2003 BPAC, and basically the testing of platelet efficacy by following corrected count increments in thrombocytopenic patients. So we would like to see that the platelet quality is preserved in a pooled state out to five days or seven days, and the way we think this can be done is by following a corrected count increments, or CCIs, in a clinical trial with thrombocytopenic patients. And this trial would compare the pre-storage pooled platelets to post-storage pooled platelets, and approximately 50 patients per arm would be required.

So this was the study that we proposed in March 2003, and it was endorsed by the Blood Products Advisory Committee. So we are in discussion with companies about the appropriate designs of these studies, but so far no products have been approved for this purpose.

So, to summarize where our progress is towards having a validated bacterial detection release test and pre-storage pooling, first of all,

FDA and AABB have been working on a joint protocol to develop the validation of bacterial detection devices as a release test. So the study I described to you was a result of work between FDA and the AABB, and we think that we've actually reached a happy medium, and we're hoping that this study will be able to move forward.

The modified field study design has been set up to reduce the cost of the study, and we hope that that will also remove some of the major hurdles.

In terms of pre-storage pooling, we have been able to clarify the bacterial testing requirements for pre-storage pools, and this will now be based on analytical testing. And we've outlined the studies necessary for clearance of pre-storage pooled containers.

So thank you very much.

DR. BRECHER: Jay?

DR. EPSTEIN: Thank you very much, Jaro. Just one small added point. Another issue in defraying cost is whether non-leukocyte-reduced

units can be used in the off-line study, and it has been suggested that a small pilot experiment to establish the sensitivity of the method on a non-leukocyte-reduced unit can be done, permitting use of non-leukocyte-reduced units.

DR. BRECHER: Merlyn?

DR. SAYERS: Thanks. This dealt with whole blood derived platelets, and one of the things that is different now and certainly different when reviewing the Hong Kong study is that whole blood collection systems now include a diversion pouch so that the first 60 or so mL, which theoretically contain skin contaminants, is collected and doesn't end up contaminating the whole blood derived platelets. So I'm wondering how that consideration influences some of those figures that you gave for predicted risk of bacterial contamination of the platelet product.

DR. VOSTAL: You mean in terms of the study size?

DR. SAYERS: Well, you're giving--I think your risk predictions there were one in 2,000 to

one in 4,000.

DR. VOSTAL: Right.

DR. SAYERS: And I think those figures referred to whole blood derived platelets collected before the diversion pouch system was introduced.

DR. VOSTAL: Right. I think the advantage of the modified study design is that we're going to be looking--the endpoint will be the upper confidence limit of less than one per 5,000 units contaminated, 95-percent upper confidence limit. And that will limit the size of the study no matter what the initial contamination rate is.

DR. BRECHER: Jay?

DR. EPSTEIN: In other words, Merlyn, it ceases to matter what the current contamination rate is, as long as the rate at seven days is less than one per 5,000, 95-percent confidence limit. That's the beauty of the new endpoint.

DR. BRECHER: Matt?

DR. KUEHNERT: What if the initial rate is one in 10,000? Then there's no way--or you don't have a risk reduction.

DR. EPSTEIN: Well, there are two ways to look at that. One is that we're meeting a current acceptance standard because, after all, a product is still suitable if there's no diversion pouch and no day one culture. So what we're saying is that as long as the day seven product meets the current standard, it's an acceptable product.

DR. KUEHNERT: So this doesn't set any parameters for risk reduction. It just sets an absolute frequency for acceptability.

DR. EPSTEIN: That is correct. But, again, the real-world perspective is that the best current rate reported is one in 4,000. So we do think that it also represents risk reduction. But, again, mind you, what we're trying to do is control the risk of extended storage on the belief that there are some organisms that will grow out later than the day one sample. So what we're trying to show is that we have controlled that risk at day seven.

I'm simply restating your point. What we're doing is establishing a standard for the

upper level of risk at day seven.

DR. BRECHER: Jerry?

DR. HOLMBERG: Just a point of clarification. In your whole blood derived platelets study design, if you had an investigator go through and do a pooling sample study, then there would be no problem with pooling--I mean culturing and then pooling at five days. You couldn't--the rule would stay in effect as far as four hours. The four hours for pooling?

DR. VOSTAL: No. We're trying to extend--we're trying to pool the products at the beginning of storage, so you would collect individual units, you would probably wait 24 hours to get all the other testing done. But you would pool them together at that time and then be able to store them together out to five days or seven days, whatever validation you have.

DR. HOLMBERG: Okay, because I'm looking at this a little bit differently. I'm looking at--there's an advantage to pooling the sample and still not having to do the clinical part of that.

DR. VOSTAL: Oh, I see what you're getting at. Yes, you could--you can actually do sample pooling up front, and that way you wouldn't have to have an approved container to store the pooled product. You could actually sample individual units, combine samples from individual units, determine if they're negative, and then still storm them as individual units and pool them four hours before transfusion.

DR. HOLMBERG: But if the manufacturer wants to get seven days pre-storage pooling, they would have to be able to do the clinical study on an approved bag.

DR. VOSTAL: Right. Now we're talking five days. We still don't have a bag that's approved for five days pooled platelet product.

DR. HOLMBERG: Okay.

DR. BRECHER: John?

DR. PENNER: I have a concern about the in vivo platelet recovery. If the patients selected who have thrombocytopenia are the autoimmune type, frequently platelet counts will not increase after

the administration, even if checked in an hour. If it's a patient who's had a lot of chemotherapy and has thrombocytopenia based on that, those patients often have had a lot of blood products, oftentimes may have HLA antibodies. So I think one has to be very careful in selecting those thrombocytopenic patients to be able to demonstrate that you're getting a consistent elevation in the platelets, which would be one issue. And then, of course, the second issue which we don't address on this is the efficacy of the platelets in controlling bleeding. In other words, if these are bunch of ghost platelets rolling around, the numbers look good, but the patient bleeds to death.

So you still have to have some element there to test that. Bleeding times are really not very accurate, but I think one is having to deal with that.

DR. VOSTAL: Right. I think in terms of your first question, these are difficult studies to design because the patients are non-uniform, as would be healthy donors. There are different ways

of designing those studies. We propose that there be 50 patients per arm. Hopefully that would even out the differences between the two arms. Dr. Heddle is going to talk about a slightly different approach today where you test the different products in the single patient. So you can try to limit some of the variability that way.

If you have alloimmunized patients who clear their platelets, I think they should not be entered into the study because you would not be able to evaluate the platelet product itself.

In terms of bleeding, CCI studies are actually a surrogate for platelet efficacy. Our concern about the platelets working is not that great in this situation because there is a long history of pre-storage pooling in Europe, and they haven't had much of a problem with bleeding, or actually no problem with bleeding as far as I'm aware. So we're confident enough that if you can demonstrate that platelets circulate in the transfused patients that they will actually work to stop bleeding.

DR. BRECHER: Jay?

DR. EPSTEIN: Studies in non-thrombocytopenic patients are also achievable but with a caveat. It would not be ethical to give a pooled product to a normal healthy individual because you will alloimmunize them. On the other hand, there may be some individuals, such as those with a terminal disease, who might consent to such a study, knowing that they will become alloimmunized.

DR. PENNER: Would you add any platelet function studies, in vitro studies, to at least indicate the functional capability of these?

DR. VOSTAL: Yes, actually, the platelets are tested by a battery of function studies before they go into the clinical study. So we do have a high level of assurance that they will work.

DR. BRECHER: Celso?

DR. BIANCO: I just want to wrap some thoughts. I'm very happy to see the change and the simplification of everything. I just want to remind everybody that when we came up with an HIV

test, nobody asked how many cases of HIV the test was going to be able to prevent. What we wanted was to go and do the test. And then a lot of studies and all that came out with the answer.

I think that in a similar way there are 100 years of history of cultures. We know that we shouldn't transfuse units that are culture-positive, so I think that a lot of these--the simplification is great, but a lot of these studies can be left until later, and we should have a material test for release.

DR. BRECHER: Jay, and then Andy.

DR. EPSTEIN: Celso, unfortunately your statement is untrue. For the HIV test, we did require field trials before approval, and the yield, as it were, of screening was reported in the package inserts, along with the positive predictive value of screening. So it's simply not true that that was not part of the approval process.

DR. BRECHER: Andy?

DR. HEATON: I'm very pleased to see the progress in the evolution of the trial design

standards. What I observed from your presentation is that the gold standard is that the new system should be better than, i.e., a unit tested on day one should have less risk on day seven than the current unscreened platelet products. In the past, the agency has talked about a positive predictive index or positive predictive value. Do you still have any secondary standards that might be applicable in terms of a positive predictive index by organism? Or have you completely discontinued that standard?

DR. VOSTAL: I think actually what I presented is the approach that we want to take, and we don't have any additional secondary standards at this time.

DR. HEATON: Excellent. Thank you.

DR. EPSTEIN: We're not proposing a standard for the positive predictive value, only that it should be part of product labeling. And the method for determining it is that there is a follow-up culture to confirm a screened culture result. In other words, you revalidate every

positive culture, and then the yield at day seven is the thing that determines the validity at day one. But the culture at day one is also confirmed by both isolating an organism and re-culturing the unit from a retention sample. So we do determine true positivity.

DR. HEATON: The reason I asked the question is those of us that are involved with developing nucleic acid testing rather than the culture testing, which the current standard appears to be very focused on, might not necessarily want to do cultures on every day seven sample. We might wish to use culture on day one as the reference standard and then use a new assay-based bacterial detection at the end of the storage period rather than having to culture every single unit. That's very expensive to do that and very burdensome.

DR. BRECHER: In the interest of time, I think we're going to have to move on. I just want to make one comment, and I have a conflict of interest. I have to say that I receive research funding or consulting from virtually every company

that's interested in this.

That said, I think that for the committee members I just wanted to bring to their attention, there is a paper from the recent Transfusion looking at culturing of pooled random platelets. It's inadvertently placed with the hepatitis articles. So if you look for it, it's with nine organisms looking at pools of six, cultured at--that were inoculated to roughly five CFUs per mL, which showed very good sensitivity with the BacT/Alert system.

Also, in addition to the Hong Kong study, it's probably worth mentioning that there are a couple other studies that have been published, one from my lab that looked at 2,400 apheresis platelets which were tested early and then at time of issue or outdate, plus two days if they outdated, where we did not find any units that were not detected by the early culture. And there's a similar study from Ireland where they looked at 500 outdated apheresis platelets that were pre-screened with an early culture and did not find any that

were missed early on.

DR. HOLMBERG: That article was inadvertently placed on the last tab. It's the second article.

DR. BRECHER: I guess I should also say that spiking studies where a single unit is spiked rather than the pool will be started in a few weeks in both my lab and another lab. So we're going to move forward with the pre-pooling.

Okay. I'd like to move to our second speaker, which is Steve Kleinman, talking about the AABB Task Force on Detection of Bacterial Contamination of Platelet Products.

DR. KLEINMAN: Good morning, and thanks for the opportunity to present to the committee. Some of what I say will, I think, be a little bit repetitive from what you just heard, and I would like to preface my remarks by saying that I think that our task force, which has interacted with FDA, has helped FDA to get some new input and to evolve their ideas. And, in general, I think we're in alignment, that we are making progress in getting

better protocols by which to move some of these new products forward.

This task force, Interagency Task Force on Bacterial Contamination of Platelets, was established shortly after the bacterial detection standard took effect in March 2004. And there are a number of purposes of the task force. A primary purpose is to provide a forum for discussion between the transfusion medicine community that represents both the large transfusion services and blood centers, subject matter experts, that is, those people who have done a lot of research in bacterial contamination of platelets, and PHS agencies--FDA, CDC, Jerry as a member of this committee, and the NHLBI--on some specific safety and availability issues. And we've had good participation by FDA, by HHS, by blood center representatives of the three major organizations--Red Cross and ABC and--two major organizations, and AABB, transfusion services. And so I think we're successful in bringing the right group of people together.

Another purpose of the task force is to interact with test manufacturers as appropriate, and in our one-day, full-day meeting that the task force has had, there were invitations to known test manufacturers to attended, and many of them did attend to hear that discussion.

We have some other purposes. We also have a primary purpose to the AABB membership, and that's to provide guidance on a number of issues that have arisen since bacterial contamination testing has begun. So issues to be addressed include how do we get standardized definitions of test results, how to follow up initially positive tests, the need to identify the organism, what to do if a positive platelet unit has been transfused, that is, it's negative to date on the culture, it's transfused, and then the culture grows out afterwards; notification and possible deferral of the donor, and possible interaction with public health departments if rare organisms are found.

All of these items are the subject of work on a new guidance or maybe two guidance documents

that will be issued by AABB to membership, hopefully within the next four to six weeks.

Now, another goal of the task force is to get a better handle on what's actually happening throughout the country with regard to methods--number one, with regard to methods of detection that are being used; number two, with regard to the results that people are obtaining; and, number three, with regard to impact of bacterial contamination testing on platelet transfusion practice, meaning outdating, switch from one type of product to another, inventory levels, et cetera. And as I think members of this committee are aware, there was a survey sent out by AABB to all of its members right after the initiation of the standard, and the results of that survey were reported to the committee in April, at the April meeting.

Since then, we have been spending the last couple of months redesigning that survey to send it out again. The first survey obtained useful information. We're trying to make the second

survey a bit more extensive so that some of the questions that have arisen since the first survey can be answered.

We had hoped to get that survey out and back and analyzed prior to this meeting to be able to present to the committee. However, it has turned out to be a more complex task than--well, actually, we probably should have realized it was a very complex task to begin with, and so that time line turns out to not have been realistic. But, again, the goal is to have--the survey is almost finalized now in terms of many people, 10 or 15 people, thinking that we have the right questions on the survey. And we hope to have that finished and sent out again by the middle of September and then accumulate the data as to all of these issues and have that ready for presentation sometime subsequent to that.

Now, I want to just summarize a few facts about what we do know. Current platelet usage--and when I say "current," this is the last available data, which I think is now probably about four

years old--is that in the U.S. we're using--we're transfusing three million whole blood derived platelets, and they're generally transfused in pools of six, leading to 500,000 therapeutic doses from whole blood derived platelets. In contrast, we use about one million apheresis platelets, so one million therapeutic doses of apheresis platelets.

Now, that doesn't mean necessarily one million apheresis collections because we know it's very common practice now for an apheresis unit to be collected in large quantities so that it can be split and used--so-called split product, and used for two patients, sometimes even three patients. So there are a couple of ways to look at this; that is that--two ways to look at this. While two-thirds of the therapeutic doses are apheresis platelets, however only one-quarter of the collections are apheresis platelets, and probably less than that because we probably do less than one million collections and we do three million whole blood derived platelets.

So depending on how you look at that, when you assess the proportions of where bacterial contamination is coming from, that's an important issue.

We believe that the trend over the last several years, certainly prior to the survey that found one million apheresis platelets, if we go back to several years before that, the use of apheresis platelets was not that great. And so we believe that, historically, there has been a trend for the increasing use of apheresis, and anecdotally we think that trend has continued from the last time information was gathered until now.

However, it's important to point out that there is substantial regional variation in which platelet product is used, and so we know there regions of the country or regions supplied by specific blood centers that use almost 100-percent apheresis donors. On the other hand, there are still regions of the country that use almost 100-percent whole blood-derived platelets. So it's certainly not easy to standardize and say that one

type of platelet will be used or that the system could be moved in specific localities from one product to another, at least in the short term.

And so it's important then to have adequate systems in place for detecting bacterial contamination in both whole blood-derived and apheresis platelets, and it's also important to assure availability of both types of product.

So what impact has bacterial detection testing had on platelet availability? So we had that survey from 2004, which suggested that no severe shortages had been created by introducing bacterial detection testing. However, we think that at least some of the respondents indicated that there was some impact on availability, either with increasing outdating or with less platelet product left in inventory, and I'm sure people on this Committee remember how difficult it is to actually obtain that information. So not a major impact upon availability, in terms of shortages, but yet availability probably has gotten tighter because of this.

So we still think we need solutions to increase availability, and you've heard about two of them so far. One is the licensure of prepooled, whole blood-derived platelets for five-day storage, and the second is the extension of shelf life of apheresis platelets to seven days.

And I want to just address these two issues in specifics now. So, first, is the need for five-day storage of whole blood-derived, prepooled platelets. And on this, I echo what Jaro has just said. According to the April 2004 AABB survey, the primary methods used for bacterial detection of whole blood-derived platelets are pH and glucose. It's quite clear--it was known before, and it's certainly being substantiated now--that these surrogate tests have poor sensitivity and poor specificity for detecting bacterial contamination.

And so, in addition to wanting a five-day product in order to potentially have an impact on availability of prepooled product, more importantly, in this instance, we need that product

so that we can increase the safety of whole blood-derived platelets by using the same kinds of bacterial detection methods that we use on apheresis platelets.

Secondly, as was mentioned, these tests are not standardized. Each institution is determining its own assay cutoff based on its own validation studies. Obviously, these are off-label uses for the devices, so they clearly don't have any validation for these uses unless the user provides that validation.

Well, so how about culture-based testing of whole blood-derived platelets? It's generally not being performed in the U.S., and that's for several reasons:

Number one is the QC culture-based tests that are approved require the use of leukoreduced platelets. And in general, as far as I know, whole blood-derived platelets are not routinely leukoreduced in this country because that increases their cost dramatically.

Secondly, the volume required to set up

the cultures is small, but it's significant when you're taking it out of each platelet unit. And so if you have to take 4 mLs out of a 40- to 50-mL unit to set up a culture, you've presumably just reduced your therapeutic efficacy by 10 percent. You've removed 10 percent of your product.

And then, obviously, as was just mentioned, you'd have to culture, under current schema, each concentrate individually. So you'd be doing 4 to 6 times as many tests as you would with a pool, and that leads to an extremely expensive protocol.

Now, you'd have another potential solution to the problem. If you had a sensitive point of care direct detection method. So, rather than using surrogate tests, there are a number of manufacturers that have been working to develop tests that are really targeted to detecting bacterial detection in platelets, and their sensitivities are considerably, in preliminary data, considerably improved over pH and glucose. The problem is none of these are yet available.

They're only under development. I know that none have completed clinical trials, and I'm not really aware whether any are even in clinical trials, although some I think are soon to start. So that solution is not yet available as a test for whole blood-derived platelets.

So, again, to recap a little bit, so what would happen if we do get to prepooling of whole blood-derived platelets with culture-based--what are the consequences of that? Well, we think it's feasible based on the data that's already been accumulated because we know it's been done for years in European countries, although they use a different method of platelet production, the buffy coat method.

And I think that we heard that the FDA has taken this into account, and their current thinking is, as was summarized, is that, with approval of a bag and with the right analytic spiking studies, we could move towards doing this, and I think that's a tremendous step forward to allow this product to get on the market.

And just to point out something that Dr. Brecher said, the paper, which is in your package, shows that at least there are some preliminary studies that have looked at this, and they look promising. And so I think that once the analytic spiking studies are done in the right fashion, FDA-required fashion, then I think it's likely that we will be able to show that these tests work, and then it will leave the licensure of the bag, and then we can move towards the product.

Now, there are a couple of consequences to culturing the product after you pool it. Again, if we're using the culture-based systems on the market, we will, as a consequence, move towards leukoreduced platelets because that's the only product you can culture now. And the advantage of leukoreducing after you pool is you only need one filter rather than five separate filters, so that's probably an advantage.

And the economic constraints against producing leukocyte-reduced platelets that we're currently faced with because it's very expensive to

leukoreduce each individual unit will probably be solved by being able to leukoreduce the pool, although it will increase the price of the product.

Another consequence is, if you do get a positive test on the pool, now, you would need to do some additional work. You need to track back and find out which of the individual units were positive. You'd have to guarantee co-components from five units rather than one. So there are some effects that we would have to work through, but I think, in general, these have been worked through in the European model, and they can certainly be worked through here. So this is one of the issues that the task force has been discussing and thinking about.

The second is this seven-day storage of apheresis platelets. Now, why is this useful? Again, there have been consequences of implementing bacterial culturing. And, again, while they haven't produced major shortages, there are some considerations. Number one is you do, because you have to hold the product before you set up the

cultures, you have to hold it for 24 hours, and nobody will release the product, except in emergency situations, prior to at least setting up the culture. This leads to a delay in the release of apheresis platelets, compared the prior to bacterial detection. And so when they get out to the institution, they have less of a shelf life, and perhaps up to one day less in some regions. So that's a consequence.

Secondly, it's required a number of revised inventory management procedures to, because of this reduced shelf life, to avoid shortages on specific days of the week. In general, I think that's been successful, but until we do our next survey we don't really know. There's certainly the possibility of local shortages that escape the survey instruments.

And, finally, culturing does increase the expense of the product.

So the clinical study to validate the bacterial safety of seven-day stored platelets that we heard described in some detail previously, I'm

going to recap the progress on this right now. FDA has stated that a large clinical trial is required to license an assay, and it has two purposes really--the clinical trial. And one is actually to say we have a bacterial screening test and not a QC test.

And so this large clinical trial, independent of increasing platelet storage to seven days, will be a way for the manufacturers that participate to get this claim, and clearly FDA wants this claim, and isn't really happy, I think--I hope I'm not speaking out of turn--with the fact that products are being used in 100-percent QC mode because that's sort of like screening, even though there's no screening claim. So I think that's one of the purposes of the study.

And then the second purpose is to increase the storage to seven days, and one clinical study can combine those two aims.

The sample size, which we have worked out to be about 50,000 units, and the need to retain the expired product, so, unlike testing for any

other agent, where you only have to have the test tube available in the freezer, and you don't have to worry about the product, in this case, you actually have to have the platelet unit available at the time of expiration. So that platelet unit cannot have been transfused. Not only that, but it needs to be back in your hands at the time you're going to culture it. It can't be out at the hospital and then having to be retrieved.

So those items, the size and the logistics, make this study complex and very expensive. So, as you've heard, it's been a joint work on this protocol by a subcommittee of this task force, the AABB Task Force, and FDA to develop a protocol that fulfills FDA requirements and is logistical feasible. We I think have solved a number of significant scientific and logistic issues, although I think a few remain. But we haven't yet got to the point of addressing how this study will be funded. The rational has been let's develop the optimal protocol, and then we'll obviously you can't secure funding until you have a

good protocol, and that's the stage where I think we're getting close to.

However, it's important to point out that, other than people at FDA, many subject matter experts; that is, transfusion medicine specialists who have worked in this field, continue to believe that such a clinical trial really isn't necessary based on scientific or safety concerns to extend storage to seven days.

And that belief goes from the fact that this has been very successfully implemented in Europe, where many of the countries who have used bacterial culturing have increased their storage from five to seven days with no--and that's on the next slide here--with no deleterious effects reported and that multiple studies have documented that the major clinically significant bacteria are detectable within initial culture result that's set up as it is currently at 24 to 48 hours.

And so we still seem to be in disagreement about why we couldn't just do analytic spiking studies out to seven days at low levels of

bacterial spiking. And if the concern is it needs to be demonstrated in the field, it could be done at multiple sites in the field. And so FDA is not persuaded by this argument and still requires a clinical trial, but I do want the point out that many people outside of FDA feel that this is really not necessary.

However, just to recap, so at the same time we might want to not do this study, we still think, while it's required, it's important. So we've been working out a protocol to make the best study possible.

But there are still a couple of concerns about the clinical trial. In the best-case scenario, given the volumes, it will probably take at least one year to actually perform the cultures required in this study. Obviously, the study has not yet begun, so there is a delay in--we haven't started yet. We need to work out the careful protocol, get consents, if we need them, take a year to perform the study, analyze the data, submit it to FDA. And so I think we're looking at a

minimum time frame of getting to seven days of at least two years under the current protocol.

And there's another concern, and that is we think that we have ample evidence that it's likely that new storage systems will allow platelet quality to increase, and therefore that platelets can be stored for longer than seven days, in terms of their clinical efficacy. And the problem is, if we need to do a study to extend platelet storage life for seven days, then have we set a precedent that each time that we think we can extend platelet storage based on clinical efficacy and platelet quality, that we'll have to repeat the same kind of study, which I think will be a major effort to do in the first place. And we've been in dialogue with FDA about that, and it's an unresolved issue at this point.

The recently resolved issues in the study protocol, as Jaro alluded to, the first one is that we would use whole blood-derived platelets specifically manufactured for the study purposes. And this is important because it's really hard to

use outdated products that you retrieve from the field. So this study design allows for control of the product, centralizing of the protocol in several facilities and avoids the needs to retrieve expired products from hospitals.

The current protocol is for the use of leukoreduced platelets. I was glad to hear Jay say that it would be possible to do a pilot protocol, and if we could prove that nonleukoreduced platelets, the test systems perform the same on nonleukoreduced platelets as leukoreduced, we could use nonleukoreduced platelets. The main issue here is the leukoreduction is an additional step in the manufacturing process. It's not a complicated step, but it does add a significant amount of cost, as I'll show you.

A few issues that have not yet been completely resolved is in the last rendition of the protocol that was discussed at the BPAC. The FDA had indicated that there would probably be a need for a gram stain to rule out false negative cultures at seven days, and that point being that

maybe the bacteria have grown up to such high concentrations by seven days and exhausted the nutrient systems and they've all died, and so that by the time you culture them, you get a negative culture, but in fact the culture--in fact, there were bacteria in the unit. That theoretical concern led to, well, you have to have another mechanism to evaluate whether the seven-day platelet is contaminated and that mechanism would be gram stain.

However, we have tried to pull together the data that exists to show that this really, in fact, doesn't happen and will be submitting that to FDA because I can tell you 50,000 gram stains is a considerable logistic challenge as well. Of course, those are read by observers, and then you've got the issue of subjectivity, and analysis, et cetera.

So we do have experiments that have been performed on 158 units in which cultures were done out to Days 7 or 14, in spiked units, with 15 different organisms and, at least in this sample,

no senescent cultures were found. So, hopefully, that will be convincing data to not have to do gram stain.

Now, another point that I think is still unclear in the protocol is the study endpoint with regard to anaerobic bacteria and how that will influence how the study was analyzed. As was pointed out, we expect to find some anaerobic bacteria at seven days that we don't find at Day 1, and primarily P. acnes, which is known to be a slow grower. So the question is how are we going to evaluate that with regard to interpreting the yield of Day 1 versus Day 7.

And then, finally, the study as initially laid out, was to use BacTAlert, but the issue is should we do this only with one manufacturer's test or should we try to incorporate more manufacturers' tests. We have a second QC device from Pall that could potentially be used, and then we have other manufacturers who are trying to get into develop testing devices. How should this study be designed for their participation? We really haven't

broached that yet because we're still resolving the study protocol.

So I want to then turn to the funding issues now from where we think we are currently, and here's a preliminary study budget. We would have to manufacture these 50,000 whole blood-derived platelets and leukoreduce them according to the current protocol. And at $20 to manufacture and $20 to leukoreduce, that's $40 per unit. So we've got $2 million in the budget for that.

We'd also have to culture these at Day 1 and Day 7 by the BacTAlert. And then assuming that we would also have the participation of the Pall bacterial detection system, we're essentially doing three cultures or series of cultures because we do both the anaerobic and aerobic BacTAlert culture. The costs for that are somewhere estimated, if we had to pay list price, at $4- to $4.5 million.

For the BacTAlert--because we would have close to 2,000 cultures incubating per week in this study--we obviously need dedicated equipment. We

can't use the testing systems that are in place in blood centers for their actual QC testing. We need separate modules. We'd have 2,000 cultures, each with an aerobic and anaerobic bottle. So that's 4,000 bottles. So we're talking about $800,000 to get the necessary equipment.

And then we haven't really worked out the rest of the budget that carefully. So some rough figures are $100,000 for other equipment, and the whole project management data analysis part of the budget has really not been worked out, and I've just thrown in $100,000. That may, in fact, be low. I really don't know.

Anyway, if you add it all up, it's a tentative study budget of $7- to $8 million. I do want to add one thing that's not on the slides, and that's the proposal to pool the 7-day cultures. We haven't costed it out, but I fail to see how that's going to help us very much. There will be increased labor to pool the cultures. The primary cost of the culture is not the culture bottle. It's in the sample collection device and the labor.

So I think, while it looks like a potential cost-saving measure, I think if we look at it closely, it may not be, and then--it may be, but it may not be. And then, secondly, it changes the protocol enough that I think we'd have to worry about contamination in that process. So I don't think that's going to pan out to be as helpful as we might have hoped.

So we have this tentative budget of $7- to $8 million. So how is this going to be funded? Well, the potential funding sources include the manufacturers, and there hasn't been an in-depth discussion with them yet, and the NHLBI, and there hasn't been an in-depth discussion within NHLBI yet either because the protocol hasn't been finalized.

So I think the bottom line on the budget is we think that it is an expensive study at the current sample size and that sufficient funding is going to be difficult to obtain. Whether it's possible to obtain or not remains to be seen.

So I'll close there.

DR. BRECHER: Comments? Questions?

Jay?

DR. EPSTEIN: Just one or two points of clarification.

Regarding the need for gram stain, we appreciate the difficulty of gram staining such a large number of units. However, we have discussed with the AABB Task Force the option to do a glucose and pH screen and gram stain only the units that have low pH and glucose, which would then be a remarkable labor-saving and cost-saving step.

And then on the issue of budget, as you know, it's been a moving target, and I would just ask a couple of questions.

First of all, you've suggested that if nonleukocyte-reduced units are used, the cost of preparation would be halved, right?

DR. KLEINMAN: That's a rough estimate. I didn't make that estimate. I assume that's correct, but that's right.

DR. EPSTEIN: But ballpark, you know, if it goes down from $40 per unit to $20 per unit reduction--

DR. KLEINMAN: Sure. It would be half, yes.

DR. EPSTEIN: That would be half.

And then a second question is whether the manufacturers of the culture reagents might provide them at cost for the study, and I don't know how much that would offset the $4- to $4.5- million cost with no harm to the manufacturer. It would be revenue neutral.

Your point about pooling, as a labor cost, and the potential for false positives, is of course correct. However, if one could reduce by a factor of 10 the number of bottles incubating, then it might substantially reduce the carrying cost, as it were, of maintaining those cultures. Additionally, the equipment need not, on the one hand, it need not be purchased. On the other hand, it could be rented pending the result of the study or even on loan and that there might be a strong incentive for current manufacturers of whole blood platelets to acquire those instruments in the interim, looking forward to implementing them at the closure of the

study. So that's another point.

So I think that there might be a lot of room for cost reduction which isn't apparent in the numbers that you showed, but of course would require some more detailed analysis.

DR. KLEINMAN: Yes. I think that's very true. And this is, you know, I just presented it just as a preliminary budget without attempts being made to look carefully at how we could reduce the costs.

DR. EPSTEIN: And then just one final comment. As you say, FDA is well aware of the practices in Europe involving bacteriological culture and the use of pooled buffy coat platelets. FDA is not unwilling to look at data on systems that have been developed with buffy coat platelets.

The big question is whether results on buffy coat platelets can or cannot be extrapolated to platelet-rich plasma-derived platelets. Of course, if systems in the U.S. wish to switch over to buffy coat platelets, the data would become more immediately applicable. And then it begs the

question of what the quality of the data might be that would be submitted to the FDA, and my point here is that nobody has brought any such data to the FDA.

DR. KLEINMAN: Right. But my point, Jay, was not about the buffy coat platelets for 7 days, but the fact that apheresis platelets, which we were talking about in this study, have been extended to 7-day storage in Europe, as well as buffy coat platelets.

DR. EPSTEIN: Yes.

DR. KLEINMAN: So, I mean, the likelihood of switching over--I mean, you want to talk about a long-term time line that you're talking about switching to buffy coat platelets, that would be a huge project. And I think, realistically, that isn't going to get us where we want to go in any kind of timely fashion in the U.S.

So I was talking about the extension of apheresis platelet storage to 7 days, which has been done in a number of European countries. I don't have that data, but it seems to me that that

should not be irrelevant that they've made those decisions. But, again, that's not U.S. data.

DR. EPSTEIN: But someone should provide those data to the FDA if someone wishes to make a claim. That's my point.

DR. BRECHER: Dr. Gomperts?

DR. GOMPERTS: Steve, could you talk to the issue around why 50,000?

DR. KLEINMAN: I don't--I can talk to the issue. It's determined by the statisticians. And my understanding of statistics is that--actually, Sunny Dzik had a great line in his editorial that "The way statistics are done, no author, editor or reviewer can really understand them, so they accept them."

[Laughter.]

DR. KLEINMAN: And I don't know why 50,000. I just have to assume that the statisticians worked it out correctly, and that was basically FDA statisticians. So I can't really address why 20,000 wouldn't be acceptable, but Jay probably can.

DR. BRECHER: Jay?

DR. EPSTEIN: It's actually not that hard. If you want to get a point estimate of 1 in 10,000 that you'd have an upper limit of 5 positive cultures out of 50,000. Five positive cultures is about what you might expect, with given rates, with current rates, and that level is sufficient to give you 95-percent confidence of an upper bound of no greater than 1 in 5,000, which means that you are at or better than the best current contamination rate of an unscreened platelet.

So that's where the figures are coming from. They enable us to achieve the goals, which is to show that a platelet at Day 7 is no worse than a current platelet at Day 5, even absent culture.

DR. KLEINMAN: And I guess it's worth adding that we have made some progress on sample size because, when originally proposed, the sample size was 100,000, and so we've gotten it down I think to 50,000, based on these statistical considerations.

DR. BRECHER: Lola?

DR. LOPES: We've heard several cases over the last 2 days where progress has been slowed because people, industry advocates, have not brought a request to FDA. Is it necessary that FDA has to be in a passive role, where someone else initiates looking at a process? Could the FDA ask for the data from Europe?

DR. KLEINMAN: Well, we can do that kind of thing at workshops. We can have a workshop on bacterial contamination. This is a public meeting, and anyone could have brought those data.

We read the literature like everybody else reads the literature. Again, it's a question of where do the burdens lie? By generally speaking, the burden lies on sponsors who wish to make claims.

DR. BRECHER: Matt?

DR. KUEHNERT: I just had a question on the costs, which are indeed substantial, and the big item here is the culture. I wondered does this include labor costs? Are you assuming $25 per

culture for--actual for the bottles?

DR. KLEINMAN: No, it includes labor costs. It includes, in the case of the BacTAlert, the sterile connection device and the sampling bag, as well as the bottles. So it's all costs--supplies and labor.

DR. KUEHNERT: But the manufacturer providing it at cost would substantially reduce this, I would assume.

DR. KLEINMAN: Well, as an example, I mean, the way we've costed out the BacTAlert, it's the two bottles--the aerobic and the anaerobic bottles--are $8 in total, but the cost of the culture is $27 when you add on the other factors.

So, yes, it will reduce, but only by a third, a quarter to a third, at least in the way it's been costed out preliminarily. And, again, I would have to say, actually, Dr. Brecher has done some of those cost estimates, so he might want to comment, and he certainly has a lot of experience with culturing. So I think he's probably fairly accurate in estimating the labor costs.

DR. BRECHER: Go ahead.

DR. KUEHNERT: I was just making a point that the bottles in the machine are a big part of this budget. That's my only point there.

DR. KLEINMAN: It certainly would help if they were all free.

DR. KUEHNERT: The other point I had on your presentation was about issues about multiple manufacturer test systems and also about future detection systems. I wondered if people were thinking in the protocol about saved specimens, as well as saved isolates, which may be of value in the future. Of course, there's an issue then about storage, but I think we might be able to work that out.

DR. KLEINMAN: Well, saving isolates I think we didn't mention, but, sure. I mean, anything that's positive, you'd save. Now, saving specimens, what's a specimen--an aliquot of a 7-day platelet? I mean, 50,000 units saving on Day 1 and Day 7--well, you wouldn't have to save Day 1, presumably, but if you're going to evaluate a test

that then is done at the time of release, you don't have the right length. The release could be Day 4. You don't have a Day 4 specimen, so I think there's a lot of issues about saving specimens, but maybe, for manufacturers who would perform their tests on not--I mean, you have to perform your tests on an aliquot of platelets. So that's an issue.

DR. KUEHNERT: I have one more point, but I'll yield to Jay.

DR. BRECHER: The floor is yielded to Jay.

DR. EPSTEIN: Well, there's another approach. If we ever get to a point of characterizing the performance of some up-front test, the standard for approving follow-on products of even different technology would simply be equivalent analytical sensitivity because then you would predict an equivalent clinical performance. So you don't actually have to repeat the study.

There may be some value in retaining samples to look at discrepancy; you know, Test A picks up certain ones that Test B misses and conversely. Bank ut the bottom line is that

equivalent analytical sensitivity can get you to the finish line, and that's much, much easier to demonstrate because you can do it with spiking studies. So I'm not sure you ever would have to repeat the study to--

DR. KLEINMAN: Just a couple of points.

Certainly one point, I think retention of samples would be an expensive budget line item.

Secondly, I may as well say the obvious, you know, that a manufacturer would say. I don't think I'm putting ideas in their mind. Why participate in the study now if it's going to be easier in the future? I mean, let somebody else go first and not have to bite this off at this point. So it becomes that, you know, Jay's solution, which is a good one, is also a disincentive for anybody to do the study.

DR. BRECHER: An additional disincentive that we probably ought to put on the table for these manufacturers is that if we go to 7 days, they're going to sell less test kits.

DR. EPSTEIN: Why wouldn't they sell the

same number if it's--

DR. BRECHER: Because the outdates would decrease, and therefore we would have to produce less platelets.

DR. EPSTEIN: You're talking about the containers, not the cultures or both?

DR. BRECHER: Both.

Dr. Sandler, a last comment, and then I have one question to end.

DR. SANDLER: Steve, two immediate benefactors of a 7-day platelet would be the United States military and Homeland Security--the military because they could make out-of-theater platelets, which aren't available in Iraq, as I understand it, right now in theater and Homeland Security because the logistics of the pipeline would provide a larger reserve that would be available.

There's a model, and that's the frozen blood. We had frozen blood made out of theater for Vietnam, and the Navy paid for that and a lot of its development.

Have you considered approaching either of

those two larger budgets, rather than approaching NHLBI?

DR. KLEINMAN: That's the first time I've heard the suggestion. I don't know if anybody else has considered this in the past.

DR. BRECHER: Does anyone from DOD or NIH want to comment on budget before we close this discussion?

DR. KLEINMAN: Mark, if I can make one comment. I think we are nearing the point where the protocol is, as I said, we've developed, we've solved a lot of the issues that were being debated about the protocol. I think there are some minor ones that still need to be solved, but essentially I think the protocol is together enough now where it could be presented to potential funding bodies who would then say, okay, I'm willing to participate or not.

I think, until we've made the last rendition of the protocol, and we just had a conference call with FDA about two or three weeks ago, where some of the additional progress was

made, until then, it was really premature to distribute the protocol because there were significant design issues that were still pending. But I think we have now reached the next point where the protocol is mature enough that you could present it. And, yeah, there might be little tweaks to it, but you could present it to NHLBI or the manufacturers and say: This is sort of what we're going to do. Are you interested, and would you consider funding?

So I think we're just at the bridge of really doing that now.

DR. BRECHER: George?

MR. NEMO: George Nemo, NHLBI.

This study clearly fits within the mission of the National Heart Lung and Blood Institute. I can't speak for Homeland Security or the other agencies. You're certainly free to approach them as well as a potential source of funding. However, we've been in the loop all throughout the development of this protocol, and so we're very much aware. We're certainly willing to look at it

and to make a recommendation for further submission of an application. However, we do have other mechanisms other than just submitting a clinical trial application. So we would have to consider that too.

But the Director or the Acting Director of the Institute has been kept apprised of this trial. In fact, last week she was just updated on the FDA's modification of the protocol to save money, to streamline the protocol. So even the highest levels of the Institute are aware of this, but I must add a real sticking point would be if the manufacturers weren't willing to step up to the table.

The Institute usually doesn't support studies, whether it be on devices or therapeutic drugs, without the manufacturer usually supplying those at no cost or significantly reduced costs. And from what I have seen and heard doesn't appear that the manufacturers are terribly enthusiastic about providing funding for, say, cultures and related equipment. So that could be a sticking

point, but we're receptive. We'd certainly be willing to talk.

Another issue is that it will be coming, this protocol will be coming as the result of a committee. Somewhere along the line, an investigator, who has a little fire in his belly, who wants to put this thing together and really get it done, and an institution associated with that has to be a part of this. And that's something that has to be considered. The Institute doesn't fund committees to do these. It has to be an institution and an investigator with an interest and expertise in this area.

So that's all I have to add.

DR. KLEINMAN: One additional point is the concept was to do this in four, probably spread the work across four centers--four blood centers. And which blood centers would actually want to participate and gear up to participate has not really been determined yet, but clearly there would have to be four investigators at four sites--at a minimum, four investigators at four sites. And

obviously a principal investigator would have to be developed out of that.

DR. BRECHER: Commander Libby?

COMMANDER LIBBY: To go back to Dr. Sandler's question about DOD requirement for such a test method. We do not ship platelets from the States into the theater of Iraq, so therefore we don't have a requirement to fund this type of study. We'd want to use this technology for bacterial detection.

And in fact we do, do some shipping of host nation products to some of our, whether Coalition forces or multinational forces. I'd like for us to--in Iraq, and we may want to consider a 7-day platelet product. That would give us a product that's most fully tested. It's possible a 7-day product, if we were to extend that, could definitely benefit from this technology to do the bacterial contamination study.

DR. BRECHER: Our last comment, Karen?

MS. LIPTON: And the other thing, just with respect to funding from DHS or any other

sources, we're not talking--we wouldn't get in this year with this dollar value. I mean, we'd really be talking about fiscal year 2005, at this point, to even begin to put that together. So that would delay this until that time. And as we know, we're already in there with some competing priorities for national blood reserve that haven't been resolved yet.

DR. BRECHER: We're behind schedule. I would propose we take a 10-minute break here. We'll come back at 10:35, and we will start at 10:35.

[Recess.]

MS. HEDDLE: Thank you, and I would like to thank the Committee for asking me to come and speak today.

What I'm going to talk about is a study which we've completed, looking at whether or not we could store whole blood-derived platelets as a pool, and we've used what's called a randomized block noninferiority design, and I'll go through that.

So, when we started this study, actually, the reason that we did it was because in the Hamilton area, we were looking to move forward to a centralized transfusion service, and we just thought that having platelets that were already pooled prior to storage would facilitate the whole operation. But because the study took a number of years to complete, it turns out that it's become a hot topic because of the requirement for bacterial detection. And the major concerns that we were able to find at the time when we started this study was, of course, the bacterial contamination and whether there would be interaction between the leukocytes.

And every time you've got a great idea, you search the literature, and you find out that somebody's already thought of it. And Ed Snyder and Gary Moroff had actually done these types of studies back in the late '80s, early '90s, and their conclusion at that time was that you could store platelets as a pool. But those studies were done on non leukoreduced platelets, and so we felt,

in order to make this move in Canada, that we needed some additional data.

The studies, as it went on, and I may refer them to as POPS 1 and POPS 2, so it just refers to our Pooled Platelet Storage studies, which is a little easier to say, than going with POPS 1 and POPS 2.

The study had two phases. The first phase was actually an in vitro study, where we just looked at a lot of different parameters at both 5 and 7 days of storage. And our intent was that if those parameters looked good, then we would go on to our POPS 2 study, which is actually to compare the in vivo effectiveness of platelets stored as a pool up to 5 days, compared to individual storage, by assessing the 18- to 24-hour CCI as the primary outcome and looking at adverse events and bleeding as secondary outcomes.

Just to quickly tell you about the first study, POPS 1. Similar to what's been described today, where basically we pooled platelets in pools of five prior to storage, sampled them and did a

variety of in vitro tests. And the control platelets were platelets again stored for 5 days that we pooled at the time that the patient was going to receive the platelets. So they were actually transfused. But any platelets that weren't transfused, we actually kept them up to 7 days to get the 7-day results.

And I've just provided one slide, in terms of summary, which I'll show you. These are all the different tests that we did in the study, and they're sort of the standard group of tests that is usually performed in these types of studies.

The leukocyte activation at the bottom, we actually stopped that after the first few pools because we had great difficulty actually doing that test with the flow cytometer. The leukocyte counts were so low that we almost needed the entire sample in the platelet pool, and we wouldn't have had any sample left to continue storing. So that was actually eliminated from the protocol.

When we analyzed the data from these different tests, we did find some significant

differences, as I've indicated either with the yellow or the white lettering. And these differences, although they were statistically significant, we didn't consider them clinically significant because we looked at what had been published in the literature, and they all fell well within the published ranges. And the reason that I believe we had these statistically different results was because of the large sample size in the various groups--anywhere from about 31 up to 38 platelets.

We did find one positive culture in the in vitro study. That was actually in a controlled platelet. It was a coagulase-negative staff and was felt by our microbiologist specialist to actually be a skin contaminant. There were no positive cultures in the products that were pooled prior to storage.

So, having this information, we went back to the Ethics Committee, and they did approve us to actually do the clinical study, which was designed as a noninferiority study, and we looked at the 18-

to 24-hour CCIs of platelets that were stored as a pool compared to platelets stored individually, which was our routine technique.

This is a just an overall summary of the design. There were eligibility criteria, which I'll go into, patients who were eligible, we then randomized their platelet transfusion in blocks, and I'll show you that design in a little more detail because it's certainly different than what's being proposed by the FDA in terms of a parallel RCT design.

We then, the platelets, the blocks were either platelets stored as a pool or stored individually and pooled at the time of transfusion. And then the outcome that we assessed, the primary outcome, was the 18- to 24-hour CCI, with secondary outcomes being adverse events in bleeding. And these were captured through a, predominantly through a chart review, as opposed to prospective documentation.

So what do I mean by a randomized block design? I've outlined it here. So patients that

met the eligibility criteria, we prepared a randomization schedule for their platelets, and the schedule was prepared in every block of two, where within that block the assignment was randomly allocated to either prestorage pooled platelets or platelets that were stored by the routine technique.

And you can see here it's really the patient who determines how many blocks that are actually going to be observed based on how many platelets they require. And the other thing I'll just point out is, again, you can end up at the end of the observation period with incomplete blocks if a patient needs an odd number of platelet transfusions, and that's an important consideration when you actually go to analyze these types of studies.

Noninferiority was the study design. And just to review what I mean by that, so, if this black line here represents the proportion of platelet transfusions with a successful CCI, and we defined that as greater than 4.5 based on what had

been consistently used in the literature with other platelet studies. So this goes from zero to 100 percent.

We made the assumption that about 50 percent of our platelet transfusions in our control arm would have an acceptable CCI, and that was really based on information in the literature and information from previous studies done at our center. We then sat the lower boundary of the 95-percent confidence interval at 37.5. So this actually means that, as long as the point estimate can be anywhere along this line, and as long as the lower limit of the confidence interval doesn't go below the 37.5-percentage mark, then we would actually claim noninferiority. That 37.5 percent, again, was sort of based on previous studies at our center. And what it represents is that you're retaining 75 percent of the affect of the platelets stored by standard technique.

Now, when you think about this, and when I show you the analysis, you have to sort of think backwards from normal studies because our null

hypothesis here is that the relative risk is less than or equal to 75 percent, and our alternative hypothesis is that it's greater than the .75. And so if we get a statistically significant result, then we can reject the null hypothesis and basically claim noninferiority.

We included patients in the study that were predominantly hematology/oncology patients, and we selected patients that the physician felt were going to require a number of platelet transfusions. We excluded patients if they required apheresis platelets, and our center that's predominantly because of the need to give CMV-negative platelets.

And patients were temporarily excluded from the study if they were bleeding, if there was clinical evidence of DIC or if they were outpatients, and the outpatient exclusion, as a temporary exclusion, was simply because they may not be coming in the next day so that we could get the platelet count to calculate the 18- to 24-hour CCI.

The intervention, our standard platelets were just whole blood-derived platelets prepared from PRP stored under normal conditions. And when they requested transfusion, they were pooled into pools of five. If we did have a platelet shortage, our routine was to actually go down to pools of four, but that happened fairly infrequently.

The prestorage pool platelets again were targeted at pools of five. We usually received these platelets from Canadian Blood Services on Day 2 of storage. So this is a little different than if this pooling was actually done at the blood center. They were stored in a bag supplied by Pall, which is a 1,000 mL bag with CLX plastic and again stored under normal conditions. When they were issued for transfusion, a sample was collected on which we did a platelet count. The bag was weighed so that we could actually work out the corrected count increment.

All of the platelet pools that we transfused were screened using the BacTAlert system, but that was done basically at the time of

transfusion, so that result was actually not available at the time that we transfused the product. If something came up positive, the protocol was to inform the clinician at that time.

The outcome measure. We selected the 18- to 24-hour CCI and defined a successful CCI as greater than 4.5. So we dichotomized the result into successful and unsuccessful. And the reason we chose the 18 to 24 hours is because it really does reflect clinical practice. That's what physicians look at in terms of do they need to give platelets to the patient. There's also evidence in the literature from Bishop that the 1-hour and 24-hour CCI are highly correlated. And, in fact, at our center, they really don't like us taking 1-hour CCIs because you're reentering the Hickman catheter, and there's a potential for increased risk of infection.

Secondary outcomes were adverse events in bleeding. And as I mentioned before, that information was collected through a chart review, with the individual doing the reviews being blinded

to the actual type of platelets.

So to show you the results, we had 23 patients that were entered into the study. The majority of the patients were newly diagnosed AML patients, although we did have some lymphoma ALL and MDS, pretty much equal male and females, and the majority of patients had actually been previously transfused. And you can see the median age of the group was actually 53 years, but it was quite variable from 19 to 78.

The platelet product characteristics. Between the two types of products, the platelet count was very similar. The age of the product was similar. The median age was actually at 4 days,b ut certainly ranged from 2 up to 5.

As far as ABO compatibility, again, between the two groups, the platelets were--it was very similar. And we didn't have any positive cultures throughout the study.

So here's the results. On the 23 patients, they used 189 platelet transfusions. But for the way we intended to analyze the data, you

could only use complete blocks. So, if there was that uneven number, the ones that weren't complete were not used in this analysis.

There were 85 complete blocks we could use in the analysis. Seventeen were incomplete, and one block that was complete was actually missing the information to calculate the CCI. This 2-by-2 table, let me just walk you through it. It's set up as sort of a paired table. So, for pooled storage, the CCI greater than 4.5 and routine greater than 4.5, there were 32 of the complete blocks where the information was the same in both. There were 27 where the CCI was less than 4.5 in both, and these are, of course, the two discordant cells in the table. But when you work out the percentage, it actually works out to a success rate of 52.9 percent with each of the two different product types. And so when you work out the relative risk, the relative risk worked out exactly to being one.

So where did the 95-percent confidence interval fall? Well, we calculated it two ways.

Remember, our lower limit of noninferiority, as long as the confidence interval did not go below .75, we would claim noninferiority. And when you assume independence between the pairs of subjects, the lower limit actually fell at .83, and it fell at .85 if you accommodate the association between the pairs of subjects.

So, when you do your significance testing, we got a highly significant result, which means we can reject the null hypothesis, and the null hypothesis, of course, was that the value would be below 7.5. So that means we can actually claim noninferiority in this study.

Let me just show you some of the information plotted out because sometimes in overall tests people like to see, well, what did the data really look like? So, in this particular plot, these are box plots where you've got the medians and interquartile ranges plotted. The "Ps" at the bottom is the pooled platelets, the "Rs" are the routinely stored platelets. These are by block. So this is the first block, second, third

and so on.

And I've drawn the line across here at 4.5. So anything above that line represents a successful CCI; below, an unsuccessful CCI. And you can see within each pair, sometimes the routine, the median is a little higher, sometimes they're right on. Sometimes the pooled is a little higher. So it just shows that it bounces back and forth and is sort of consistent with our relative risk of one.

We also looked at the difference in CCI within blocks and plotted that out. So the zero line here, of course, would be absolutely no difference between the pairs of transfusions, and it's plotted out again for the different blocks. So anything above the line favors pooled storage, and you can see that a number of them, the medians are above the line. Anything below the line favors routine storage.

I've been asked the question, why didn't we treat CCI as a continuous variable, and we actually did the analysis that way too. If you

actually work out the mean CCI between the two groups, very little difference between the means, and again the confidence interval is not significant. And you can also use what's called a random effects model to estimate the effect of CCI, accounting for the fact that the data isn't independent. And, again, even when you use the random effects model, it's not significant.

So let me tell you about adverse events. This is just a 2-by-2 table. So pooled storage, routine storage, no reaction and reaction. So you can see for pooled storage, the reaction frequency was 9.7 percent compared with 4.2 percent for routine storage.

And when you do a Fisher's Exact Test on that, it turns out not to be significant, although some people might look at it and say, but you know it certainly looks like there's a trend for more reactions, when you actually look at the adverse reactions, so that was 6.9 percent overall of all transfusions. And with this data, we have included all transfusions not just the complete blocks.

We had nine patients that accounted for 13 reactions. Five of the patients reacted to prestorage pooled, only one to routine and three to both. And when you look at the type of reactions that you see, they're predominantly the very mild, febrile types of reactions. Most people would probably consider these reactions as not of major clinical relevance.

Adverse--sorry, we didn't move there. There we go--bleeding days. So, again, this was through chart review. The overall number of bleeding days with the pooled storage was 10.6 percent versus 5.2 percent with routine storage. And, again, statistically that is not significant.

And when you actually look at the types of bleeds that were occurring, they would all be considered and classified as your WHO Grade 1 bleeding, so mainly petechiae and some bruises, that type of thing. And those 15 days of bleeding occurred in nine patients.

So, in conclusion, the 18- to 24-hour CCI for prestorage pooled platelets was not inferior to

that of platelets stored individually, and in fact the relative risk is sitting exactly right on one.

The frequency of adverse events was not significantly different between the two types of storage, and all reactions that were noted were mild.

All bleeding episodes noted in the two groups were mild--WHO Grade 1 bleeding--and the frequency of bleeding days again was not significant between the two types of products.

So we feel that the study provides strong evidence that whole blood-derived platelets can, in fact, be stored as a pool for up to 5 days and transfused without any increase in adverse events and also giving acceptable CCIs.

And lots of people helped with this study, and I've just acknowledged them here.

Thank you.

DR. BRECHER: Thank you, Nancy.

This is open for comments and questions.

Jay?

DR. EPSTEIN: Just a couple of technical

questions.

Were these buffy coat platelets or were these PRP-derived platelets?

MS. HEDDLE: Canada still has PRP-derived platelets.

DR. EPSTEIN: I expected that answer.

When was leukocyte reduction done?

MS. HEDDLE: Leukocyte reduction was done by CBS prior to storage, so at source when the platelets were prepared.

DR. EPSTEIN: So it was early on. And did you look at cytokines in the products, compare pooled to nonpooled? Because I'm at least struck by these trends of increased adverse reactions that are basically febrile reactions. One would think they might be related to cytokine release and might suggest MLR, even though MLRs are reported not to occur at room temp. So how do you explain it, if the trend proved real with larger numbers? What would it suggest to you?

MS. HEDDLE: First of all, in terms of some of the cytokines, all of our previous studies

related to febrile transfusion reactions. You know, the leukocyte-derived cytokines just are not present in your prestorage pooled products. So it can't be them.

Can it be platelet-derived cytokines or other types of biological response modifiers? I think the answer is probably, yes, it could be.

I agree with you. The reactions are mild, so, clinically, I don't think that's an issue. And in fact it's interesting, our febrile reaction studies, everybody always wondered why we had such a higher frequency than was reported by everybody else, and it was probably our monitoring system. So, you know, I'm just not sure that people would consider those reactions as clinically relevant.

I think, but I agree with you, from a scientific point of view, you could imagine that if you pool platelets together, that something could happen in terms of an interaction between platelets that could generate some type of modifier that might initiate these reactions.

If anything, this is where a postmarketing

type of surveillance approach I think would be useful. The other thing is we've got the European buffy coat data that certainly suggests that you can pool whole blood-derived platelets prior to storage. They use it all the time there. Do they see more of these mild reactions than what we see with whole blood platelets? It's hard to say. That study hasn't been done.

So it's true, there could be something there. The study was not powered for adverse events in bleeding, but I'm not sure--in Canada, it's a little different, so we're not under the regulatory control in the hospital. So, based on this information, our hospital, and we are considering using prestorage pooled platelets. The only downside is the cost of the wafers for the sterile connection device, which adds an additional cost, but we could change.

And I think my impression is I would not be concerned about it, but I think some surveillance, if we change or if this is used, would be useful.

DR. BRECHER: Matt?

DR. KUEHNERT: I'm just wondering, the adverse event surveillance you have in place in Canada, would that pick up these events or not?

DR. BRECHER: Not the--we have a system called TTISS, Transfusion-Transmitted Injury Surveillance System, which is run by Health Canada. These types of reactions are not the types of reactions that we are obligated to report to Health Canada. Now, a lot of sites that are participating in the TTISS program actually do document these events, so the information would be there, but I don't think it would always get reported on to Health Canada. So the answer is probably, no.

DR. KUEHNERT: Thanks.

DR. BRECHER: Harvey?

DR. KLEIN: Nancy, were these platelets pooled by blood group, by any chance?

DR. BRECHER: The one slide had ABO--sorry, that was ABO compatibility with the patient. The pooling in our center is done ABO identical. We find that if we don't pool ABO

identical platelets, they start clumping in the bag and then the wards call us because they can't run them through the filter and the tubing. So, yes, they were.

Can I just also make a comment? Because as Jaro mentioned earlier, this design is different than what the FDA has proposed. It's a design that we felt was the best approach to use in this study because it not only accounts for between-patient variability, but within a patient you're accounting for that using the paired design. So you can probably get away with a smaller sample size. Our sample size calculation at the beginning of the study was 73 pairs for that noninferiority design. We actually went up to past that and ended up with 85 pairs that we could include in the analysis.

If the parallel design is going to be used, again, I think you need some discussion about how to analyze that data because it's not simple, straightforward taking the proportions between the two groups and comparing them, especially if patients are contributing multiple transfusions

within each of those parallel lines or each of the parallel arms of the study. So it's a little tricky. People have different periods of thrombocytopenia. They may require different numbers of platelets. So that needs to at least be considered.

DR. BRECHER: Jay?

DR. EPSTEIN: Well, Jaro might be able to elaborate on this, but we actually contemplate a double radiolabel, where each infusion would get both products, and the patient is the patient's own control, and you would look at the CCI of both products concurrently in the recipient. So it's very highly internally controlled at that level.

DR. VOSTAL: I think that's correct. And we can discuss different study designs as well, and I think this is a nice study design.

The question I had was, in your patients, would any of them qualify as being alloimmunized by two subsequent CCIs of less than 4.5?

MS. HEDDLE: So I don't know if we've actually looked--well, we have looked at that, but

I don't know if we formally analyzed it that way. I can tell you that there were very few patients who did have, just from observing the data, who did have consistently poor responses that we, in fact, would say this is an alloimmunized patient. And that's probably not unexpected, based on the fact that Canada has universal leukoreduction. But that's something that perhaps we should look at a little closer.

DR. VOSTAL: Right. I think it would be important to see because if you do identify alloimmunized patients, then the platelet survival in them would probably be related to alloimmunization and not to the storage lesion of the platelet.

MS. HEDDLE: Yes. Again, the nice part of the randomized block design is, at least within the patient, they're getting both products, so you actually control for that. It's not like one alloimmunized patient ends up in a parallel design arm.

DR. VOSTAL: I think that's true, but if

you're looking at noninferiority, and both products do equally badly, then you can see you've reached noninferiority. So I think that needs to be accounted for.

DR. BRECHER: Steve?

DR. KLEINMAN: Nancy, the number of successful CCIs in both groups were about 52 percent, I think. Is that surprising? That seems low. Is that normal in a study like this?

MS. HEDDLE: Yes, it's not surprising. In fact, it's higher than what we've even found in some of our other studies, so we seem to be getting better, but, no, in this type of patient population, they don't always have the increment that we would like to see when we get platelet transfusions. So it's not surprising at all, and I believe it was reported something similar in terms of the Trapp study and other studies that's been--

DR. KLEINMAN: And my second question is why is 4.5 the figure that's the acceptable CCI; is it just by convention over yours?

MS. HEDDLE: I think it--yes.

DR. KLEINMAN: Yes, it came down from on high.

MS. HEDDLE: I'm not sure of that background. That's what people have tended to use, and that's why we did look at the continuous CCI too. The problem, when you look at the data as a continuous variable, you've got somebody who has an increment and gets a post-transfusion platelet count of 30 and somebody else gets 35. Those are both good increments, but yet they're considered significant.

Now, people might turn around and say, "Well, was the interval between transfusion longer because you got somebody up to 35, as opposed to 30?" And, unfortunately, with this type of study design, you can't answer that question. You do need a parallel design in order to answer that.

DR. BRECHER: Jerry.

DR. SANDLER: Nancy, could I ask you to clarify the response you gave to the question concerning ABO pooling platelets of different ABO types. If I understood the answer, it was that you

wouldn't be mixing in this study platelets from a Group A person and platelets from a Group B person because the fluors saw clumping as they went through the filter.

My question is, is that a property that you observed related to storing the platelets or is it something that you observed in general when you make them and just pool them and send them out?

MS. HEDDLE: It's something that I would say that we've just observed on the clinical services. When we do mix ABO groups, we have gotten calls from the clinical area saying, I'm having trouble running this. It's not going through the filter. And, oh, this is probably going back a few years, we actually did a little experiment pooling different groups, and you could actually see the clumps of platelets sometimes when you did that. So it's standard. It's a policy and procedure at our institution that when we pool, they're always the same group.

And in the table that I showed you, we don't always give ABO compatible platelets to the

patient. CBS tends to make A's and O's and B's and AB's are, you know, kind of out of luck as a general rule. But the information that I showed you showed that that balanced out between the two different groups, in terms of what percentage were ABO compatible versus a major or a minor incompatibility. So we don't feel that that has affected the results.

DR. BRECHER: Last comment, Jay?

DR. EPSTEIN: This is a philosophical question. You've heard some here today, and of course elsewhere argued that these kind of studies are not necessary given the European experience with prestorage pooling. What led your institution to think that it was important to do this study, which I personally am glad you did?

MS. HEDDLE: I think there is that argument that people put forth, and I put it forth today, too, that you know the European data shows that you can do it, but from a scientist's point of view, I think I probably asked the question of myself that the PRP platelets aren't the same as

the buffy coat platelets. It's not the same procedure. So I felt I couldn't necessarily generalize to the PRP platelets and say we don't need to do any studies. I felt that the study was necessary to do. That's the academic side of me coming out.

DR. BRECHER: Merlyn, did you have a comment?

DR. SAYERS: Thanks, Mark.

Were the CCIs different in the nine patients that had the bleeding events?

DR. BRECHER: I think you mean the febrile events, right?

MS. HEDDLE: We haven't specifically looked at that. Again, I wouldn't--we'd have to look at that. So the answer is I don't know. The bleeding events were such mild WHO bleeding that, you know, I doubt that there is any correlation there, but we haven't looked at that.

DR. BRECHER: Thank you, Nancy.

We'll now move into the public comment period. Is there anyone who would like to make

public comments? We would hope that these would be related to the discussions that have occurred this morning. Perhaps maybe there are some industrial reps that might want to comment or maybe not?

[No response.]

DR. BRECHER: All right. Then, we're going to move into a discussion period, then, and I'd like to, given my possible conflict of interest in this field of platelet products, I'd like to step down as chair in this discussion of possible resolutions about platelets and defer to Mark Skinner, who has agreed to be acting chair for this discussion.

MR. SKINNER: Lola?

DR. LOPES: I wanted to ask, my concern in asking the question about whether or not the process could be speeded up by different kinds of consideration by our regulatory agency wasn't really based on the cost of the study that we saw presented in dollars, but the cost of that study is two years in time, even once the funding is obtained. I think that the time issue is really

just as important, maybe much more important than the money issue, particularly when we hear things like Dr. Sandler's situation just yesterday.

And I think that in the basic sciences, we're sort of used to taking results from Europe and considering them just as good as our own results. Obviously, where there are differences in methods, that has to be taken into account, and the issue would be buffy coat platelets versus the way we get them is certainly a serious one. But I am concerned when time slips away and where, in fact, deaths could result because of the absence of available platelets.

MR. SKINNER: Jerry?

DR. SANDLER: Yes. I'd like to follow up on that. I hadn't thought too much about that line, but the standard that we're listen to, with P values and other things, is are platelets at 7 days, and under certain conditions, equivalent to a nice, fresh platelet? And the standard from where I think a lot of clinicians are right now is a 7-day platelet versus nothing, versus absolutely

nothing, nothing and two years.

So I don't know where we can find common ground between two years and a lot of money and something now for the standard of, when there's nothing available, isn't this better than nothing? I don't know where we could find. But if anyone with regulatory authority wants to address that and suggests that something like the model we did with the HTLV3 test or with other things when we had, well, this isn't perfect, but let's not interfere with the good. That kind of thinking might get us forward with this.

MR. SKINNER: Merlyn?

DR. SAYERS: I say this at risk of sounding anecdotal, but like all politics all blood is local, so let me tell you something about the experience in the Dallas-Forth Worth metroplex. We had to increase apheresis platelet production this year by 30 percent to make up for the move away from whole blood-derived platelets to apheresis platelets, and there certainly are limits on how much you can increase recruitment of apheresis

donors.

I think there is urgency in ensuring that there is some way of maintaining whole blood-derived platelets as an inventory product for platelet transfusion-dependent individuals. Only yesterday we were discussing whether it would be possible to maintain fresh frozen plasma inventories exclusively from male donors. And it wouldn't surprise me if in two years' time we weren't sitting around this table discussing whether it was possible to maintain platelet inventories exclusively from male donors.

And I'd to think that we were staring that possibility in the face without having rescued whole blood-derived platelets as an inventory product that we could transfuse to patients.

MR. SKINNER: John?

DR. PENNER: Just a question maybe to Mark. Do you think we have enough data present to indicate that the safety of the 7-day versus the 5-day is not an issue and that the efficacy is particularly not an issue, from wearing all of your

hats?

DR. BRECHER: Well, I think that would be a professional opinion and not a factual answer, and I hesitate to answer that.

DR. PENNER: Can you cite some information that would--

DR. BRECHER: There is substantial data for the clinical efficacy of platelets out to seven days and, for example, the FDA has cleared two bags to go out to seven days. And so then the question becomes is it a question of safety with bacterial contamination?

The majority of deaths related to bacterial contamination are gram-negative organisms. Most of those, in fact, all of those gram-negative organisms, grow very quickly and would be expected to be picked up with an early culture. And so I think that providing an early culture will interdict a majority of fatalities related to contaminated platelets. And so I think a combination of the two, using bags that have proven efficacy out to seven days with an early

culture, makes a lot of sense and probably I think that argument is a very strong one.

DR. PENNER: I can understand Jay's considerations here, but since there's no real standardization now for the 5-day program, with respect to contamination, why not take the next leap, based on the information we have available to us, to accept a 7-day platelet outdating, with information then to be obtained as we proceed, recognizing that there's sufficient information out there to indicate that the risk factors are really not significant.

DR. SKINNER: Matt?

Harvey?

DR. KLEIN: We've heard a lot of issues about platelets and platelet storage, and I'd just like to make a couple of points that I think we don't want to lose track of in our discussion; one is that virtually all apheresis platelets are now being tested by a licensed culture method. Now, it's quality control. You can call it what you want, but one of the issues with safety I think has

been addressed.

If you want to do a longer study and more scientifically valid study, I think that's terrific, and in two years we may have the answer, and we may have 7-day platelets based on that study, and I think that would be terrific. But to my mind, the real pressing issue is the issue of whole blood-derived platelets because they're being tested now by a number of methods that, in my opinion, and I think the data support this, are useless. I think the dipsticks are terrific for diabetic urine and for swimming pools and not much good for anything else.

[Laughter.]

DR. KLEIN: And so what's happening is that we're not using those platelets.

The Blood Products Advisory Committee felt, and I think they're on record as saying this, that the in vitro data for storage of pooled whole blood-derived platelets was sufficient and what we really needed was some CCI data. We've heard this morning a well-designed study with some CCI data,

and I think now perhaps this Committee needs to think about whether there's a way to move forward so that the issue of availability for a product that seems quite effective and could be tested so that the issue of bacterial contamination could be dealt with is readily available, and I think we need to do something about that as maybe one of the first items on our agenda.

DR. HOLMBERG: Harvey, in those comments, was there the beginning of a formulation of a Committee recommendation?

DR. KLEIN: There might be. I might need a little time to formulate that, but I've been thinking about that.

DR. SKINNER: Matt?

DR. KUEHNERT: I think that there are data existing, I mean, as we speak, with 100-percent QC. I mean, clearly, there are data. The problem is that it's being collected in a nonstandardized fashion, and it makes it very, very messy to try to derive any conclusions from it, but you have the quick and perhaps the dirty there, where you could

at least look at some of these issues, although I think the study would be the final word on it.

Unfortunately, on that issue of the study, the silence from the manufacturers are deafening. And in looking at a combination of "carrot and stick," as far as trying to entice people to the table, I really don't know what all the issues are, but it seems both for manufacturers that already have products licensed, but also manufacturers who might be considering them, you'd think there'd be some incentive to participate in the study. And I don't know if storage specimens or isolates would help or not, but certainly I think there are value to those, and there would be value in thinking through what incentives might be brought to bear on the manufacturers trying to make it happen.

The other issue I wanted to mention after Jaro's talk, was the issue about absolute risk as sort of the point of comparison here, and I don't have an issue with that, and setting it at 1 in 10,000, but it's just interesting that, in looking at bacteria, if you compare it to a standard such

as viruses, where you'd say, "Well, for all viruses, we're going to accept a 1 in 10,000 standard," it would seem a little bit strange to put all the viruses in one category.

So I would just encourage FDA to consider the virulence of organisms as sort of a relative consideration in this. We've heard about P. acnes having very little evidence of clinical significance. On the other hand, you have gram negatives which have incredible clinical significance, and you would not want to accept a 1 in 10,000 risk.

So I think there's a spectrum here that needs to be considered. I, again, don't have a problem with the absolute risk idea, but I think it needs to be tempered by consideration of what organisms there are.

DR. SKINNER: Celso and then Dr. Heaton.

DR. BIANCO: As part of the discussion, the points that Harvey raised, we maybe, and probably unintentionally, have created a loophole for the manufacturers. We allowed them or gave

them an approval for a quality control assay without even a protocol for quality control in the package insert. So we have taken away the incentive for further study or even support for these studies. We have been begging the manufacturers for support for these studies and all that.

And even we heard today from Dr. Nemo that even the NIH or NHLBI would not be too excited if the manufacturers didn't contribute something to those studies.

So we've been stuck for a couple of years, and in a certain way we have to find a solution and correct that, and probably these may not become the routine, but probably we should try to put together all the data we have. And we heard spectacular data from Nancy Heddle today, in terms of the pool, that could address the issue of, at least for the five days, for the random donor platelet, with some rules like don't mix blood types or things like that.

And we have also there is a lot of data

about the 7-day platelet, particularly from the manufacturers that got the bags approved, that could be a tremendous help to maintain the supplies, to rationalize the approaches. I think the protocol presented by FDA--and I'm sorry, Jay, if I said it in a way as if we didn't need to do anything--the protocol presented by FDA is tremendously improved, but it's not there yet. We still are not going to break the logjam with the type of studies proposed. We have to find a shortcut to kind of correct that loophole and move ahead.

DR. SKINNER: Dr. Heaton?

DR. HEATON: Yes, I have a number of comments on different issues--three major areas:

First, buffy coat platelets. One of the key issues in introducing any development is that you shouldn't compromise the product that you're already making. And when you make buffy coat platelets, what you do is you extract about 20 to 30 mL of the red cells, and you pull the platelets out of these red cells. You also have to hold the

red cells for about 12 to 24 hours in order to maximize your platelet recovery.

So the net effect is the buffy coat platelet method is very good for platelets, but it slightly compromises and reduces the quality of red cells. You lose 15 percent of them, and you remove all of the reticular sites, which are the very best red cells that you want your red cell recipient to receive. So the first issue you have to consider in the buffy coat platelets is don't damage the red cells.

The second issue is that buffy coat platelets do result in slightly better platelet quality. They survive, and I think I've done the only U.S. isotope studies reported to date on buffy coat platelets, and you get a better quality platelet. It's been used in Europe for nearly 20 years in a pooled fashion. I don't believe there's been a single report of a bacterially contaminated buffy coat platelet concentrate during that 20-year period, and they perform very, very well clinically. So they're a good product, but mostly

they've been used with leukoreduction and mostly they've been used for no more than five days. So there's very little operating experience with seven-day buffy coat platelets.

To shift to a different topic, the issue of the licensing trial. As a manufacturer, the numbers that we look at, this is a very expensive trial. You saw $7.5 million of direct cost. You could add another 50 percent to that of indirect costs with tracking, data monitoring, multiple centers. So let's say you do add that, and you're at now a $10- to $11-million trial. There's about 1.5 million to 2 million platelet doses a year, and you're going to spend $10 million to get that product approved. It's very hard for a manufacturer to get terribly enthusiastic about funding that sort of trial for that size of market.

Lastly, there's the issue of competition. The first manufacturer does not want to end up proposing a trial that allows the second manufacturer to run along behind it. And after you've spent $10 million, they spend $200,000 and

then get approved. So there's a competitive issue, as well as a cost issue.

So one recommendation I believe that we should make is that there is an appropriate funding mechanism to support studies of this type. NHLBI does have an RFP mechanism. It allows open competitive bidding to pursue grants, to allow the developments of the scientific improvements that would result in improved safety and a defined product. And I believe that this Committee should seriously consider asking the Secretary to recommend that monies be available through an RFP, in a competitive funding mechanism, to allow the pursuit of studies to support 7-day bacterially screened platelet concentrates.

Thank you.

DR. SKINNER: John?

DR. PENNER: Since we're talking about a time line, and again we've already--for this business of two to three years before we'd see any action, I'll ask Jay if there would be a possibility for having a loophole sufficient for

provision of 7-day platelets for those areas which are compromised by lack of platelets, in other words, a platelet deficiency in an area that would allow 7-day platelets to be made available from other areas that might be outdating them, to be able to provide them, so Jerry wouldn't go down the tube with having to explain why he let his patients die because they didn't have platelets.

DR. SKINNER: Jerry?

DR. SAYERS: Yes, if I might just make a slightly alternative thought or a parallel thought, and that would be a way to have a national reserve that could be tapped if it were necessary. In other words, the logic would be that you would use this, and you'd have a certain reserve of platelets that would be able to go to 7 days and that that could be tapped if there were need.

DR. SKINNER: Jay?

DR. EPSTEIN: You're suggesting that currently outdating platelets go into the reserve for two days and that if not needed they then are discarded, but if needed they can be used? I'm not

exactly sure what the proposal is, but--

DR. SAYERS: That's one logistical situation. Alternatively, we're talking about freezing an awful lot of blood and just having it in various places. An alternative would be that from those units that are collected specially, you could have platelets that would be part of the national reserve in some way, and when you need blood you'd be able to tap it.

DR. EPSTEIN: Well, I think we're flirting with a lot of difficult issues. I mean, putting unapproved products into national stockpiles has all kinds of issues that have arisen in other contexts like smallpox vaccine and vaccinia-immune globulin. There are a whole host of issues that go with that idea.

As far as allowing products to be approved, but only in regions with shortage, that's a very difficult thing to contemplate because products are allowed to move freely in commerce, and how do you make that decision because today's approved area becomes tomorrow's not approved area

because it's a moving target.

I think also the idea of linking a safety and efficacy standard, modifying a safety and efficacy standard based on an argument of supply is inherently difficult because supply conditions are a moving target determined by multiple factors that have nothing to do with safety and efficacy of a product. So I'm a little reluctant to think that that's the right avenue to go.

I think what we do have to focus on, though, is what constitutes the adequate scientific basis to determine that a 7-day platelet or a pooled, prestorage-pooled 5-day or 7-day platelet is safe and effective. That's the crux of the issue, and I think that these other things, although we need to consider global impacts, they're really confounders in thinking through the basic question; the question of what are the adequate scientific data?

DR. BIANCO: But there is one point there that I'd like you to address, Jay, is that there are two apheresis platelet containers that have

been approved for seven days. What is holding them back is release, bacterial contamination tests that is approved for release. That's the only thing holding it. Could that be dealt with?

DR. SKINNER: Jay?

DR. EPSTEIN: Well, I think that we could decide that the current available culture methods approved for quality control are adequate, but that's not the current position of the Agency, but it is a thing that's open to debate.

Just to clarify where we stand, we understand that the industry has argued that it's on-label use of the product is simply 100-percent quality control. It's not quite what FDA envisioned, for a set of reasons, including the absence of well-standardized procedures for the cultures, such as when is it done, what is the volume, does it include an anaerobic culture or not, and it's restricted to leukocyte-reduced units. Whereas, there might be a desire to apply it to nonleukocyte-reduced units.

So there are a number of things that were

not evaluated or validated that have caused FDA to think that it's not yet approvable as a release test, above and beyond the issue of establishing negative and positive predictive value.

So I think that those points need further discussion before we would take the step of saying, well, these were approved as QC, and as long as you're using an approved QC test, it's fine. So there's a debate to be had on that point.

I would also suggest that we can potentially consider separating out performance information from the current use of these products from the issue of establishing residual risk. We could regard residual risk as a research question, just as it was done for residual risk of virus transmission, and we could perhaps draw the line and say that if we get post-approval data on the field performance of these tests, perhaps that's sufficient for us to label them in some way that can make some meaningful claim about the quality of a released unit.

It would be a claim short of establishing

their sensitivity or residual risk, but a claim nonetheless. So that's another way that we could potentially get at this if there are coherent data from the field use that could be brought to the Agency.

So I think that there are a number of pathways, but that we shouldn't ignore the fact that the manufacturers did not come forward with standard procedures for the quality control sufficient to address the variety of schemes of use that are in place and that that's part of the problem.

I see the heads are shaking, but there's no standard whether you need an anaerobic culture, there's no standard on the volume, there's high variability of the time to sampling.

DR. KLEINMAN: Isn't there a standard on the volume?

DR. EPSTEIN: If you would look at the survey of current practices, the answer is, I don't see a standard.

DR. KLEINMAN: But the product inserts

have standards.

DR. EPSTEIN: The product inserts do have standards for the volumes used. That is correct.

DR. SKINNER: Celso?

DR. BIANCO: Jay, I like what you've said, but what I would suggest is that, in considering the lack of knowledge in those standards, a lot of things can be determined by past experience and common sense. I'd love to see a guidance from FDA saying those are the parameters, a draft guidance that we can all review, discuss, see how competitive it is with the things we do, but that would then move things ahead without having to directly depend on the manufacturers that obviously feel very comfortable in the position they are, where we are paying them for what they have, and they don't have to invest a penny to get anything else.

DR. SKINNER: I'd like to take a couple more comments and then maybe start some of the people that have suggested ideas for recommendations to start moving to consensus.

So, Dr. Heaton, I don't know if you've begun to conceptualize yours, and I think maybe Harvey has.

Jerry asked to speak and then Mark.

DR. HOLMBERG: I just wanted to make sure that the Committee reflected back to our last time that we met because at that last meeting we did go through and identify a lot of the variables. It was very amazing, even though we did have a survey provided by the American Association of Blood Banks, to hear the variations to the procedures. And even to hear people talk about the different validations that they had done for the different surrogate testing, it's all over the place. But even as far as the culturing, there was a lot of variance there.

DR. SKINNER: Mark?

DR. BRECHER: I really welcome Jay's last suggestion. I think that that would be very attractive to the blood-banking industry; that if we went with a quality control test, and I don't know whether you need the anaerobic bottle--that

can be debated--but at least an aerobic culture, and then extending to seven days with approved bags, with a postmarketing surveillance by the blood manufacturers, say, on outdated units, that maybe 80 percent of outdated units would be recultured, I think that that would be a major advance, and we could move on very quickly to 7-day platelets.

DR. SKINNER: Matt?

DR. KUEHNERT: I'd like Dr. Brecher to comment on the importance of anaerobic culture. I read the paper that was included in the packet, and it looked like that there was some benefit to having an anaerobic culture and particularly for certain organisms. So I'd just like to hear his thoughts.

DR. BRECHER: Actually, I look upon it two ways:

One, we really don't know what the significance of anaerobic bacteria are. There are several case reports in the literature of P. acnes associated with features, although it's not clear

whether those patients would have had fevers without having received the P. acnes because fevers are common in the recipient patient population.

There is one death from a clostridium reported from England that was not isolated in an aerobic culture. There is one case in the entire world's literature. The anaerobic bottles do allow for a faster pick-up, with some organisms that we would normally think of as aerobic organisms. And so there is some advantage to that.

There is also an advantage to setting up two culture bottles, rather than one, which may largely reflect the fact that you're using greater volumes.

DR. KUEHNERT: Particularly, was it Strep viridans that--

DR. BRECHER: Strep viridans.

DR. KUEHNERT: I mean, it was very impressive how much quicker the anaerobic--

DR. BRECHER: Right. The culture time went down from I think 40 hours to 20 hours, something on that order.

DR. KUEHNERT: And that could be the difference between picking it up and not. So I just wanted to make that point.

DR. BRECHER: That's correct. And, in fact, if you think about study design for spiking studies of prepooled random platelets, in my mind it doesn't really make a difference whether you spike into a single random platelet and then pool them together and test them versus you've prepooled your platelets and then put a few bacteria in the bag. I think the real scientific question is can you pick up low levels of bacteria in a matrix of pooled platelets?

And that is the paper that the Committee has in front of it, and I'm not sure that spiking into a single bag is really adding that much more.

DR. SKINNER: Jay?

DR. EPSTEIN: Thanks, Mark. I want to challenge one point there. Certainly, you're correct whether you spike one bag in pool or spike the pool doesn't matter. What matters is the level of that spike. But the problem is that spiking at

10 CFU per mL may be spiking at a much higher level than would actually occur with a low-level contaminated single unit pooled on Day 1.

See, the problem here is that we don't actually know what the level of contamination is, clinically. We've conjectured that it might be anywhere from 1 CFU mL to 100 CFU per mL. But for argument's sake, if it's 10 CFU per mL, then you pool 5 units, you're down to the range where you might or might not get enough bacteria in your sample to grow it out.

So that's why validation of the analytical sensitivity of the culture system after the dilution effect is important. So that, in other words, if you spiked one bag at 10 CFU per mL and then pooled, that's not the same thing as spiking the pool at 10 CFU per mL. So I think that the experiment that was reported in the study kind of misses the mark, which is the effect of reducing the level of contamination due to the pooling.

DR. BRECHER: Right. I understand what you're saying, Jay. However, the two culture

systems were approved basically based on data in the 10 to 100 CFU range.

DR. EPSTEIN: That's the very point. If they were approved in the 10 to 100 CFU per mL range, and we know that those tests were highly stressed at the 10 CFU level, we did not pick up all organisms and there was some missed rate for beta strep and for staff epidermidis, and if you then dilute a sample before it's had time to grow out by pooling soon after collection, you may in fact be below the analytical sensitivity that was validated for those products. And there might be ways to offset that either from a larger volume sample or from waiting longer than one day to take the sample for culture. But that's the thing that has not yet been studied and verified.

DR. BRECHER: Right. But at least in this particular study, the recovered CFUs per mL was 5 CFUs per mL. So, even with a dilution factor, it still would have been in that 10 to 100.

DR. EPSTEIN: Ten divided by five is less than five.

DR. BRECHER: Yes, and 100 divided by 5 is 20.

[Laughter.]

DR. EPSTEIN: Right, but really--

DR. SKINNER: I'm not sure the Committee, at this point, is going to actually design what the correct study is, but I am hearing three what I think are kind of distinct areas for possible resolution, and one is the whole blood-derived platelet issue that Harvey mentioned, there is the importance of the funding issue and who is participating that Dr. Heaton mentioned, and then the more general issue that a lot of people have mentioned is that it's a very long time table that we're talking about--two years--and is there a way, although the FDA has made a lot of progress, is there a way that we can further urge expediting and bringing this about.

So I would like to move the Committee to thinking about a resolution, if somebody's ready to put one of those concepts up on the board in the interest of time. And maybe while that's actually

occurring, we'll take a couple more comments.

DR. PENNER: Just kind of to Jay. Admittedly, the more definitive study everybody's interested in, but I gather there's a kind of a consensus that it seems reasonable to get a 7-day platelet on board very quickly. And you had mentioned the possibility of at least some preliminary data or sufficient data to move that along a little faster, and Mark was mentioning it too.

Could you guide us in what might be reasonable to provide some earlier information or early enough study that we could at least accept the 7-day, while the more definitive study is ongoing, perhaps would be, through it, would become available in 2 to 3 years?

DR. EPSTEIN: I can't make policy at the meeting.

DR. PENNER: Guidance--

DR. EPSTEIN: I think what I've already suggested is the guidance, which is that one could propose that quality control with an approved test,

coupled with Phase 4 data, might be a sufficient mechanism, but again I'm not taking that as an FDA position. I think that we will have to consider that and look at the pros and conservation.

DR. SKINNER: Dr. Heaton, are you at a point where you are ready to articulate a--

MS. LIPTON: I was just going to say to Jay's point, I think that we don't want to design. I think what we want to say is go back and think about some things, but I don't think we should, you know, dictate to FDA, "This is how you have to do it."

I think you've heard the comments, and I think something generically that talks about the need to shorten the time frame to make these products available and to solve both the 7-day platelet storage and then the issue of right now we have an inferior product in whole-blood derived, and they're a very significant and important part of transfusion practice. And I think you've heard that. I don't think we should sit around and design it or dictate specifically how this happens.

DR. BRECHER: Matt?

DR. KUEHNERT: I mean, I would agree, just really highlighting, you know, the dual system we have now between whole blood derived and apheresis platelet testing is important. But the post-marketing surveillance is, I think, sort of a breakthrough here, and I don't think we need to design that either, except to say that, you know, I think the AABB Task Force has taken some strides in trying to, in fact, create a structure for this as far as having common case definitions, which I think is critical here and essential to have. What is a true positive? What is a false positive? And same for true and false negatives for calculating sensitivity and specificity but also, you know, making sure that there are common data elements.

So, I mean, I don't think the whole thing needs to be designed here as much as just a summary of what needs to happen to allow post-marketing surveillance to yield any useful data.

[Pause.]

MR. SKINNER: I think of the three

sections I mentioned, people are working on drafting them, so unless there's anything else, there will be a lull for a moment.

[Pause.]

MR. SKINNER: In the interest of utilizing our time efficiently, there are three kind of pieces of this resolution coming together. So I think they're going to go ahead and work on it and maybe try to harmonize them into one, and we'll take the resolution up immediately after lunch. But because it still is a little bit before noon, I believe Larry had something--did you want to bring it up at this point instead of bringing it up at the end of the day? So we're going to shift topics. I believe this is a different topic.

MR. ALLEN: First of all, I wanted to say that trust is--in my community, "trust" is a fragile word. "Knowledge" is a powerful word universally, but once again, in my community it's not.

With that knowledge in my community, for some reason there's still a lot of distrust. And

we're trying to figure out how we can help people who believe that there's always an underlying reason for us being there. Blood donations is an example.

On the other hand, when helping hands show up and immediately show their uneasiness once they see you, we are left to show them the same. If there is no working history, who takes the first step regarding trust--the dysfunctional community or the entity coming in saying they want to help?

The only solution I have is to find individuals within both structures who are willing to let their guards down, roll up their sleeves and try. My solution is only on the planning stage in my community; however, in the hemophilia community, in spite of all the history, there is some trust again.

You have heard both sides come together yesterday regarding issues regarding adequate reimbursement and the heavy burden of the 20-percent co-pay. I ask this committee to assist the community and those providing life-saving

products and care with these issues. I realize some of these issues must go before Congress, but I would like to draft a recommendation to assist those groups who are trying to find a level playing field.

So I do have a recommendation if you want to put it up at some point.

DR. BRECHER: Why don't we have that typed up over lunch? We can all look at that as well.

I'm not sure if--to stay on schedule, we have speakers that have flights to meet, so after lunch probably what we're going to do is go ahead with the speakers and then come back to these resolutions at the end of the day. But why don't we have that typed up so we can all look at that over lunch.

Okay. With that, let's break for lunch. We'll be back in one hour at 1 o'clock.

[Luncheon recess at 12:00 p.m.]

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

[1:03 p.m.]

MR. SKINNER: If the committee members can look at the handout that was placed at each of your places at lunch, there are two statements, and the Chair has decided that they want to go ahead and try to finish, as expeditiously as possible, the bacterial contamination discussion. So there are--I said two. There are three, I guess. The three pieces of the resolution that I talked about earlier relating to whole blood platelets, looking at the process to expedite the time frame...I guess the point I was trying to say is we need the committee to start reading through those quickly, and then we can take them up, merge them into one, or they can be passed stand-alone.

DR. BRECHER: As I see it, there are basically three resolutions here. One deals principally with whole blood derived platelets, which is the first one. The second one and the third one deal with apheresis platelets. One is aimed at funding the large study, and the other one

is aimed at short-cutting the large study. So I think two and three will need to be combined in some form and then say in the absence of this scenario not happening, then the committee would recommend the other option occur.

DR. KUEHNERT: The other issue is that the second resolution sort of focuses on the need for screening while the last one focuses on the seven-day storage issue. So you could combine--add a "whereas" about seven-day storage to the second one, and then combine the resolution together.

DR. BRECHER: Okay.

MR. SKINNER: Why don't we hold that thought, and maybe you can be thinking about that as well. And we'll take the one that's up on the board, which is the first one on your printout, first.

Harvey, I think you offered this. Do you want to make any comments?

DR. KLEIN: The only comment I want to make is I don't have any pride of authorship in the words. What I really wanted to do is put the

concept up there for people and see if the committee agrees with the concept, then you can determine if you want to wordsmith that any way you like.

MR. SKINNER: Karen?

MS. LIPTON: This is a small thing, but rather than the blood bank industry, it could be called "the transfusion medicine community," because it really was pushed by the transfusion medicine clinicians.

MR. SKINNER: We're taking the first resolution up first. So comments on what's on the screen? This one appears to be a resolution that can stand alone by itself, and then we'll look at combining the other two together. Are there any comments, discussion, amendments to this one? Jay?

DR. EPSTEIN: First, a minor comment. The current bacteriological tests are not licensed tests. They're approved devices. So if you would change "a licensed" to "an approved."

DR. BRECHER: Jerry?

DR. SANDLER: I think it's very thoughtful

and it captures the sense of what I was hoping we would be moving toward.

MR. SKINNER: Any other--Merlyn?

DR. SAYERS: Could we have an approved quality control method for the detection of contamination by bacteria?

DR. EPSTEIN: I would prefer that. Actually I was mulling over a similar thing. Not actually approved for release even though they're de facto being used that way. But at least it's true that they are being used by an approved quality control method.

MR. SKINNER: So that would be down in the last paragraph?

DR. EPSTEIN: The first sentence, point 1.

MR. SKINNER: Any other comments or discussion? Are we ready to vote on this one?

DR. KUEHNERT: Well, just a--well, I think it will all get fixed. That's okay. Minor stuff. That's okey. No factual issues I have. It's all grammatical.

MR. SKINNER: I believe the staff has the

ability to make grammatical, technical--

DR. KUEHNERT: That's fine.

MR. SKINNER: --clean-up kinds of errors.

All in favor, signify by raising your hand.

[A show of hands.]

MR. SKINNER: Opposed?

[No response.]

MR. SKINNER: The recommendation passes unanimously.

We'll shift to the next two recommendations, and I don't know that we have the ability to post them both on screen together, but I think you should read them both and think about them together because there probably is a need to think about combining them if the committee's interest is in passing both. They deal with slightly different concepts or aspects of the same issue. Jay?

DR. EPSTEIN: Mark, I do have a concern. You know, we heard the McMaster data, and it's certainly impressive. But we also heard the

comment made that the data were confounded by pooling alloimmune patients with low CCIs in an analysis of non-inferiority. And the problem with that is that it dilutes the power of the non-inferiority test.

If you were, in fact, to omit the subjects that had alloimmunization and low CCI, the power drops to the point where the conclusion would not have been sustained. Now, that's not an analysis that was presented at this meeting, but my general point here is that there are, in fact, a few caveats about Item 3.

MR. SKINNER: Item 3 of the first resolution?

DR. EPSTEIN: Of the first resolution. Now, I'm okay with the ultimate conclusion, you know, urging strategies to expedite licensure. And, of course, I'm an ex officio, not a voting member. But I just wonder if, you know--I mean, we didn't do a critical analysis of data here.

DR. KLEIN: I would agree with that, Jay. I'd like to make one point, and that is, although

the term has been thrown around very loosely, we didn't hear any data about alloimmunization. What we heard data about was patients who were relatively refractory, as you see in every clinical trial, whether they were alloimmunized or whether they were sick, had a big spleen, all of the other things.

Now, that may not be relevant in terms of the analysis of the data. They didn't respond to the platelet transfusion. But it's not because they were alloimmunized. We don't have those data.

DR. EPSTEIN: Well, putting it another way, if you drop the subjects with CCIs less than or equal to 4.5, you lose the significance, in other words, you lose the ability to reject the null hypothesis, and you do not conclude non-inferiority, and the reason is smaller numbers. So that's sort of the point.

And then I would make a like point about the European data. We heard about European data, but we certainly didn't review European data. So I'm just trying to add a note of caution that, you

know, we've sort of taken at face value a number of things that the committee did not critically review.

DR. KLEIN: That's correct. The European data, by and large, published, however, for buffy coats. There aren't any data, as you know, for platelet-rich plasma.

DR. EPSTEIN: But, again, they were not reviewed by this committee.

DR. BIANCO: Jay, would you be happy if in the conclusion here that "The committee urges DHHS to adopt strategies to expedite review and potential licensure," or something qualifying that, leaving the judgment to--the final judgment to those that are going to address this.

DR. EPSTEIN: What I was going to propose--I agree, Celso--is that "The committee urges DHHS to adopt strategies to expedite licensure of a pre-storage pooled WBDP component for transfusion based on a critical review of the available information." So I'm proposing a friendly amendment.

DR. BIANCO: How could I disagree with that?

MR. SKINNER: We need to get on the second resolution.

DR. EPSTEIN: The suggestion is to add the phrase "based on a critical review of the available information."

DR. HOLMBERG: A point of order here. Are we amending the already passed--okay. Then we'll have to vote on that again.

MR. SKINNER: So we are still on the first resolution.

DR. LOPES: Jay, that was "based on a critical review of the data"--

DR. EPSTEIN: "...of the available information."

MR. SKINNER: Are there any additional comments or discussion?

[No response.]

MR. SKINNER: So, in essence, the committee is reconsidering its previous action and is going to adopt the resolution as it's now

currently reworded. We'll take it all in one motion. All those in favor, signify by raising your hand?

[A show of hands.]

MR. SKINNER: Opposed, raise your hand.

[No response.]

MR. SKINNER: The resolution as now re-amended is adopted.

Now moving on to the two additional resolutions--

DR. BRECHER: Mark, for the record, I am a voting member, but I am going to abstain from these votes.

MR. SKINNER: The record will reflect that.

DR. HOLMBERG: And I also believe, Dr. Heaton, did you abstain?

DR. HEATON: I did abstain, yes.

MR. SKINNER: Now moving on to the two additional resolutions, is there a suggestion on how to combine them first so we consider them as one? Or do we want to take them--okay, Karen?

MS. LIPTON: Yes, I think, in talking to Matt, we were both thinking that we could take all the "whereas" clauses and combine them with the two, one dealing with really the whole blood derived and then the seven-day apheresis platelets, so that the "whereas" clause would have the three paragraphs and then take the two paragraphs from the next page under seven-day apheresis.

The other thing is I would just like to suggest an amendment to the second paragraph that starts, "The Blood Bank Industry," and instead say "The transfusion medicine community has adopted a voluntary standard"--and technically what it is--"that requires the implementation of methods to limit and detect bacterial contamination." That is what the standard says.

MR. SKINNER: We need a moment for a lot of them to catch up. We may have to offer your rewording for the blood bank industry. So we'll now have five "whereas" clauses and two recommendations that will all flow in order?

DR. SAYERS: Mark, can I speak to the

first "whereas"?

MR. SKINNER: Yes, Merlyn.

DR. SAYERS: I don't agree with that one. We didn't concluded what we say we concluded there, and we certainly didn't decide what incidence of a risk justifies the adjective "significant." So as an alternative, could we say that, "We recognize that bacterial contamination of room temperature stored platelets is a risk for transfusion recipients"?

DR. BRECHER: Although in January 2003, this committee did reach that conclusion based on a lot more presentations. So we could say we "previously concluded."

DR. SAYERS: Well, are we relating this to what we've discussed at this meeting?

MR. SKINNER: That's why I was wondering if we needed a preamble to this resolution to tie it into the continuity of our last resolutions as well.

DR. SAYERS: Mark, I think you're conflicted on this one.

DR. HEATON: As the proposer of this, I would support Mark's statement. We did previously conclude that this was a major risk, and it is--

DR. SAYERS: Andy, I think you're conflicted on this one.

[Laughter.]

DR. KUEHNERT: Merlyn, what rewording are you suggesting?

DR. SAYERS: My rewording was, "The ACBSA recognizes that bacterial contamination of room temperature stored platelets is a risk of transfusion."

DR. KUEHNERT: Okay. Am I conflicted because I've written a paper on it, or--I mean, it is the largest risk to transfusion, infectious complication, period.

MR. SKINNER: So what's the committee's pleasure? We can take a specific amendment and propose it and take a vote on an amendment if there isn't a general consensus. The language stands as--

DR. PENNER: The language is "concluded"

versus--what word do you want to use instead of "concluded"?

DR. SAYERS: "Recognizes."

DR. PENNER: If we recognize or we conclude, I don't get an awful lot of variation in the interpretation.

DR. SAYERS: I think my only point was that whenever we see these decisions, they seem to have a temporal relationship to what we have done over these two days. And reading "concluded" there sounds to me like we reviewed the literature, we heard presentations. That was something that we did historically and not something that we did currently.

DR. PENNER: Again, as was mentioned before, "previously." "The ACBSA previously has concluded"--

MR. SKINNER: And we've often started resolutions something like "Consistent with recommendations," "previous recommendations of the committee." We can start with phraseology of that nature, the type of historical testimony.

DR. PENNER: I would think that would at least incur this continuity.

DR. SAYERS: I'll go for that.

MR. SKINNER: So adding at the beginning of the first "whereas," "Consistent with recommendations of the"--"previous recommendations of the committee, the ACBSA has concluded..."?

DR. SAYERS: No. "Consistent with previous recommendations that concluded"--because, you know, we didn't conclude this time.

MR. SKINNER: Okay. Let them catch up, and then we'll have them put it up there.

Are there other comments?

DR. BIANCO: And the word "infectious." We mean "infectious risks of blood transfusion." We still have errors.

DR. KUEHNERT: That's an important addition, yes.

MR. SKINNER: Okay. We'll let our typist catch up.

Any other discussion on the first "whereas"?

[No response.]

MR. SKINNER: Why don't we just walk--

DR. SANDLER: Do we want to distinguish that from apheresis platelets in any way? In other words, some people would regard a platelet concentrate--I understand the technical FDA language is it is a--but some people might confuse whole blood platelets at apheresis platelets. This doesn't necessarily separate those two at this point. We are talking about whole blood derived platelets, aren't we, in this? Not necessarily? Okay.

MR. SKINNER: Okay. And then there is--before "risks," "remaining infectious risks of blood transfusion" in the first "whereas," the very end of the first "whereas," right there. Okay.

Moving on to the second "whereas," any comments or suggestions there?

[No response.]

MR. SKINNER: The third?

[No response.]

MR. SKINNER: The fourth?

[No response.]

MR. SKINNER: The final "whereas" clause?

[No response.]

MR. SKINNER: So now--

DR. GOMPERTS: Mark, the fourth bullet point, "The current availability," that's not quite clear. It's really inadequate supply, the current status of inadequate availability. It just needs to be qualified.

MR. SKINNER: Okay.

DR. GOMPERTS: That's better.

MR. SKINNER: Any other comments on the fourth or the fifth bullet?

[No response.]

MR. SKINNER: Okay. If we can scroll the screen down now to the two conclusion/recommendation statements, please.

DR. KUEHNERT: There might be sort of a non sequitur here now that we've merged things in between the fifth bullet of the "whereas" and what then follows. I'll wait for them to scroll back up.

MR. SKINNER: Celso?

DR. BIANCO: Do we need the fifth bullet if we are going to the recommendation of the second paragraph? I think that there is a lot of change in the FDA current thinking going on at this time.

MS. LIPTON: I agree, we looked at that. My only concern is that the study issues were not just cost, and the solutions seems to suggest that cost is the problem, but that there's also a timing issue. There's a sense that even if someone were to fully fund the study that's proposed, two years is too long. So we can phrase it differently, but I do think there's a sense that study design has to somehow expedite this. Originally--I didn't draft this, but I thought we could take it out. But we need something in there, I believe.

MR. SKINNER: Jay?

DR. EPSTEIN: Just a couple of points.

First of all, on this bullet, I don't think like the word "delay" because it implies that one can or ought to do better than one potentially can. I mean, "it would necessitate two years to

accomplish" is a more neutral way of putting it. You know, anytime FDA does the right thing, we're always accused of having taken too long, and that's not always a legitimate point of view if indeed we did the right thing. So, you know, the debate is over whether those are necessary studies, and I don't think we should color it by calling it "delay" because it begs the question of whether they're necessary and appropriate studies. So at a minimum, I think we should just say "would require at least two years."

Also, I'm concerned that Karen's wording of the second bullet was not recorded correctly. I heard you say "methods to limit and detect bacterial contamination." I believe that's not--those are not the words that are up there. Yes, so we need to come back up to the second bullet.

MR. SKINNER: Instead of "delay," what would you like?

[Inaudible comments off microphone.]

DR. BIANCO: Instead of "required" a

second time, because it looks awkward, "it would take at least two years to implement."

DR. SAYERS: Is that the FDA's current thinking? Is that the fifth?

You know, I think it's just an opinion that it's a large and expensive study. I mean--

DR. EPSTEIN: By what standard? I mean, this really bothers me. I have to be very blunt here. We're talking about the leading infectious cause of fatality from transfusion, and we're saying that the estimated costs, which, quite frankly, are all over the map, are too great. But compared to what?

The real problem here is not the magnitude. The real problem is that the funding source has not been identified. And it's not that the resources don't exist in our system either. So I have a lot of trouble, you know, framing this as a barrier based on the study design. And I just want to say for the record that when the issue of cost is taken momentarily off the table, anytime this issue has been discussed, the value and

critical design, scientific design of the study have been minimally contentious. Or scientists agree that these are the right things to do. They only disagree based on how they're situated as to whether they can afford. And I think that we are substantially muddying the debate by saying that the study is inherently flawed, which is the implication of this bullet.

I would rather that we focused on encouraging the Secretary to find the ways and means than get into the debate of that the study design itself is an inherent flaw or an inherent obstacle, because it's conditional on what resources are mobilized.

MR. SKINNER: I'm wondering if perhaps some more neutral wording might--

DR. PENNER: Could you say an "extensive study" instead of "large and expensive"?

MR. SKINNER: What about something like, you know, "based on information presented to the committee, the committee is concerned about the time and the cost of the study," or that "the time

and the cost required to achieve seven-day platelets" and, you know, "encourages" or "wants to look for ways to expedite"--something along those lines. I mean, taking note of the information that we heard, but not pointing blame at anyone in particular. Lola?

DR. LOPES: Do we even have to mention cost?

DR. KUEHNERT: Yes, I thought the issue was about timing. We could take out "large and expensive" and just say, "The FDA's current thinking"--

MS. LIPTON: Why can't it just be "the currently proposed study"? Because that's what's on the table, is a current--

DR. EPSTEIN: I agree with that also because, you know, after all, even the initial study design that was presented more than a year ago at the BPAC was endorsed by the BPAC. And as Karen, I think, is correctly suggesting, even the current design is itself a cooperative work product of an AABB task group and the FDA.

Again, the perspective that I'm taking is when money is taken off the table, scientists seem to agree on the value of the protocol as designed. We shouldn't be impugning the protocol. We should be focusing on the practical issues.

DR. BIANCO: As suggested by Lola, the currently proposed study would take at least two years to complete.

DR. KUEHNERT: Can you undelete what--because it described the study. I thought that was nice.

So "The currently proposed study of bacterial screening for release control would take at least two years to implement." So delete all the way to "of."

"Release control of seven-day stored platelets would take..."

DR. SAYERS: I think this is a study that needs completion rather than implementation. I think "two years to complete" rather than "to implement."

MR. SKINNER: Other comments on the fifth

"whereas"?

[No response.]

MR. SKINNER: If we can go back up then briefly to the second "whereas," I think we needed to check the wording.

MS. LIPTON: "Limit and detect." Actually, it's "limit" first and then "detect." It is "limit and detect." We don't have a "reduce" in the standard.

DR. EPSTEIN: Take out the words "the risk." "Limit and detect bacterial contamination."

MR. SKINNER: The "whereas" clauses, are we comfortable at this point on all of them?

[No response.]

MR. SKINNER: Okay. There's two committee recommendations now, if we can scroll back down. Comments on the recommendations?

DR. KUEHNERT: There needs to be some qualifier, I feel like, on the second resolution. It's sort of--because I think the spirit of it is while the first avenue is being pursued, the second one needs to be pursued in conjunction. But I'm

not getting the wording right, so maybe someone else can put that in a thought.

MR. SKINNER: George, did you want to make a comment?

DR. NEMO: Nemo, NHLBI. Just in your first bullet, it's not clear to me what you mean by "support industry application to develop." Is that the blood collection industry or is that the manufacturers of the test? I don't know exactly what you had in mind there. Probably better just to be put "application" or leave it open.

DR. SAYERS: And can we delete "through existing mechanisms"? Because we're certainly not going to get funding through non-existent mechanisms.

[Laughter.]

DR. EPSTEIN: Merlyn, I'm not sure that's actually true. I think that the point is that non-routine mechanisms could be used.

DR. SAYERS: Well, then maybe it should be "routine." Oh, I see what you mean, Jay.

DR. EPSTEIN: Existing mechanisms are the

routine ones. We can wordsmith this, but I think the suggestion here is we might need to use--you know, of course, existing legal mechanisms, but they could be non-routine ones.

DR. SAYERS: Maybe we need creative mechanisms.

MR. SKINNER: Any other comments? Are we comfortable with those the way they are worded now?

DR. EPSTEIN: Well, I suggest that we strike the words "through existing mechanisms," just "that will allow availability of funds..."

I also think there's some peculiar redundancy "to support application"--I guess that might be plural--"to develop a bacterial screening test capable of allowing the development"--no. The test itself is a test for release suitable. So "to develop a bacterial screening test suitable for release testing of platelets in routine practice."

MR. SKINNER: You want me to get rid of "capable of allowing the development."

DR. EPSTEIN: Yes.

MR. SKINNER: To just rid of everything

all the way to "bacterial."

DR. EPSTEIN: Yes, the revised sentence would say, "to support application to develop a bacterial screening test suitable for release testing of platelets in routine practice."

DR. SAYERS: Are we on the second recommendation there?

MR. SKINNER: If there's no other comments on the first recommendation, the second, the two committee recommendations here. So the first paragraph. Are we comfortable with the language of the first now?

[No response.]

MR. SKINNER: Okay. On to the second, Merlyn?

DR. SAYERS: As far as the second one goes, lest we ever think DHHS could move backward, I propose, "The committee recommends that DHHS plan to make seven-day apheresis platelets available..."

MR. SKINNER: Jay, did you have a comment?

DR. EPSTEIN: Yes, I think that it's too specific a proposal because people may yet come up

with alternatives. And I think we simply should call for, you know, creative strategies to expedite approval of seven-day apheresis platelets and, you know, let the relevant parties work out the best strategies. Why do we need to be so directive that this is the answer?

MR. SKINNER: Is there consensus about that change? Okay.

DR. BIANCO: Would you remove even "post-marketing surveillance," Jay?

DR. EPSTEIN: Yes. I think that the core of the recommendation is to recommend that the Secretary, you know, find ways to expedite approval of seven-day platelets?

MR. SKINNER: One option could be to leave that in there as an example of what the committee's interested in them specifically considering.

DR. EPSTEIN: Well, we could say, "For example, the following scheme might be considered." But it troubles me for the committee to be so directive.

MR. SKINNER: What's the committee's

pleasure?

DR. BIANCO: It's that we like the proposal, Jay.

DR. EPSTEIN: I hear you. I even made it.

MR. SKINNER: George, did you have another comment?

DR. NEMO: I don't know the answer to this, but, again, in your first bullet you state "to develop a bacterial screening test. Do you want to be more specific, "culture," or anybody could come to the table?

DR. PENNER: If we leave it just as "bacterial screening suitable for release testing," that's all you need. You don't need "test" in there. That's redundant. Just remove it. Yes, "bacterial screening."

DR. SAYERS: In that second bullet, "apheresis" is now spelled with a concession to the Greeks, which is a concession we have made before.

[Laughter.]

MR. SKINNER: I think after "platelets available," then I think we need a "for example" or

an "e.g." I don't know what the committee's pleasure is.

DR. EPSTEIN: I think that what we're looking for is "encouraging DHHS to consider alternatives that would expedite."

DR. KUEHNERT: The point here is that the first bullet might take, you know, as it says in the "whereas," at least two years to complete. So, in the meantime, you know, these--in the interim, so maybe prefacing by "in the interim to a"--"in the interim to a funded study, the committee recommends that"--does that sound reasonable?

MR. SKINNER: Jay?

DR. EPSTEIN: My proposed wording would be, "The committee recommends that DHHS consider alternatives that could expedite the availability of seven-day dated platelets."

MS. LIPTON: Is it really an alternative? I mean, I don't know that it's an alternative. If they go along parallel tracks, we're okay with that.

DR. EPSTEIN: Well, let's be careful. You

know, an approval is a discrete action. I'm not sure I really follow the idea. You know, we could have these products under IND, but nobody wants them under IND.

MS. LIPTON: But it's not just bacterial culturing we're talking about in the first one. We're talking about possibly even point of release or all sorts of different kinds of tests. And so I think that that's a very nicely stated support of we really want this field to move along and could apply to everything. The second one is very specific to the timing issue relative to seven-day platelets.

DR. EPSTEIN: I'm sorry, but how is that different than expediting the approval of seven-day platelets? Isn't that the same thing? Because you're not talking about--the idea of "in the interim" bothers me because in the interim the products are either under IND or, if they're licensed, it's not the interim. You're at the end game. So what is this interim? I don't see an interim here. I think what we're calling for is an

expedited pathway to licensure.

DR. KUEHNERT: Why not say that?

DR. EPSTEIN: That's what I'm trying to say.

[Laughter.]

DR. EPSTEIN: That the committee recommends DHHS consider alternatives that could expedite the approval of seven-day dated platelets. And I'm not sure why you would limit it to apheresis, incidentally.

DR. HOLMBERG: Jay, where did you have "expedite"?

DR. EPSTEIN: "The committee recommended that DHHS consider alternative strategies that could expedite licensure of seven-day platelets."

DR. KUEHNERT: How about prefacing it with "in addition"? Because you're trying to set the two off from each other, right? Isn't it in addition to the first bullet? "In addition, the committee recommends that DHHS consider alternatives"--or is that--I mean--

DR. EPSTEIN: I don't have a problem with

saying "in addition."

DR. KUEHNERT: Because you're trying to set the two apart.

DR. BIANCO: I think Jay's suggesting deleting the remainder of the sentence.

DR. HOLMBERG: Is that true, Jay, drop--

DR. EPSTEIN: That would be my preference, but there was an alternative motion, I believe, by Mark Skinner to cite an example.

MR. SKINNER: It wasn't really a motion. I was trying to bring the group to consensus. So it's whatever the committee's pleasure is. Some want it to stay?

The consensus seems to be take out the balance, then. Jay, wasn't your intent to delete that sentence as well?

DR. EPSTEIN: Yes, it was.

MR. SKINNER: Delete the final sentence.

DR. SAYERS: Mark, one other thing. You know, unless DHHS is in the same category as the royal "we," that should be "considers."

DR. KUEHNERT: It reads very nicely and

concisely, but the key here is "considers more timely alternative"--isn't that the--it needs to be an alternative because it's more timely than the first, right? So wouldn't "more timely alternative strategies" capture the--

DR. EPSTEIN: Isn't that what expediting means?

DR. KUEHNERT: Expedite..well--

MS. LIPTON: It depends on if we thought that the combined study protocol is expedited already. I mean, I think that's part of the--

DR. BIANCO: I think that we have to keep separate there are two things there. One is support for research that extends to several methods, to several things that would resolve the issues. The other one is a potential solution or alternative, as Jay said, that could resolve from the immediate point of view the issue with the fact that the release--there are no release tests, that the only tests that we have are tests for quality control.

DR. PENNER: Couldn't we say "expedite in

a more timely manner licensure of seven-day platelets" and that would get that sense in?

MR. SKINNER: How about, "The committee recommends that DHHS note the urgency and to consider alternative strategies"?

DR. SAYERS: How about "prompt alternative strategies" or "considers promptly alternative strategies"?

MR. SKINNER: Jay?

DR. EPSTEIN: Or add the words "more timely" after "expedite"--"expedite more timely licensure."

MR. SKINNER: There seems to be consensus.

DR. LINDEN: Well, but more timely than what?

DR. EPSTEIN: Two years. In other words, it refers to the previous sentence.

Again, it presumes that two years is untimely. We could say "more rapidly."

DR. LINDEN: Well, the current thinking back in the last bullet.

[Pause.]

MR. SKINNER: Are we comfortable with the way it reads? Do we want to leave the "timely" in?

DR. BIANCO: I think that we can be more direct and reduce the time.

DR. EPSTEIN: How about "that could expedite licensure of seven-day platelets in significantly less than two years?"

VOICES: Yes.

MR. SKINNER: Another improvement.

DR. SANDLER: I would suggest that adding "in addition" seems to fit.

MR. SKINNER: Yes, we're still missing the--before the second recommendation, I think there was going to be a transition, "In addition, the committee recommends that..."

Any other comments on these? Then are we ready to move to a vote, if we can go back to the top?

DR. SANDLER: Why is "agency" used? Because it's the Department of Health and Human Services. What's "the agency"? I know what the Department is. I don't know what "agency" is.

And if they get a capital letter, shouldn't we? We're the committee. We could get a capital. if you're going to give them a capital D, we could get a capital C.

MR. SKINNER: Speaking of being timely, we do need to move us along. Okay. Let's go back to the--

DR. PENNER: "The committee recommends" in that second part. If you're going to be consistent, "In addition, the committee recommends that DHHS consider"--"recommends that" and then "consider alternative..."

MR. SKINNER: And I think in terms of the grammatical and the formatting corrections, the staff does have the authority to make us correct.

MR. : Yes, and we do better on Mondays.

MR. SKINNER: Okay. Let's go back to the top, and we'll all read it from the top down, and then if it captured everything, we'll move to a vote.

"Whereas, consistent with previous

recommendations of the committee, the Advisory Committee on Blood Safety and Availability has concluded that bacterial contamination of room temperature stored platelet concentrates represents one of the most significant remaining infectious risks of blood transfusion.

"The transfusion medicine community has adopted a voluntary standard that requires the implementation of methods to limit and detect bacterial contamination in all platelet components.

"There is now inconsistent practice in the application of currently available bacterial screening test application and recognizes that public health would be improved by the availability of a release test approved for this purpose:

"Given the current inadequate supply of platelets, the committee recognizes the need for seven-day storage of platelets to meet patients' needs.

"The current proposed study of bacterial screening for release control of seven-day stored platelets would take at least two years to

complete.

"The committee recommends to the Secretary of DHHS that the Department support the use of grant or contract funding that would allow availability of funds to support applications to develop bacterial screening suitable for release testing of platelets for use in routine practice.

"In addition, the committee recommends that DHHS consider alternative strategies that could expedite licensure of seven-day platelets in significantly less than two years."

DR. PENNER: The title doesn't include the release of seven-day apheresis platelets when you combine the two, the bacterial detection of platelet concentrates and release of seven-day platelets.

MR. SKINNER: Jay?

DR. EPSTEIN: I would suggest that we put all three topics together, that it's bacterial detection of platelet concentrates, approval of pre-storage platelets, and seven-day dating of platelets, and that the previously voted

recommendation regarding pooled platelets can come down as a second section to the current section. It just needs to start as "whereas" again. "Whereas, the committee has heard evidence that," dah, dah, dah. Because these are related issues. I mean, you know, the Holy Grail as far as whole blood is concerned is to have a pre-storage pooled, cultured, seven-day dated platelet. These are related issues. They really are under one heading.

MR. SKINNER: Okay. So then the motion before the committee then would be to approve the language that I just read, and as a part of that, then, as a follow-on, add the second resolution so they all tie together into one single document.

DR. EPSTEIN: And to correct the title.

MR. SKINNER: The title would reflect the merger of the two. Any other discussion?

[No response.]

MR. SKINNER: We're ready for a vote. All those in favor, raise your hand, please.

[A show of hands.]

MR. SKINNER: Opposed?

[No response.]

MR. SKINNER: Any abstentions? Mark is abstaining. And Dr. Heaton as well. So with two abstentions noted, the resolution passes. Thank you.

I think Mark is back.

DR. BRECHER: Thank you, Mark. We're behind schedule. I know there is another resolution on reimbursement, but I'd like to, Larry, put that off until the end and move ahead with the hepatitis because I know people have planes to catch.

So we're going to begin with the epidemiology of hepatitis B. Miriam Alter from the CDC.

[Pause.]

DR. ALTER: Sorry for the slight delay. I'm Miriam Alter. I'm with the Division of Viral Hepatitis at the CDC in Atlanta, and I want to thank Dr. Holmberg for inviting me today to represent CDC and give a presentation on the epidemiology of HBV infection and the status and

progress that we've made in its prevention.

I happened to come in during the lunch hour when most of you were not in the room, and I thought, "Gee, I wonder who's on the committee now." And I looked around and I looked at the labels, and I thought, "All of my friends are here." And I'm delighted that I know so many people in the room, and it's very nice to see everyone again.

What I hope to cover in the next 30 minutes is a brief overview of the clinical features and natural history of HBV infection; screening and diagnostic markers and how they apply to the donor setting; the trends in the epidemiology of HBV infection and today who is at greatest risk and who acquires infection; and progress that we've made in prevention.

As most of you probably know, the incubation period for hepatitis B virus infection averages about 8 to 12 weeks, with a range of between 6 and 26 weeks, and this is usually symptomatic infection. Jaundice or illness,

symptoms associated with illness, are indirectly related to age. So the younger you are when you get infected, the less likely you are to develop symptoms. So clinical illness occurs in less than 10 percent of infants and young children, but in about 30 to 50 percent of older children, adolescents, and adults.

Case fatality rate is low, but, again, chronic infection, the most serious consequence of HBV, is also inversely related to age. Infants who acquire their infection from their mothers at the time of birth have about a 90-percent chance of becoming chronically infected; whereas, adolescents and adults have about a 2- to 6-percent chance of developing chronic infection.

Chronic infection can lead to chronic hepatitis, cirrhosis, and primary liver cancer, and the premature mortality from chronic liver disease related to HBV infection is about 15 to 25 percent.

The markers of HBV infection, to those of us who deal with them all the time, seem--I wouldn't call them simple, but we're used to it,

and we deal with it easily; whereas, to those who do not deal with it routinely on a day-to-day basis, it can be extremely complicated.

The serologic markers for HBV infection have been used for decades to define the epidemiology and natural history of hepatitis B. So without any nucleic acid testing, we actually have been very successful in diagnosing and monitoring this infection and in being able to study it. This is unlike hepatitis C.

There are three antigen antibody systems associated with HBV: hepatitis B surface antigen and its corresponding antibody; antibody to hepatitis B core, which is a serologic marker, and its corresponding antigen, hepatitis B core antigen, which does not circulate in serum, there is no free core antigen, it's found only in the liver, and there are no tests; and then the third antigen antibody system is hepatitis B E antigen and its corresponding antibody anti-HBE. Not all of these are necessary for either screening or even for diagnosis.

And then more recently, actually in the last decade, hepatitis B virus DNA has become useful primarily as a marker in predicting--in management of chronic hepatitis B in patients for the purposes of determining therapy. But all of the--and for monitoring therapy, the response to therapy. But, interestingly, all of the transmission studies and epidemiology that we have defined in the U.S. has been based on serologic markers.

So I'm going to discuss those first--well, actually, I'm going to discuss hepatitis B surface antigen first and its implications in the course of HBV infection. It is the first serologic marker to become detectable. It appears an average of 6 to 8 weeks after exposure, usually about 1 to 3 weeks before ALT becomes--liver enzymes become abnormal, and about 3 to 5 weeks before the onset of symptoms or jaundice.

HBSAG reaches a peak in terms of the level at which it's detect during the acute stage of infection, and in people who recover, it declines

to undetectable levels at variable periods during the first 6 months, but the recovery is defined by its absence. However, it usually remains detectible in chronically infected persons, and as I mentioned before, it is the marker that we've used for transmission and other epidemiologic studies.

Now, how does HBV DNA fit into this pattern? It is detected prior to HBsAG. It is detected two to five weeks after infection, up to 40 days before HBsAG, and you're going to be hearing the very specifics of this from Mike Busch. It tends to rise slowly at relatively low levels during this pre-seroconversion phase or period during early infection called the sero-negative period, and it's also detected during chronic infection. So it obviously reflects the presence of virus as does HBsAG, the surface antigen.

Anti-core, or antibody hepatitis B core antigen appears after HBsAG, usually at the onset of symptoms or ALT abnormalities. At this point it's predominantly the IgM class which is fine for

the purposes of diagnostics, but for the purposes of blood screening, IgM anti-core is not routinely used. Anti-core remains detectible lifelong and the tests are formatted so that by six months after onset of infection the predominant type of anti-core detected is total of IgG anti-core. Therefore, newly-acquired from remote infection can be distinguished based on this marker. It is present in both resolved and chronic infections, and as I mentioned, usually lifelong, remains detectible lifelong.

There is one pattern, however, that will cause anybody who screens for any purpose a lot of confusion, and that's the pattern of isolated anti-core when it's present all by itself. It can mean many different things. It turns out that this pattern occurs in about 2 percent of asymptomatic persons tested for HBV and the frequency with which it's detected is usually directly related to the frequency of infection. So in a really low risk population like blood donors, it could be as low as .1 percent, perhaps even lower, but in a high-risk

prevalence population like injecting drug users, you might find 20 percent of them have isolated anti-core. This could be a marker of--this could be false positivity, and in many instance it is, and HBV DNA is detected in less than 10 percent.

So anti-core alone can reflect waning of neutralizing antibody, do it's present in a person who recovers from infection. But it can also represent very low levels of virus, which would have to be extremely low if HBsAG is not detectible. But as I pointed out, at least several studies have shown that HBV DNA is detected in less than 10 percent.

In people who recover, neutralizing antibody develops, anti-HBS. It develops during recovery. It's detectible along with anti-core, although in up to 20 percent of patients, it can become undetectable over the lifetime of the individual even though they've recovered from infection, although if they were to be exposed, in general they would show an anamnestic response. This is also the antibody that marks evidence of

immunization. That's when it is found alone. However, after successful immunization it too can become undetectable in about 40 percent of individuals by five years even though protection from disease continues.

So here's the pattern of these markers. If you are negative for all of them, then you're assumed to be susceptible. If you're positive only for HBV DNA, that indicates early acute infection in the pre-seroconversion or what's being called the window period for people, I guess, born after, I don't know--who came into the field after 1970, I guess, and I'll explain that in a minute. Then there's early acute infection which we used to define as HBsAG positive alone, but if you're also testing for HBV DNA, that too will be present. In either acute or chronic infection, you'll find both markers of virus, HBV DNA and HBsAG as well as anti-core.

So after the early phase is completed, during the next few months you'll be positive for both markers as well as antibody, and if you're

chronically infected you'll generally be positive for both markers. If you're recovered and you're immune, you'll have both antibodies and--I realize have chronic infection there twice. That's the most straightforward of the explanations.

Then you come up with different combinations of markers that are much more difficult to interpret, especially in asymptomatic individuals. So you have an individual who has isolated anti-core. If they also have HBV DNA then that's likely a chronic infection. On the other hand, if their HBV DNA is negative, then this could be a resolving infection if their IgM class is predominant. It could be a past infection if their IgG class is predominant, it could be a false positive, which those of us who do studies or screen low prevalence populations are very familiar with.

If anti-HBs is detected alone and it's greater than--or it's at least 10 milli-International Units per mL, it indicates evidence of immunization. One note of caution,

that there have been reports of individuals who test transiently HBsAG positive with no other markers during the first three weeks after receiving a dose hepatitis B vaccine, which needless to say does present some problems for the donor and the blood collection establishments.

So putting that all together, as you can see, while HBsAG is the first marker to become detectible, usually 4 to 8 weeks after exposure, HBV DNA is pre-dates HBsAG. Anti-core, on the other hand, becomes detectible usually by the onset of symptoms and remains detectible even in individuals who recover. HBsAG declines becomes undetectable, and anti-HBs develops.

There is a period of time in here which those of us in the field before HIV--that's what it is, it's HIV that changed the nature of our terminology, but pre-HIV this was the window period. In between HBsAG disappearing and anti-HBs developing, the only marker detectible was IgM anti-core or total anti-core. That was the window period. So it's been redefined. If you become

chronically infected you remain HBsAG positive, anti-core positive and HBV DNA positive.

In the United States there are estimated about 73,000 newly acquired infections in 2003. this number is actually based on a model that counts for both under reporting as well as asymptomatic infections by coming age-specific incidents of acute disease and overall prevalence of infection, or prevalence of infection by age. So we know what we have, how much infection has occurred in the past. We know how much is reported, and you can put the two together to determine how much really occurred as opposed to just reported. Of these, about 21,000 were estimated to have been clinically ill. There were less than 300 deaths and about 4,400 developed chronic infection.

Overall, about 5 percent of the population has been infected and this has not changed very much in the last 20 to 30 years. Our chronic infection rate also hasn't changed all that dramatically, and it's been about a million to a

million and a quarter. About 4 to 14 percent of newly-diagnosed chronic liver disease is related to HBV and about 3,000 to 5,000 deaths per year are related to HBV chronic liver disease complications.

Hepatitis B virus infection is blood-borne and sexually transmitted and it's vaccine preventable. It is spread by exposure to blood or body fluids containing blood that have the virus in it through modes of transmission are either percutaneous in which the skin is pierced with something contaminated with infectious blood or mucous membranes are contaminated with infectious blood or other body fluids containing blood.

The primary risk factors injecting drug use, and actually high-risk sexual activity including sex with an infected partner or having unprotected sex with multiple partners, or being a man who has sex with men. Perinatal infection, which used to be a significant cause of infections in the United States, has dramatically been reduced due to screening and vaccination programs.

But the issues today are essentially the

risk from transfusions. This slide was adapted from Harvey Alter and a variety of others who have taken it and played with it over the years, but keeping in mind that sensitive for HBsAG have been employed since the early '70s, and the most dramatic impact that we've ever had on post-transfusion hepatitis, whether it be B or C, was the change from a mixed commercial and volunteer donor base to all volunteer donors.

In the mid to late 1980s anti-core was introduced as a surrogate for non-A/non-B hepatitis or hepatitis C, but obviously that also reduced any residual risk from HBV, as did actually the introduction of screening and tests for HIV.

As you can see on the graph, essentially this measures zero because it's virtually impossible to do surveillance on such a rare event, and in fact, when we look at risk factors among reported cases of acute hepatitis B in the United States, in our sentinel surveillance system, which we often use to validate changes in particularly sensitive risk factors because the interviewing is

excellent as is the diagnosis and reporting, we find that there have been no transfusion associated cases for over a decade, whereas, obviously risk factors involving sexual activity and injecting drug use continued to play a large role. However, we do get patients reported who indicate or report to us during the interview that they have been transfused during the exposure period. And if we look at those--this is in our sentinel counties which has varied between four and six counties during the 1982 to 2003, we find that during this period 51 patients with acute hepatitis B reported that they had been transfused during the exposure period, and we were able to confirm that. Eight of them had other risk factors. Two of them were injecting drug users. Three had an infected sex partner, and three of them had had sex with multiple partners, unprotected sex with multiple partners, and their donors were negative. 43, however, reported no other risk factors.

You'll note that the proportion of these or most of these occurred in the 1980s and has

declined substantially since then, and we haven't had any cases reporting a transfusion since 1998. However, in the '90s, the latter half of the '90s, we implemented follow up of anyone reporting a transfusion who didn't have another risk factor, and convinced the blood collection centers to follow up on the donors, and we found that of these three cases, all of the donors were serologically negative for HBV. In addition, all three cases had been hospitalized during the incubation period, one for the entire six months prior to onset of illness.

Which brings us to the problem of rare events and detecting them. Like other blood-borne infections we get outbreaks related to particular sources that can't be identified among sporadic cases, and nosocomial transmission of HBV and actually HCV have become increasingly recognized over the last few years in the United States. Because these are so rare relative to other sources for infection, we're not able to identify them unless there is a cluster. They have been

primarily due to unsafe injection practices. I'm only bringing this up so that you'll understand the difficulties in doing surveillance and coming up with any numbers in terms of residual cases.

But because of sentinel counties, because we are dealing with a rare event and the sentinel counties has a limited population, we decided to implement what we call enhanced surveillance of all cases reported nationally throughout the United States to our National Notifiable Diseases Surveillance System at CDC. There were about 7,000 cases of acute hepatitis B reported, of which 49 indicated on the form that the state submitted to CDC that they had received a transfusion in the six weeks to six months before onset of their disease. They are clinically apparent cases. Of these, the majority either didn't have acute hepatitis, had never been transfused or had not transfused during the potential exposure period, had been a long time in the past. Only 10 of them were actually acute cases that had a transfusion during the appropriate incubation period, and of these, one had a donor

who was infected, based on calling them back for additional testing, and it was a single donor pre-seroconversion.

I'd like to point out that doing this kind of thing is not routine and that it requires the collaboration between us, the state, the local health department and whoever's collecting the blood and transfusing it in that particular area. I'm not quite sure actually what the SOP for following up on a potential transfusion-associated case, but it likely requires more than one case, and we might want to revisit that.

Anyway, overall, HBV prevention and control in this country involves donor screening by history for particular risk factors as well as serologic testing--keep in mind that as I'm talking about the epidemiology of hepatitis B in the general population, at least 50 percent of the cases have histories that would be deferred by screening were they to go and donate--obviously, infection control practices, and then since the early 1980s, vaccination, which now includes

routines infant, children and adolescents, and in addition to that, adults at high risk.

As you can see, the vaccine was licensed in 1981 and became available in '82, at which point we recommended it for high-risk adults, and the incidence continued to rise. Finally, in the late '80s we began to develop a strategy for routine childhood immunization which was implemented in 1992, along with a mandate that health care workers be offered vaccine by their employers free of charge. The incidence in the 1990s has decreased dramatically, and finally by the end of '90s the Advisory Committee on Immunization Practices had recommended that any person under the age of 18 not previously vaccinated should receive vaccine.

Here's what has happened. There has been a 98 percent decline in the incidence of hepatitis B in children under 12, a 90 percent decline in adolescents, and a 65 percent decline in adults. Primary reason for this has been the successful implementation of routine childhood immunization, and in fact by 2000, 90 percent of children 19 to

35 months old had received all three doses of the vaccine. You have to understand that as they get vaccinated it also protects--as they get older, it protects them from being infected when they're adolescents.

We have not been quite as successful with our adolescent and high-risk adult programs, but our adolescent program is coming along. About 60 percent have been vaccinated in the 13- to 15-year old group, and I imagine blood collection establishments are happy to hear that as this is now going to be the new donors, the donors of the new decade.

In the general population of adults--and I chose 30 to 60 years old because this does represent a large proportion of donors--natural immunity overall is present in about 5 percent. White have a prevalence of about 4 percent, blacks about 15 percent, and Asians about 60 to 80 percent, depending on where they were born and where their parents were born.

However, we've been very unsuccessful in

getting high-risk adults vaccinated, the individuals who are truly at risk. While health care and public safety workers such as firefighters, et cetera, have high vaccine coverage, they represent a small proportion of cases. The largest proportion of cases, represented by those with high-risk behaviors, less than 10 percent have received vaccine.

This shows you that disease is very rare in both males and females, in young children and even now in adolescence, whereas the highest incidence is actually in men in their 30s, and the age at which hepatitis B occurs has been increasing as the cohorts who have been vaccinated become older. So that rather than new cases peaking in the 20s, it now peaks in the 30s, and we're seeing a resurgence of men predominating.

Today sexual activity accounts for most cases. Heterosexual activity between men and women, about 40 percent. Men who have sex with men, 26 percent; injecting drug use, about 17 percent. And only in about 14 percent can no

specific source of infection be identified.

Unfortunately, almost two-thirds of these cases could have been prevented if they had been offered vaccination as has been recommended, because they either had a known infected contact, which means they should have been offered vaccine, or in most cases they had a history of being treated at an STD clinic or having been incarcerated, and in both of those settings we've been recommending routine vaccination for almost 20 years.

In order to implement a successful vaccination program in either children or adults, there are certain elements that are required for success, and in our childhood program we have the evidence-based recommendations which we also have an adult program. We have an implementation strategy and we have partners to carry it out. We have provider and patient education, again, for both children and adults. For children we have vaccine purchase so the public sector provides vaccine free of charge. We also have an

infrastructure for vaccine delivery since children routinely get other immunizations. But for adults, we don't have those two elements, and that is one of the biggest barriers to a successful high-risk adult immunization program in which we are focusing on integrating vaccination into existing programs that see high risk adults, because that's where the disease is, and that's where we need to focus our vaccination efforts. By so doing, we will have a much more rapid decline in the incidence of disease that will then catch up to our very successful childhood and adolescent programs.

Thank you very much.

DR. BRECHER: Thank you, Miriam.

It's now open for comments and questions. Harvey?

DR. KLEIN: Miriam, do you have any data on treatment response?

DR. ALTER: In individuals for whom it's indicated, which has to do with the level of HBV DNA, high ALTs, high level of HBV DNA, I think about 40 percent actually lose HBe antigen. They

may stay surface antigen, but their HBV DNA declines and they become e-antigen negative, which is what the hematologists want to see since e-antigen is so highly predictive of more severe disease.

DR. BIANCO: Miriam, very nice presentation. Miriam, there is substantial discrepancy between the numbers that you have and that you could attribute to transfusion, and the numbers that we see in the calculations of risk that have been done by several people. You want to talk a little bit about it? Because that's the issue we are going to have to deal in a little while.

DR. ALTER: It's probably somewhere in the middle I would think. As I tried to emphasize, it is still a rare event. We're talking a handful, so to speak, of infections, even with an estimate, related to transfusions. And it's such a rare event that it's impossible for us to pick it up. In fact, I'm really surprised we picked up the one that we did.

For HCV we didn't pick up any infections. We hadn't picked up any infections I think since 1994 related to transfusion that we could confirm, even though NAT didn't go into effect until 1999. So it's really numbers. It's a rare event, and when it's a rare event it's very difficult for us to pick up because not everyone reports, not everyone gets sick, not everyone--so there are all of these issues along the line that you have to take into account as to why we don't actually see the cases.

DR. HEATON: Miriam, from a public health perspective, is post-transfusion hepatitis B reportable by state regulation or by CDC regulation?

DR. ALTER: Well, first, CDC doesn't regulate reporting. The states regulate reporting, and then the states voluntarily report to CDC, and everyone cooperates. But acute hepatitis B is reportable, and in most states HBsAG positivity is reportable. But then we know that under reporting is a notorious problem.

DR. BRECHER: Merlyn?

DR. SAYERS: Miriam, you said that 50 percent of donors that had hepatitis B would be deferred on history. But then if only 50 percent of adults that have hepatitis B are symptomatic and then the majority of them don't know that it's hepatitis B, how does 50 percent efficacy of donor history work?

DR. ALTER: Actually, I might have--or you might have misunderstood the point I was making. I might have miscommunicated it. What I was trying to say was that 50 percent of people who get acute hepatitis B have histories that would be deferable by the donor's screening questionnaire, history questionnaire. Therefore, if they went to donate, and they responded yes that they had been an injecting drug user, they were a man who had had sex with men, or they had had contact with an infected household member or sex partner in the previous, in this case, six months, then they would be deferred from donation before they even got a chance to be tested. So I was just extrapolating

that to the fact that when you test the donor population, you presumably are going to have at least a 50 percent lower incidence in the donor population than you would expect in the general population.

DR. BRECHER: We have to start wrapping this up. I just want to take one more comment from Mike Busch.

DR. BUSCH: Thanks. Just two comments. One, in terms of the disparity between the projected risk and the observed cases, part of it is that the assumptions in all the modeling are that people are infectious from the date of exposure to HBV until they detect surface antigen, or during that entire phase. Even with single donation now we can only detect very low levels of HBV DNA in a portion of that portion.

So the question, Miriam, is with vaccination we're seeing data from other countries like Taiwan, and actually two I think of the four or five yield cases in the U.S. clinical trials were people who had been vaccinated, in whom very

low levels of DNA were detected in the absence of clinical and even detectible surface antigen. So just the question is what do we know about sort of the infectivity or the rate of breakthrough vaccine infections, whether there's consideration of boosting people? Essentially these look like there's a fairly high rate at which previously vaccinated people may still get exposed and transiently infected, but do they develop--might they be infectious and do they have a much reduced risk of clinical disease and carrier status?

DR. ALTER: The rate at which there are, quote "breakthrough infections" are so rare, particularly in this country, that I don't think it's going to be an issue. Doesn't mean you don't have to screen, but presumably you would detect that individual if in fact they were transiently viremic, but none of these individuals have transmitted in the community setting. None of them have developed chronic infection, and there have actually been very few even detected in the long-term follow-up study. So it's only been in

places with extremely high rates of infection like the Gambia and a few other places where they've actually had these anti-core seroconversions. We've had a few of them, but very few.

So it appears, at least for now--what, 20 years--we're still not recommending a booster. We will continue to follow our vaccinated cohorts as well as the literature from other parts of the world to determine if and when a booster is needed.

DR. BRECHER: Thank you very much, Miriam. Okay, quick question from Jeanne.

DR. LINDEN: Just to follow up on Andy's question, in our state the reporting of hepatitis cases is similar to what other states use. There's a question that says, "Has this patient been transfused recently?" And, you know, they check it off yes or no, but just because a patient's been transfused doesn't mean that the transfusion was the source of the infection. And our particular state has the resources to investigate that, but a lot of states may not look into it. So you don't really know if it's transfusion associated or not.

So that may not ever really be determined. That may or may not be reported to CDC, so a lot of cases you really don't know.

DR. ALTER: That was sort of the point of the follow up that I presented, was how few of them who actually say--doesn't mean that they don't occur--they obviously do occur. They must occur because there are infections in the donor population. But they're a very rare event. And unfortunately, surveillance data is not going to be the way to capture them.

DR. BRECHER: Thank you very much, Miriam.

We're going to change the order because of flight considerations, and Paul Holland is going to be our next speaker, talking about Hepatitis B Virus Nucleic Acid Amplification.

DR. HOLLAND: Thank you. I want to thank Dr. Holmberg for inviting me to speak today. I would point out that I do not have a conflict of interest in that I do not work at any blood center at the moment, and I'm not a paid consultant for either of the companies that make NAT tests, Roche

or Chiron.

My focus is primarily on the use of hepatitis B DNA NAT testing at a blood center, and so most of my comments will be related to that.

Basically, NAT has the power to identify some infectious donations during the infectious part of the sero-negative window period, and that could actually be the window period as now defined, meaning before the appearance of antibody to core, and of course before the appearance of hepatitis B surface antigen.

In many countries of the world the power of NAT is also of value where there are low-level carriers, where hepatitis B is endemic, and while that is not a big consideration at the moment, it can be more important in the future as we make efforts to get more non-Caucasians to be blood donors especially among minorities who were born in or whose parents were born in parts of the world where hepatitis B is endemic. And we'll not talk about it today, but NAT has the potential of being useful in reentering donors who are falsely

positive for some of our serologic tests.

These are data from the Red Study as published by Schreiber and Busch, et al. from several years ago, but I think they're very instructive in that they looked at the best estimates at the time in 1996 of the risk versus the safety, is what I'm going to focus on, of a blood or plasma transfusion from a volunteer, meaning an unpaid repeat United States donor. And at that point in time the risk was estimated for HIV 1 and 2, about 1 in 676,000; for hepatitis C, about 1 in 125,000; for hepatitis V was 1 in 66,000, or 10 times the risk of HIV and twice the risk of hepatitis C.

And yet our focus then was on implementation of NAT tests for this virus and this virus, but not for this virus. I can never resist the opportunity to point out that in fact if we turn this around and talk about the safety of a unit of blood from this particular kind of donor--and we're going to come back to this issue of a repeat donor--for HIV is 99.999 percent safe.

It's certainly safer than the medical and surgical procedures for which we actually give transfusions. I would venture to say it's even safer than the air we breathe, the water we drink and some of the politicians we elect.

[Laughter.]

DR. HOLLAND: In any case, the focus was on NAT testing for this virus and this virus, and so we're going to contrast the findings in a moment of the pickup from the Roche clinical trial, of which I was a part, for hepatitis B DNA.

I'm sure Mike Busch will show you the slide again, and/or Sue Stramer. This is really a slide from them. It's based upon seroconversion panels from source plasma individuals. The point of this slide is that you have hepatitis B DNA appearing days or weeks before surface antigen is detectible. And of course, individuals who would provide plasma or other blood components for transfusion in this period of time are probably infectious if not actually infectious. Certainly if you give a unit of blood or even a unit of

platelets from those individuals. So we do have serologic tests which come up later, surface antigen, eventually anti-core, as Dr. Alter pointed out.

I also want to focus on the impact of this disease on individuals, and this is overall a summary of what, again, Miriam Alter gave you, but I want to emphasize that, that is, certainly 90 percent of individuals infected with hepatitis B recover and are fine. However, 5 to 10 percent go on to chronic disease, and 1 to 3 percent die of that disease. So it is clinically important.

But there are three caveats here. First of all, if you're an adult and get this disease, 75 percent of them are symptomatic when you look at prospective studies, especially of transfusion recipients. The rate of chronic carriers is very much related to the age at acquisition, especially, as Miriam pointed out, if you are a neonate. And the risk of death is not just from chronic disease--from acute disease, but the chronic disease burden of these individuals which may

result in deaths from cirrhosis or liver cancer, albeit usually many years later. So it does have significant morbidity and mortality including among transfusion recipients.

As was pointed out, the risk of becoming a chronic carrier is very dependent upon the age at acquisition, so if you receive exposure to hepatitis B at birth, approximately 90 percent of individuals will become chronic carriers, and 30 to 40 years down the line will have 300 times the risk of people who recover of getting liver cancer. And this group of people are often transfusion recipients, and this is before they get exposed to the vaccine.

At the other end of the spectrum a lot of transfusions are given to individuals over 40, 50 or 60 years of age, and the vast majority of these individuals have not received the hepatitis B vaccine, and these are also individuals likely to have morbidity and death. In fact, in our transfusion series back early on, approximately 10 percent of patients over 60 who got

transfusion-associated acquired hepatitis B died of that infection, so it is significant in morbidity and mortality.

I always like to use this experiment because it will never be duplicated again, and it has some very important lessons for us. This is a series of experiments initially performed at the NIH in the 1950s by Dr. Roderick Murray in prisoner volunteers who were injected with one milliliter of pooled plasma from individuals with presumed hepatitis, certainly were jaundiced. And in that experiment, serial dilutions of one mL of that material were injected into other volunteers and they were followed at the time for clinical hepatitis, as subsequently tested in the '70s by Dr. Lou Barker for evidence of hepatitis B infection by hepatitis-associated antigen, hepatitis B surface antigen.

The two points that are important here are, one, that certainly as the dilutions are made up to here you've got clinical hepatitis, but more importantly, as subsequent dilutions were made, up

to 1 in 10 million, that is, 1 mL was diluted 10 million times, and then 1 mL of that was injected into individuals, and both individuals in this case came down with hepatitis. And there's no serologic test, and maybe it pushes the limit on a DNA NAT test to pick up such individuals, but 1 mL of a 1 in 10 million dilution of plasma from individuals with a history of hepatitis was infectious. It wasn't until it was diluted 100 million times that the two individuals infected did not appear to develop hepatitis B surface antigen. So there can be a lot of virus and very little virus can infect individuals, certainly below the limits of detection of current and even not yet licensed surface antigen tests.

This is a clinical trial conducted at five U.S. sites. Our site in Sacramento was one of those. Over 700,000 specimens were tested with hepatitis B minipool NAT. These were in pools of 24, and the focus of the results presented at the BPAC were on almost 600,000 and where the testing was complete, but I'll give you those results and

also a bit of follow up from the continued testing at three of the sites, one of which was Sacramento.

In essence, for purposes today, we're just going to focus on the bottom line, that is, 23 individuals out of almost 600,000 who appeared to have hepatitis B DNA alone without any evidence of serologic markers, and whether or not these are individuals who qualified as donors and whose blood could have been transfused if it were not for this study.

These individuals were enrolled in a follow-up study, or meant to be, where alternate NAT was performed, and there was quantitation if it was positive. They were intended to be followed for up to six months, and a variety of serologic and subsequent NAT tests were to be performed on these individuals as well as on the index donation and the index unit, because don't forget, they were testing samples in the pools for this trial. Of these 23 donors who were apparently hepatitis B DNA positive, 14 were enrolled in the follow up. 9 donors declined follow up but were presumed to be

false positive by additional index testing, that is, the unit itself was negative, and in most cases there was another hepatitis B positive unit in another pool on the same plate, so there was probably contamination there.

Of the 14 enrolled donors only two were confirmed window-period cases. The other 12 are again false positives, and were shown to be so by persistently negative other tests, and once again, there was probably a contamination event as to why the pool was found to be positive and traced to one donor.

Here's one of these donors, a 28-year-old male repeat donor who had no known risk factors. You see the index donation was positive. Other tests were nonreactive or not performed. As you see, by 17 days this individual became surface antigen positive, remained so, became a chronic carrier. Hepatitis B DNA remained positive. Antibody to core was reactive at 48 days. This individual never had surface antibody, and had at the time of initial donation a relatively low level

of virus in terms of copies per mL, but it went up very high and he ended up having greater than 5 billion copies per mL of virus.

This is a second donor picked up in this study. This was our donor in Sacramento, a 49-year-old female repeat donor, health care worker, who had a history of vaccination. She had negative anti-HBs results 8 weeks prior on her previous donation, and at that time was also not picked up, and the two recipients of her donation were not infected. But the index donation was hepatitis B DNA positive, low copy number, luckily picked up with a 24-unit pool. There was simultaneous antibody. What we don't know, of course, is whether or not if that unit had been transfused to one or two or three people, whether or not it would have been infectious because we don't normally do this. But this is the only donor of the five who was proven to have simultaneous antibody at the time of the donation. The other four, three of them were proven not to, and one has not been tested, so we don't know for sure.

As I mentioned, three of the sites elected to continue any pool NAT testing from April 2003 to the present, and three additional window period cases were detected over the next 1 million donations. Our center in Sacramento was one of the sites that continued.

This is a brief summary of those five window-period cases, and what you see is that individuals, the first two were part of the study, this one was antigen positive 17 days later. Our donor, the vaccine recipient, who did not clinical disease, but was clearly transiently infected, never made antigen. The other individuals were antigen positive within a week or so afterwards, and the last one is still pending, but all of them had detectable virus.

So in the clinical study, the rate of clinical yield was 2 in 700,000 donations, a rate of 1 per 350,000. In the continuing data, 3 in a million, again, 1 in about 330,000. So the yield of hepatitis B minipool NAT testing was approximately equal to hepatitis C minipool NAT and

certainly greater than HIV minipool NAT which we now do.

So in fact I will show you--this is my last slide, which is a summary from the recent publication of these groups here, which is giving you an update and a comparison of the pickup for hepatitis C NAT minipool testing, which is about 1 in 230,000, as you see here; for HIV, 1 per 3 million; for hepatitis B in this clinical trial, 1 in 340,000. And so I believe, and my recommendation--that's as an individual, not representing anyone--that it would be appropriate to do hepatitis B minipool NAT testing because of the significance of the morbidity and mortality of the disease and because the pickup is certainly comparable to this and better than this.

And you will have a statement, I know, from the three blood organizations shortly, from Dr. Sue Stramer. I would disagree with that statement and say that I find it disingenuous at best that they could recommend NAT Testing for this and this and not support NAT testing for this. The

pickup is essentially equivalent, and this disease is at least as clinically significant as this and this in terms of morbidity and mortality, especially among susceptible transfusion recipients, especially the neonate and the elderly, most of whom would not be immune, would not have received the vaccine, and would have clinically serious consequences.

Thank you.

DR. BRECHER: We have time for some questions and comments. Celso.

DR. BIANCO: One question, Paul. Have those positives--would they have been picked up by more modern ELISA tests?

DR. HOLLAND: That's a good question, Celso. I believe all of them have been tested by the only other licensed test of improved sensitivity, the Ortho third whatever is it, and one of those would have been picked up, but four would have been missed.

What we don't know, and I thought we knew, but we don't know, is what would happen if those

had been tested with the PRISM. The copy number's very low, however, and I think it would be highly unlikely that even the PRISM would pick up those other four.

DR. BIANCO: But those tests are not looking at DNA. They are looking at--

DR. HOLLAND: At surface antigens.

DR. BIANCO: Right.

DR. HOLLAND: Correct.

DR. BRECHER: Judy.

DR. ANGELBECK: Dr. Holland, if you could just clarify a point for me here. You had mentioned, I think the statistic was 10 percent of patients greater than 60 years of age--

DR. HOLLAND: Yes.

DR. ANGELBECK: --who got transmitted--transfusion--

DR. HOLLAND: Transfusion transmitted hepatitis B, died.

DR. ANGELBECK: --died.

DR. HOLLAND: Correct.

DR. ANGELBECK: So this number would

potentially go up as the aging of the population increases?

DR. HOLLAND: That's correct, and those over 60 are a major group of patients who are transfused and who are not protected by the vaccine and are no immune by virtue of prior exposure.

DR. ANGELBECK: Thank you.

DR. HOLMBERG: I'm just curious as far as the one person from Sacramento, the breakthrough. When was she vaccinated? Was it years before or recently?

DR. HOLLAND: The best we can determine it was between 5 and 10 years before, so she fits in with the 40 percent of individuals that Miriam mentioned, who apparently lose detectable antibody, but who are--probably do not have disease. She was clinically well, but certainly was transiently infected during that eight-week period of time, and actually for about 11 or 12 weeks, or up to that long, potentially was infectious for her sexual partner, and certainly if she donated blood, as she did, for a recipient, potentially.

DR. HEATON: Paul, do you know what percentage of the population in California has been vaccinated for HBV? Because I noticed that you had a case that was HBsAG negative, and I know there's been a case in Germany that also was HBsAG negative and seroconverted as a result of vaccination. So obviously, the frequency with which you would see this circumstances will be related to the prevalence of vaccination.

DR. HOLLAND: I can't tell you specifically for California. The best estimate I believe from the CDC is about 70 million Americans have been given the vaccine. That would say that three-quarters have not, and of those, the vast majority of course would not be immune. And keep in mind that if you receive this vaccine after age 40, 20 percent of people do not respond to the vaccine, are not immune. So it's another factor to work in here.

DR. BRECHER: Thank you, Paul. I know you have a plane to catch.

We can either move on to the next speaker,

which I think we should do, and then we'll take a break after the next talk. So we're going to go back to Dr. Kaplan from the FDA reviewing the BPAC discussions.

DR. KAPLAN: Hi. I'm Gerardo Kaplan. I work for the Food and Drug Administration. I will review for you the BPAC discussion and FDA current thinking on HBV minipool NAT.

So the issue here is that the FDA is considering an application for the first nucleic acid test (NAT) to screen blood donors for infection with the hepatitis B virus. I should point out that another NAT test is under development.

If the first application is approved, a decision will be needed whether to recommend this test as an adjunct to current hepatitis B screening by test for hepatitis B surface antigen, HBsAG, and the antibody to hepatitis B core antigen, anti-HBC.

The two previous talks were very comprehensive with the little bit of introduction I wanted to give you, so I will fly pretty fast

through this. HBV is an important human pathogen that the previous speakers mentioned. Most primary infections in adults are self-limited. The problem are chronic infections. As was mentioned before, less than 5 percent of infected adults develop persistent infections, 20 percent will go to develop cirrhosis, and a very important problem is that the risk of developing cancer is about 100 times more in chronic patients.

So this is a serological course of a typical acute infection, and basically the two markers that we are interested in that are currently used for screening are the surface antigen here in red, and then anti-core, and basically this in blue is the DNA. It was mentioned before that DNA test will reduce the incidence by several days because it picks up infected individuals before the surface antigen in chronic infected individuals, so the surface antigen remains high and goes downward. It could go all the way down with time and the anti-core remains high. The DNA also remains high. So in

both individuals, acute and the chronic, the DNA will pick it up before, several days before currently-licensed tests.

It was also mentioned in the talks before in assessment of the risk, and so basically for HIV is 1 in 1.9 million; for HCV it's 1 in 1.6 million, and basically the last notch was achieved after implementation of NAT. For HBV we don't have NAT yet approved, licensed, and the risk is much, much higher, as Dr. Holland mentioned, and basically there's a big gap here that we need to fill in. So here again, the risks for serological testing and for HBV it's 1 in 180,000 for pooled NAT, which is the one that was presented in BPAC for licensing, for recommendations, it's 1 in 210,000. This is an estimate from Dr. Busch. This is probably even lower at this point.

So the sources of residual risk are basically, the main one is the window period. There's no indication that biovariance will not be detected with the current tests, and the other important risk is the procedural testing errors.

However, it's also possible that typical forms of the disease also will contribute to the risk here. The forms were the surface and core not detected or very low.

So FDA received the Roche COBAS AmpliScreen HBV DNA test in minipools of 24 samples for review. The study objectives were to determine whether the COBAS Ampliscreen HBV test in minipools of 24 samples of plasma from volunteer blood donors can detect HBV DNA in surface and anti-core negative window period cases. That was the primary objective of the clinical trial. And also in all surface positive donors, that's a secondary objective.

So in the clinical trials, as Dr. Holland mentioned, there were two window periods in about 600,000 volunteers. Roche Molecular Systems claims that the use of the COBAS Ampliscreen hepatitis B test in conjunction with anti-core test would reduce the residual risk of transfusion-transmitted hepatitis B. They also claim that the COBAS Ampliscreen hepatitis B test could be used as an

alternative to the surface donor screening test.

So I will review a little bit the trial for you and give you some numbers. So basically all the index donations were tested for surface, anti-core and DNA in minipools. So the current results here, possibilities are that all the three markers are negative or all the three markers are positive. However, there are a bunch of discordant results that are very important for this trial. For instance, donations that were only surface positive, those were tested by alternative NAT and individual donation NAT, quantitative NAT, and there were follow up.

There are possibilities that two of the markers were positive, the surface and the HBV DNA were positive. Here in alternative NAT and quantitative NAT were performed and the donors were followed up. The other possibility is the surface also positive and the core is positive, and here an alternative NAT, ID NAT and quantitative NAT was performed. Out of this current possibility it's only the anti-core is positive, and here,

alternative NAT, ID NAT, quantitative NAT, anti-surface IgM anti-core were performed, and then those were followed up.

There are possibilities then anti-core was positive, HBV DNA was positive, and here alternative and quantitative NAT was performed, and also those were followed up.

And finally, the cases that were only positive for DNA, and here in alternative DNA and quantitative DNA was done on the index donation, and then they were followed up.

Let me throw you some of the numbers. The total is about 600,000. Most of them, they were negative, as expected. Only 84 were positive for all markers; 4 were positive for surface; 3 were positive for surface and DNA; 16 were positive for surface and anti-core; 2,988 were positive for core only; 1 was positive for DNA and anti-core; and 23 were positive for DNA only. Dr. Holland just reviewed some of those cases for you.

I would focus on the 23 positives because this is basically the yield of the trial. And so

basically from those, 21 were false positive samples as discriminated by this algorithm. Here w window period samples were detected in the trial, and these are bona fide window periods.

So if we can extrapolate here, these tests will pick up around 40 to 50 units that no other test will do, no other screening test will pick up, and those units could be intradicted(?).

Let me focus on another part of the trial because the company was claiming replacement of surface antigen was very important to analyzing thoroughly. So from these four that were only surface positive, 2 were negative, 1 was surface antigen false positive as tested by the antigen test, and there was 1 that was a vaccine recipient, and Dr. Alter mentioned that if someone was vaccinated and then tested for surface, there's a possibility that you would pick it up, and we believe that is the case. 2 others were not followed up. But I should point out that the index donation was negative.

The company followed up these cases after

the trial was finished, and there are clearly false positives also. So basically these four are false positives.

On the antigen and DNA positives, there was 1 positive and 2 were not followed up. So some of the sensitivity here was 110 donations were surface positive, 100 were surface positive and anti-core positive, and 7 were anti-core negative. As a remark, all four antigen-positive only donations resolved as false positive, and this was not in support of the replacement claim. However, these numbers are quite small.

The other part of the trial, branch of the trial that I would like to review with you is the 16 that were antigen positive and anti-core positive, so by ID NAT 10 were positive and 5 were negative. By the alternative NAT 9 were positive and 4 negative, and by quantitative NAT the range is pretty large. 3 were 100 copies; 1 was 200 copies; another 700 copies. It's one with 1,200, one with 2,600 and one with 5,900 copies.

So on sensitivity, 12 of the 16 were

detected by ID NAT and alternative NAT; 3 of the 16 were negative by ID NAT or Alternative NAT, and 1 in 16 was not tested. And so remark: although the 16 donations were minipool NAT negative, all were anti-core reactive. So this indicates a sensitivity issue but not a safety issue, provided that the screen for anti-core is retained.

The other part of the trial I would like to point out to you is the anti-core positive and surface negatives, and there were 2,988 cases. ID NAT found 12 positives. Alternative NAT found 3 positive and 5 negative. By quantitative NAT, one was 900 copies, the other one was 1,100, and a third one was 1,200 copies.

So this indicates that the anti-core screening cannot be dropped now since it can pick up potential infectious donations.

On July 23, 2004, BPAC analyzed the data in support of its application, and we presented four questions basically.

Do the sensitivity and specificity of the Roche COBAS AmpliScreen HBV test in minipools of 24

sample supporting licensing of the assay as a donor screen? And basically 15 members said yes, and 1 no. There was zero abstentions, and the nonvoting representative agreed with the yes vote.

So the following question was: If so, assuming continued use of screening test for anti-core, do the data support use of the Roche COBAS AmpliScreen HBV test in minipools of 24 samples to screen blood for transfusion as an equivalent alternative to the surface test? And here unanimously it was a no vote with zero abstentions, and the representative also went along.

If the data do not support the use of the Roche COBAS AmpliScreen test in minipools of 24 samples as an equivalent alternative, which was the vote of the BPAC, what additional data will be required? And so the Committee members emphasizes the need for additional data from clinical studies due to the small number of clinical samples in the study. It was suggested that ID NAT would be a better replacement for the surface antigen than the

minipool.

The following question was: Does the data support the use of the Roche COBAS AmpliScreen hepatitis B test on minipools of 24 samples to screen blood for transfusions as an added test in conjunction with the licensed donor screening test for surface and anti-core? And here the Committee declined to vote on this question, but the individual members provided comments, and some of the comments are following:

Whereas the test may identify some additional HBV positive donations, the public health benefits of routine additive testing are unclear.

Another comment was if a practical technology were developed, individual donation NAT for HBV would provide a greater benefit to blood safety than minipool NAT. However, this is not even--it is not an option for the future, near future.

Another comment is that useful studies for hepatitis B can be done in high risk groups as well

as blood donors.

So, the FDA has formed policy options first on the assumption that, in the near future, FDA is likely to approve the Roche COBAS AmpliScreen HBV test on minipools of 24 blood donor samples. The following policy options may be considered.

At first, FDA could recommend the routine use of minipool HBV NAT to screen blood donors in conjunction with currently licensed serological tests for surface antigen anti-core.

Pros and cons here. The pro is: This option would add a third HBV test that may marginally increase the safety of the blood supply and, thereby, lower the residual risk of HBV from transfusion. FDA could provide an implementation date sufficiently far in the future to permit development of alternative HBV NAT tests, compatible with the non-Roche systems.

As a con: An FDA recommendation for routine use of an additional test on blood donors will impose a significant added cost to the blood

system and increase the complexity of the blood testing. Based on the implementation date of this recommendation, it might create logistic problems for the majority of the blood collection centers that do not presently use the Roche system.

The other, the second policy option will be that, if they could state that implementation of the Roche COBAS AmpliScreen HBV test is voluntary, but reserve the option for any future recommendation on routine use of the HBV NAT on minipools of donor samples.

Pros and cons, the pro, this option will allow blood centers to make local decisions regarding the value and practicality to test donations with the HBV minipool nat. The con is that, this option would most likely result in the implementation of minipool HBV NAT, only in a number of blood collection establishments that currently use the Roche system for HIV and HCV nat. This could create a public perception of two tiers of blood safety in the U. S.

The third option is that, the FDA could

regard the use of the HBV NAT and minipools to be voluntary, but also encourage manufacturers to develop an automated high throughput system to permit routine use of the HBV NAT on individual donor samples.

Pros and cons, this option has the same benefits as option two, but creates another expectation for development of technology that FDA will be likely to recommend.

Conclusions.

As developed by Roche Molecular Systems, the HBV NAT on pools of 24 samples can identify approximately 1 in 300,000 positive donations that fail detection by current screening tests for HAsAg and anti-HBc. This is estimated to address only 25 percent of the current risk.

The conclusion is, the global assessment of the public health benefits of donor screening for HBV by NAT on minipools will help FDA to make a policy decision whether to recommend such testing as an additive safety measure.

This concludes my talk.

DR. BRECHER: Thank you, Dr. Kaplan.

Time for a couple of questions, comments.

Gerry?

HOLMBERG: I have a question that maybe I am the only one who has this question. I don't understand why the minipool came before the ID.

DR. KAPLAN: Well, there is a high throughput and currently the blood centers do not have the infrastructure to do that. So, the minipool algorithm came before the ID NAT, because it would take a while before all that infrastructure is in place to do ID NAT.

So, it would take a few years to get ID NAT even for HIV or HCV.

Yes?

DR. BRECHER: Karen.

MS. LIPTON: I just didn't understand the last thing on a global assessment. What did you mean by that?

DR. KAPLAN: Well, what--if we were to recommend this, I think it would be very important to be very clear whether this will have an added

benefit to the current testing algorithm. So--

MS. LIPTON: By global, you don't mean truly global? Do you mean in the U. S.?

DR. KAPLAN: In the U. S.

DR. BRECHER: Jay?

DR. EPSTEIN: The sense in which we mean global is looking at overall public health, considering such factors as cost effectiveness, which is not part of the FDA paradigm; you know, logistical feasibility, burden to the industry, et cetera. So, it is from a more global perspective, aggregating all factors we'd like to have some guidance.

MS. LIPTON: Perhaps, maybe a more comprehensive assessment--

DR. EPSTEIN: That would be fine.

MS. LIPTON: --or the scope rather than the geography.

DR. EPSTEIN: Correct.

DR. BRECHER: Jerry?

DR. SANDLER: Well, getting into the global picture, we don't really advise FDA. As I

understand it, we advise the secretary of health, which would bring us into the broader area of, if the government is going to invest in preventing hepatitis B, what is the relative value of a vaccination program with hepatitis B vaccine versus testing blood donors.

If we are going to get global, we have to get global. We are not really advising on blood donor issues. We are advising on a national health policy, if I understand our position.

DR. BRECHER: We will get to the specifics of what we are supposed to do. We do have a question, a specific question we need to address.

Why don't we move on to the last talk and then we will get into the discussion period. So, we are a little bit behind. The last talk today is Mike Busch and he is going to work hard to get us back on time.

Right, Mike?

[Pause]

DR. BUSCH: Yes, I will move quickly.

Most of the work I will be discussing, you

have manuscripts that were distributed beforehand, both that I published and others. What I want to do is briefly review and, again, go quickly, because must of this has been covered, the predicted yield and the observed yield of HBV NAT, both minipool and ID NAT configuration and particularly touch a little bit more specifically on the cost-effectiveness, the relative importance or value of screening for HBV versus HIV, HCV in terms of interdiction of infected donations.

Then briefly also discuss the potential that we might be able to drop one of the other serologic tests. Obviously, with HIV NAT, we were able to drop p24 antigen and significantly offset the costs of introducing the NAT system.

The question here is whether with HBV NAT, either in minipool more likely in ID format, we could drop one of the other serologic tests and save an offset. Then a little bit at the end about what studies might be needed.

This is the same kind of ramp up phase, *viremia, that we look at for all the viruses.

This is data from the Biswas collaborative study. Interestingly, with HBV, I think the kinds of studies that you've talked about trying to do for platelet detection, I think the resources have been directed to study these questions with HBV. So, we actually have real data. That's what always makes the decisions a lot easier.

What you are looking at here is a series of different surface antigen tests. These ones up here were the licensed tests at the time. The ones down here were the unlicensed assays, such as, the Abbott Prism or the Ortho 3.0. Then this is the relative ability of different NAT systems, either in the minipool or pool sample or single sample format, to close this window period.

You can see that, the antigen tests can detect down to the range of a couple of thousand copies of HBV. The NAT systems, the pool sample NAT really overlaps. Some of the pool sample NAT systems are less sensitive than the antigen tests, but clearly, the single sample NAT systems can close the window significantly. You are looking

down here at a 20 to 30-day window period closure potential with single sample NAT.

Again, this is a table from the paper, but just to point out that, if we compare the NAT assays--and we looked at the two proposed whole blood screening assays, the Roche and Chiron as well as a largely applied plasma donor screening program, NGI, against a series of assays.

A, is again the Prism HBsAg, which is the most sensitive antigen test available, still not approved for widespread use in the U. S., but used in Europe and many other countries.

You can see that the pool sample NATs actually have essentially no window period closure, with the exception of one assay, which is actually the one under discussion today. That does have some modest window period closure of a few days relative to surface antigen, the most sensitive surface antigen.

But again, all of the single unit systems had significant window period closure. So, this is the point that, once we can get to single donation

testing, then we will see a more dramatic window closure and yield with HBV NAT.

This, again, a summary from the Biswas paper, is just the window period reduction translated then into the predicted yield per 10,000,000, which is about--you know, we collect about 12, 13,000,000 donations per year, so approximately the number of infections interdicted per year.

This is relative to the previously widely used surface antigen tests. So, the better surface antigen tests, again, were essentially biased, as much window closure, as much yield as the NAT assays. ID NAT would reduce the risk and interdict a substantial number of units.

Now, this is just to put into context that, HBV NAT has been introduced in two very large programs in different countries. One is in Japan and the other is in Germany. And I wanted to just share that data. It has a couple of important messages.

In Japan, they do anti-core testing. So,

they introduced HBV DNA initially in pools of 50 and then reduced it to actually pools of ten recently. They screen with a surface antigen test that is not very sensitive. It is a particle glutination assay.

So, using, in an anti-core screened population where a surface antigen with this sensitivity was applied to the donor pool--and, again, an endemic population--they picked up 181 HBV DNA-positive surface antigen-negative units. What you are seeing is 11,000,000 total screened donations.

But what you are seeing here is, they then took these 181 positive units and they tested them by the Prism and the Auszyme, the two Abbott assays, the assay, which is very sensitive and the Auszyme. You can see that 58 percent of these what look like not yield units were, in fact, reactive by the enhanced sensitivity antigen test and 47 percent were reactive by the Abbott test that is widely used in the U. S. currently.

So, a high percentage of what looked like

NAT yield units, in fact, had surface antigen when subjected to contemporary, sensitive antigen assay. The percentage of these units that had antigen varied, depending on the viral load, fairly obviously. In fact, that is shown on this slide. This is looking at the viral load of all of these what were initially thought to be NAT yield units, 181. 105 of these, again, were reactive by the Prism assay.

Based on this relationship, which in primary infection, you see this very nice relationship between surface antigen level and DNA, they could derive an estimate for the sensitivity of the surface antigen test of 2,000 copies. But again, the main point here is, that in the context of portion of surface antigen assay, you will get a lot of not yield that would actually have been detected were one doing a good surface antigen test.

The other large study is from Germany, where Kurt Roth's group has screened for HBV DNA for now four or five years. They screened over

almost 20,000,000 donations and they picked up 42 HBV DNA-positive surface antigen units. Now, there, they do not do anti-core testing. So importantly, when these apparent not-yield units, at the rate of 1 in 500,000, were subjected to anti-core testing, two-thirds of them were anti-core reactive.

So, these were these back-end, low level infections like Miriam spoke about. They only had about 15 of these units that were actually surface antigen-negative, anti-core negative yield units.

So, this is just juxtaposing the two studies I just discussed, the Japanese, the German study and then the U. S. Roche clinical trial data prior to the most recent yield case that talked about five cases. They had four previously in 1.2 million. So, it looks as if the yield, here again, is fairly substantial, but you have to remember, relative to Germany. But again, Germany is using a very sensitive Prism assay. So, part of the reason why the yield in this U. S. trial is relatively greater than in Germany probably relates to the

fact that some of those yield cases may well have been detectable had Prism been applied to them.

We have heard a lot about the clinical impact and, again, not to push it too far, but only a proportion, certainly a small proportion of people who are exposed to HBV, potentially infectious, low titer infectious units will develop chronic infection. Only about five percent of adults and that may even be lower with the kind of very low dose inocula that we are talking about in the setting of wider vaccination, both of the donor and the recipient populations.

Of those who are chronic carriers, perhaps 15 to 20 percent develop chronic disease after decades. So, overall, probably .25 percent of potentially infectious exposures would result in significant disease.

Now, in terms of the significance of the disease, I like this slide, because this is a cost-effectiveness analysis, which Jim AuBichon in collaboration with Sue and I developed a few years ago. What it let us do is, to really look at the

relative importance of stopping HIV, HCV and HBV transmission by transfusion. This is expressed here and the quality of life here is gained by avoiding the transmission of any one of these three viruses.

What you can see here is that, by preventing an HIV transmission, we essentially buy that patient seven quality life years that they would have lost had they been infected with HIV. For HCV, that is .6 quality life years and for HBV, interdiction of an HBV viremic unit only really translates into .16 quality life years.

So, in essence, HBV is clinically one quarter as important as HCV and one-fortieth as important as HIV to interdict. Using that kind of window period modeling estimates, we estimated--these are the numbers of units that would be interdicted by going from serology to minipool NAT or serology to individual donation NAT and in parentheses are the number of qualities that would be saved by virtue of that.

So, for HIV, for example, as compared to

HCV, we pick up about five units with minipool and about nine with individual donation NAT. But those small numbers of interdictions translate into a lot of clinical gain, because the qualities per case are large.

The HBV, in contrast, we pick up 15 cases with minipool NAT. A much larger number would be detected with single donation or individual donation NAT, so 64 units. Yet, the qualities, the benefit to the public and to the patients is much less, because most of these infections don't evolve to chronic infections or clinical significance.

The other point here is that, again, only 23 percent of the yield that could be achieved by NAT for HBV would be achieved by minipool NAT. So, really, only when we get to ID NAT do we interdict a significant number of infections.

There is a second cost-effectiveness paper that I just had distributed to you that I will touch on.

These of the kinds of cost that we are talking about, the cost of routine screening in

blood programs, serologic screening is about $15. To add NAT to that for the current viruses, adds about $15 per donation. So, we go up from 15 to about $30 currently for HIV, HCV NAT. Adding HBV NAT would add about $5 more per donation.

These are the kinds of numbers that the large blood screening programs and information from the companies sort of give us a sense of what the costs would be. Again, obviously, if we can drop tests like antigen, we offset these incremental costs. Going to individual donation NAT, again, would be something in the range of 7 to $10 extra.

So, those are the kinds of costs that go in then to the derivation of dollars per quality in these cost-effectiveness analyses.

In our study, we estimated that current HIV, HCV minipool NAT is running about $4 million per quality life year. Going to single donation NAT, with those two markers, would increase--would be less cost-effective, increase the dollars per quality to $7 million. Actually, that transition from single unit--from minipool to single unit NAT,

if you focus on the incremental cost-effectiveness of making that transition, that is about $15 million per quality. Adding HBV worsens the cost-effectiveness outcome in these calculations to the overall cost-effectiveness.

Now, there is another study that was published this year. Steve Kleinman was involved with this study and it is quite similar in most of the assumptions and outputs. The only emphasis I want to make here is, again, when they looked at the value of the various viruses in terms of interdiction by NAT, you can see that with moving from routine screening to minipool NAT and even all the way to individual donation NAT, you are buying very little offset in costs related to preventing HBV disease.

So, we have $14,000 of cost associated with HBV transmissions now. That would only drop to 12,000 by adding minipool NAT.

Most of the benefits that are gained for the health care system related to NAT are driven from HCV and HIV, where you have a fairly dramatic

reduction in the health care cost from $223,000 to 29,000. So, just to point out that both these studies concluded the same thing.

That HBV NAT offers really very little gain in terms of cost-effectiveness. These are the bottom line outputs from the Marshall study, Cost-Effectiveness of Minipool NAT of 1.5 million and of ID NAT, of 7.5 million. And they comment in their discussion that, in sensitivity analysis, HBV NAT had very limited benefit, because such a small fraction of these infections translate into chronic, symptomatic infections.

Just two other points to address.

One is the potential that we can drop the other markers. I think with anti-core, there are a number of studies now, including Roche's own data. We just sort of look in this box here. They show that a small but significant fraction of donations that test anti-core reactive and negative for surface antigen are viremic. All three of these large studies have demonstrated that, about one 50,000 donations are anti-core reactive and have

low level HBV DNA, in the absence of surface antigens.

So, the potential that we can drop anti-core just on that basis is doubtful. There have been a number of studies over the years that show that these anti-core reactive only units that lack surface antigen can transmit in the presence of DNA and even in the absence of detectable DNA.

In terms of surface antigen, like HIV, what seems logical is that we could couple a sensitive antibody test, which anti-core represents for HBV, with a very sensitive front-end, window period, targeting assay. So, it would seem as if, like with HIV, we could anticipate being able to replace the surface antigen test with HBV NAT. We know that, at least, on the front end, HBV NAT can be more sensitive, particularly if applied on single donations.

Now, the problem is that, in essence, HBsAg has proven itself so effective, because it has a biological amplification. People who are chronically infected put out enormous levels of

HBsAg and this allows the detection of chronic carriers. In fact, as you will see, some chronic carriers who are even negative by minipool are ID NAT.

So, therefore, toward the goal of potentially dropping surface antigen, we really need to really look at various populations that could have HBsAg in the absence of anti-core. This includes window period and chronic carrier stages. I believe it also should be focused on populations with endemic, from endemic countries and different routes of exposure and also this concern over vaccine breakthrough infections.

Just one last study to mention that was just published this month, in collaboration with Mary Kuhns at Abbott where 200 surface antigen anti-core positive units from REDS were studied by serially more sensitive HBV DNA tests. So, the first test was a quantitative test and that picked up 64 percent of these having viral loads greater than 400. Then those negative by that assay were subjected to a test that had sensitivity of about

65 copies, about the sensitivity of the Roche HBV minipool NAT. We were still left with six percent of these surface antigen positive units that were negative for DNA.

Those were subjected an extremely, highly sensitive assay, very high volume input. That still left us with three percent of these units or six overall that were negative, had viral loads less than one copy.

In this paper, we also looked at a number of other issues, but these units down here that are negative by all the NAT assays or only positive by the high sensitivity assay, actually, many of them had very high surface antigen levels. So, these were readily detectable by surface antigen tests, but these are situations where the biologic amplification of surface antigen in these people leads to high levels antigen in the absence of DNA.

Just to mention, some of these--the real concern, though, is you might have carriers who are surface antigen positive, DNA negative and lack anti-core. We do see that. Most of the U. S.

infections that we pick up with surface antigen have anti-core, but 2 to 5 percent are negative for anti-core. Most of these are probably primary infections with high DNA levels along with surface antigen.

Some of them have proven to be negative by DNA and these could represent mutant viruses or failure of some people to evolve anti-core. Many of them may represent contaminations. That is what the Roche data showed.

I'm not going to go into the details here, but just to show that there are three studies that have reported individuals who have surface antigen without anti-core and no DNA. In several of these cases, it has been followed and demonstrated that these people were, in fact, chronic carriers.

So, in conclusion, I think, in my opinion, there is a very small yield and a very small clinical benefit to minipool NAT. It is not likely to allow us to discontinue the other serologic markers in the short term. I think, if we can move toward the single donation screening platform, we

will be able to potentially drop surface antigen. We will gain significant additional yield and some additional cost-effectiveness that, at that point, I think, HBV NAT may well be appropriate to incorporate into NAT screening.

I do think studies--and I have already discussed this, so I am not going to go into them any more--are needed. I hope you recommend them to generate the data now to, hopefully, support what I think makes a lot of sense, which is an eventual policy to drop surface antigen and add ID NAT for HBV.

DR. BRECHER: Thank you, Mike for a whirlwind tour.

Comments and questions?

[No response]

DR. BRECHER: Mike, I had a quick question.

You had that one slide that showed that the surface antigen test picked up down to very low copies in some examples. So, how is it that individual NAT would replace HB surface antigen?

DR. BUSCH: Yes, it could only replace surface antigen in the context of anti-core screening. So, you would need to continue anti-core to detect those chronic carriers who have very low level DNA. So, that makes us only have to potentially focus on the window phase where NAT, particularly ID NAT, clearly is more sensitive than surface antigen.

DR. BRECHER: Although, I imagine, in theory, there could be some of these vaccine individuals with a very low level?

DR. BUSCH: Right, yes, I think that is one of the groups that, I think, need to be studied more, are these vaccine, low level vaccine, transient infections infectious. Those vaccine recipients, you know, if they are--they shouldn't have surface antigen unless they were just vaccinated. If they were just vaccinated, that's just the vaccine. It's not an infectious virus.

DR. BRECHER: Of course, they would not have anti-core.

DR. BUSCH: Right.

DR. HEATON: Mike, for front-end infections, has HBsAg ever been shown to come up before HBV DNA for front-end infections?

DR. BUSCH: Yes, not with contemporary HBV DNA amplification assays, no.

DR. BRECHER: If there are no other questions or comments, we will move into a public comment period on hepatitis.

[No response]

DR. BRECHER: Okay, if there are no public comments, we will move--

[Laughter]

DR. BRECHER: Please come to the microphone.

I knew that was too good to be true.

MS. STRAMER: I'm sorry, I'm used to being announced.

I am going to read a statement, a joint statement from the American Association of Blood Banks, America's Blood Centers and the American Red Cross.

I am Susan Stramer and I am representing

the Transfusion Diseases--Transfusion-Transmitted Diseases Committee of the AABB.

You should all have a copy of this statement.

"HBV remains the most common clinically important viral infection recognized after transfusion since the control of HIV and HCV infections through improved donor selection and serological and NAT screening. The data today presented Paul Holland, representing the Roche Molecular Systems clinical trial, from its IND study of HBV NAT in minipools of 24 samples are an important contribution to the ongoing improvement of donor screening.

"AABB, America's Blood Centers (ABC) and the American Red Cross (ARC) see three issues of primary importance to the blood community to be addressed by the Advisory Committee on Blood Safety and Availability and the Food and Drug Administration (FDA). These are the same

issues that were reviewed at the Blood Products Advisory Committee, on July 23rd. First, is the Roche HBV assay approvable as a donor-screening test, and second, if approvable, shall its implementation be required in blood collection facilities? A third question is whether a claim for HBV NAT in minipools to replace HBsAg testing should be granted.

"Regarding the first question, the data that are available for review by the AABB's Transfusion-Transmitted Diseases Committee indicate that the Roche minipool HBV NAT assay appears to perform adequately in terms of analytical sensitivity and specificity, and generates incremental yield of NAT positive specimens over current serological tests. This suggests that the assay may be approvable in the currently proposed minipool NAT context, but its efficacy should be greater if it were applied to individual donations or significantly smaller minipools.

"The second question is more difficult to

answer. The minipool-based assay under consideration appears to yield between 1/250,000 to 1/300,000, or as Paul Holland presented, 1/340,000 positive donations that are negative on currently licensed tests for HBsAg and anti-HBcore. This rate is similar to the yield rate for HCV and minipool NAT, and substantially higher than for HIV NAT. It is comparable to or slightly higher than predicted by Biswas and coworkers in a comparative study of NAT and serologic assays that was published in 'Transfusion' and presented in summary by Mike Busch.

"As suggested from data on the evolution of markers of HBV infection, these donations tend to contain low copy numbers of HBV DNA and incomplete data suggest that some HBsAg assays, either available or under development for evaluation by FDA, may be able to interdict some of these 'yield' donations. Certainly, you have ask questions about the two, with copy numbers of 37,000 in 61,000 copies per mil of DNA. These include HBsAg tests from Abbott, Ortho

Clinical Diagnostics and Genetic Systems.
It is critical for the accurate analysis of the true impact of HBV minipool NAT that samples from these current yield cases, and those identified in the future by HBV NAT assays, be tested not only by the currently licensed serological tests, but also by the developmental tests that are likely to be licensed in the future. I would also add that, research-based assays should attempt to identify whether HBsAg is present in these samples or not. Studies of the infectivity of yield cases are also desirable, and particularly of units that have concurrent HBV DNA and anti-HBs in the absence of detectable HBsAg and anti-core (as seen on two of the yield cases in the Roche trial).

"Thus, despite measurable yield, introduction of HBV minipool NAT will offer only a minuscule increment in transfusion safety compared to currently required tests for HBsAg and anti-core. The result of this low incremental yield coupled with low rates of chronic infection and clinical disease after

HBV transmission, renders the marginal cost-effectiveness of HBV NAT in minipools very poor. Mike has also reviewed those data.

"This cost-effectiveness will decline further into the future as a larger and larger proportion of the population has vaccine-induced immunity to HBV infection.

"Regarding the third question, current data are not robust enough to support the elimination of either serologic marker, that is, HBsAg or anti-core. It is possible that HBV NAT will eventually allow discontinuation of Hbsag screening, but this will require a larger data set including parallel testing by HBV DNA on individual donations rather than minipools, anti-core and Hbsag, using maximally sensitive antigen assays.

"In summary, minipool HBV NAT is an expensive new screening assay that offers little clinical benefit and that will not be offset by the discontinuation of any current testing. More sensitive Hbsag tests are

available now and more will become available in the foreseeable future. More specific anti-HB core tests, hopefully, will also become available. Based on these considerations, AABB, ABC and ARC do not support a requirement for the use of NAT in minipools for blood donor screening at this time. Rather, if HBV DNA NAT is licensed, its use should be optional. The requirement for HBV NAT testing should be reconsidered when technology allows for individual unit testing."

Thank you.

This statement also includes information about the three associations for which this statement was presented.

DR. BRECHER: Thank you, Sue. I'm sorry I didn't introduce you.

MS. STRAMER: That's okay.

DR. BRECHER: Any other public comments?

Steve?

DR. KLEINMAN: Just one other item to throw into the consideration. That is, we have heard about minipool and we have heard about

individual donation. There is another option and that is, changing the size of minipools to get part way to the benefits of HBV NAT without having the technology to go all the way to individual donations.

So, it is not a proposed option currently, but I think that test manufacturers might be working towards reducing the size of the pools, rather than working only towards individual donations. So, it could come up in the future.

DR. BRECHER: Thank you, Steve.

We have a specific question that was to be addressed. Jerry is going to present that.

DR. HOLMBERG: As you all know, this question was raised to the Blood Product Advisory Committee in July and, after that, has been referred to Dr. Beatto and our internal Committee on Blood Safety, the Public Safety Committee within the Department of Health and Human Services.

One of the things Dr. Beatto wanted to do and originally we had opened--we had luck this afternoon and opened to discuss this issue

primarily, based on her decision that she wanted this to be discussed here in this forum since we could address some of the issues that the BPAC could not address. The major question, it is on that same presentation. It is the second slide.

The question that she would like us to address is: What is the public impact of implementing HBV minipool NAT for blood donor testing?

DR. BRECHER: Jerry.

DR. SANDLER: I'd like to begin that discussion by referring to the slide that Paul Holland was the one dissenting speaker for, I think, a sort of general trend here. Paul introduced the concept that there was more pick up if you used this or, at least, on a comparable for HIV hepatitis C and hepatitis B. I think it is unfair or a distorted viewpoint of the public health aspect.

When you look at HIV and hepatitis C virus, it is an obligation of us in the blood community to protect recipients, because they

cannot protect themselves. There is no vaccine available for two of the diseases and we had to step forward and protect people who got sick, because they could not protect themselves.

In a public health context, which we are being asked for, you could tell people there is a way to prevent getting hepatitis B and we do it for little kids and we do it for young adolescents. And there could be a public health initiative to promote hepatitis B vaccine and put the responsibility for people's health back into their hands. We didn't have that option with HIV and we did not have it with HCV. But it is there with this and, before we spend an awful lot of money repeatedly testing healthy people, we should be thinking about putting money into just once in a lifetime protecting people or letting them protect themselves.

DR. BRECHER: Karen?

MS. LIPTON: Yes, I mean, I think what was so striking to me was looking at Miriam's slide about the efficacy of vaccination programs. When

you want to talk about a public health initiative that really is worth it--but I actually was struck by another thought, Gerry. That is, so then why don't we just offer the vaccine to repeat donors, at least.

I mean, if you want to talk about trying to protect populations--I mean, it just seems there are a lot of different ways if we are really looking at it from a public health perspective, if that is what our question is.

DR. BRECHER: Or you could be even more general. Just add it to the category of recommendations for vaccination blood donors.

Miriam is shaking her head.

MS. LIPTON: Miriam, I'm sorry. You were not in the room when were asked--there is another question about the infectivity of people who have been vaccinated. Can they be infectious?

DR. ALTER: Well--

DR. BRECHER: Come to the microphone.

DR. ALTER: Vaccine responders, you have to make the, you have to distinguish between

individuals who have responded to the vaccine and those who haven't. So, if you haven't responded to the vaccine, it is as if you didn't--you never received it. So, you are susceptible. You are susceptible to getting infected.

If you have responded to the vaccine, we have seen, over the long term, some sero-conversions to anti-core, which is what people have been talking about as "breakthroughs." These are not clinically significant for the individuals or for those around them. Whether or not they are going to be clinically significant as far as transfusion, I can't say. Were they to donate in that small period of time when it is possible, they might have some residual virus. No one has ever picked up viremia in these individuals.

They are rare but, remember, they have been useful to the following people only for as long as the vaccine has available. So, that's a little over 20 years.

DR. BRECHER: Matt?

DR. KUEHNERT: What was said when you were

out of the room was that, 20 percent of vaccinees [sic] are non-responders and, therefore, would be as susceptible.

DR. ALTER: No, actually I was in the room.

DR. KUEHNERT: Oh, you were?

DR. ALTER: Yes, I was only out of the room for a couple of minutes.

DR. KUEHNERT: Was that accurate? Did you receive that and--

DR. ALTER: No, he said--when he was referring to individuals who begin their vaccine series when they are over 40, as opposed to being young. While we can talk about vaccinating donors, this is not something that is grounded in evidence-based recommendations.

The Advisory Committee on Immunization Practices, I imagine, might find it a little difficult to make a recommendation they are not a high risk group. You don't normally recommend vaccination for how many million people--eight million people based on an incidence of--I can't--

you know, it is a very small number of infections.

DR. BIANCO: But the problem is not the donor, Miriam. It is the recipient.

DR. ALTER: No, you protect--yes, but you--I think you have to consider--yes, but you are still vaccinating the donor and you are imposing something. You can't impose this on health care workers. I think it would be very difficult to impose it on donors.

You also have to consider the negative impact of transient HBsAg positive activity on your donor base. Every time your donor gets a dose, you are going to have to defer them according to the current regulations. If they test HBsAg positive, you're going to have to--you're going to be deferring a lot of donors.

I just--you know, there are a lot of issues here. I am very much, obviously, for vaccination. I would like, obviously, to broaden vaccination, particularly of high risk adults. I would like to get adults vaccinated. But you can't--to vaccinate donors, to protect and not

vaccinate high risk adults, it would be--what--it would not be, I don't think, reasonable public health practice.

DR. BRECHER: Harvey?

DR. KLEIN: I'm sorry that Paul is not here to kind of discuss his views, because there are a lot of niceties in the statement that he made, which I think need to be explored.

For example, it is certainly true that the older you are, the less likely you are to be immunized by vaccination. However, in that age group, first of all, we know that 50 to 60 percent of those people die very soon after the surgeries for which they are transfused. So, they don't go on to die of hepatoma.

Secondly, there is a fairly long period of time after one is infected with hepatitis B virus and the increased frequency of hepatoma. And, again, looking at some of the studies, liver-based disease causing death in those populations is almost unheard of. I mean, the death rate is the same whether or not they were transfused or not.

So, again, in thinking of the overall public health benefit, I don't think you can simply say, well, 20 percent don't get immunized when they are over the age of 40. So, they are a susceptible population, because most of those who get infected will not have any adverse event. Those who would be susceptible to an adverse event probably will die of their heart disease or cancer or whatever else they were operated on for long before they are at risk for hepatoma.

I think we have to explore some of these things when we are considering whether or not to introduce this test in terms of public health benefit, benefit to the transfusion recipient.

DR. ALTER: Can I just make a point about you also have to remember that, you know, I mean, it isn't just today that we have to consider. It is next year and the year after and the next decade. Your donors are going to be immune, are becoming immune by--you know, your donor is between 18 and 25 now. They are highly immune. Many recipients are also immune, which hasn't, I don't

think, has been taken into account when looking at the residual risks.

So, you have to consider that, too. That is highly--the immunity, even natural immunity rate is highly variable in the population by race and a variety of other risk factors. So, I think it would be very difficult to require vaccination of a group, some of whom are likely to already be immune,

DR. BRECHER: That is a good point, Miriam. That in the years ahead, probably the rate of hepatitis B is going to be dropping in our donor population.

DR. ALTER: We can only hope. We have a program to eliminate HBV transmission in this country. We are well on our way. I think to put resources into--I believe we should be prevent--making the blood supply as safe as possibly. But to put those kinds of resources into vaccinated such a low risk group, I think, might in the end actually pull resources away from where the disease is really being transmitted.

DR. BRECHER: The option on the table is to start testing all units, which is another expensive option.

DR. KLEIN: If I could just follow up. The question that I asked you earlier, Miriam, was not entirely naive either. That is that, unlike HIV, when you are infected, you may turn it into a chronic disease by treating it. About 50 percent of people can actually have their disease interdicted by treatment with hepatitis B virus.

Well, I'm clearly much more impressed by preventing disease than treating it after it occurs. I think if you look at the public health issue here and the individual issue, probably the impact on public health of this screening technology is very, very marginal. That does not help the individual, but half of those individuals you can treat and cure.

DR. BRECHER: The majority are going to clear the virus anyway.

DR. BUSCH: Just a minor, follow up comment on the discussion. In the REDS study and,

I think, in all of--in Miriam's data, the vast majority of incident HBV infections are in young donors, in people in their 20s and 30s, in particular certain racial ethnic groups. So, those are the populations that are now being vaccinated with the adolescence.

So, there is no need to vaccinate 40, 50, 60 year old donors, because they are not putting themselves at risk for acquiring HBV and becoming a viremic donor.

DR. BRECHER: Andy.

DR. HEATON: Yes.

I have a question for Sue Stramer. Sue, in your representing ABB, ARC and ABC, you have made the point that minipool testing, the industry does not support the use of minipool testing on the basis that the window period isn't reduced enough that HBsAg testing cannot be eliminated and that there is inadequate automation to support individual donor testing. Therefore, on that basis, you have opposed the recommendation for HBV screening.

If, however, there was an automated device which did allow individual donor testing, what would be your position then?

DR. STRAMER: The statement that I made on behalf of the AABB, ARC and the ABC represented our views on current minipool testing relative to HBsAg, both current assays and assays in the pipeline and, hopefully, assays in development. We suggested that this issue be revisited when ID NAT is available on automatic platforms.

So, again, that is something that we would support revisiting in the future, as Steve alluded to, they are using significantly smaller pool sizes, which we also did include in the AABB statement or looking at ID NAT.

Now, one thing that I do want to point out is, in the cost-effectiveness models that Mike referenced, all the studies looked at the incremental costs of adding the reagent and not the automation. I would assume that the manufacturers who were going to charge us for the reagents will also charge us for the instrumentation. So, the

cost-effectiveness then has to include both the cost and the reagent and the instrumentation, which will be a significant quantity.

Did I answer your question?

DR. HEATON: Somewhat.

DR. BRECHER: Do we have a sense of a recommendation from the committee where we have been given a direct question?

DR. SAYERS: Let me add one thing about the question. I don't think we can extricate the public health impact on the donors. This is not exclusively, I suppose, a question about public health as far as transfusion recipients are concerned. I don't think the public health impact on the donors is going to yield any more than a lot of experience for us in how to manage delivering false-positive results to donors.

DR. BRECHER: In which we already have a lot of experience.

DR. SAYERS: Yes and I can't say that is pleasurable experience.

DR. BRECHER: Jerry, were you going to say

something?

DR. SANDLER: The answer to the question is, it is a mathematical question, it seems to me. That we could just take the numbers of positive--the catchment in the donor population. That's beyond what we are catching now. That's not what she's asking. That's not the question, though, is it?

The question is, what is the public health impact. Well, you just talk about the half dozen people that you're going to pick. That's the answer. Could someone who knows what that question really is say what the question really is?

DR. BRECHER: Gerry, do you want to expand on that?

DR. SANDLER: You don't want six, do you? I mean, what is the public health answer; six a year. That's not the answer.

DR. HOLMBERG: What is the total impact, you know, not only with the number of cases, additional donors that will be picked up? But with the costs involved, what are some other approaches

that may be considered in the decision of the minipool NAT as a screening device?

DR. SANDLER: Well, once that question is opened up in that way, I would like to return to, one. I would certainly endorse everything in the AABB statement, the AABB, the ARC, et cetera, et cetera. That's motherhood and that is perfect.

But I think the real question here is, the answer to this is, it is a hell of a lot less for the money than you are going to get if you put hepatitis B vaccine on a national program. The secretary of health could recommend that insurance companies allow reimbursement for our vaccine as part of a national promotion, et cetera, et cetera.

If you really want to go after hepatitis B in this country, this is a fantastic opportunity to do it, but through vaccine and through multiple programs. Point out to the assistant secretary that, this is a drop in the bucket in the wrong direction.

DR. BRECHER: Matt.

DR. KUEHNERT: We don't have a precedent

for that in the United States. Is there a precedent in other countries, for vaccination in the donor population?

DR. SANDLER: I'm not specifically recommending donors. I'm representing the general population of the United States.

DR. KUEHNERT: Oh, I see.

DR. SANDLER: Because you are going to get your recipients, which is a very important group and it could be prioritized. It could--one could say that, persons who are at risk of being multiply transfused, such as--I mean, it's been done already with the newborns and then you have the adolescents. And now, just keep rolling it out and just push it further. Get the recipients and get the whole population.

DR. KUEHNERT: Okay, thanks for verifying--

DR. SANDLER: No, I was not thinking of donors. Donors were not the entire--

DR. KUEHNERT: Right, because I think Miriam's comments spoke to the need to really focus

on the high risk population. So, you're talking about expanding that definition of high risk population to also include other groups in the United States--

DR. SANDLER: Yes, I think the United States is the high risk population for hepatitis B, I mean, anyone who is HBsAg negative.

Before Miriam walks out the door, I would like to just see if she agrees with me. The question that was asked of her is, what is the risk of a hepatitis B vaccinated person transmitting hepatitis B? I thought that was one of the questions she was addressing.

I'd like to point out that, in the course of counseling donors, I have had about three in the last few years who have come in with HBsAg positivity, anti-core positivity and they have been vaccinated. And the first question I asked them was, do you remember when you were vaccinated for hepatitis B? Were you tested first, tested first? No, I wasn't tested first. They gave me the vaccine.

So, you have a certain number of carriers out there. They are the people who are at high risk. They are the people who you vaccinate. If you don't test them first, well, sure, they are going to show up with core and HBsAg; they are going to be infected.

You would agree, Miriam, that a person who has been infected and who is a carrier, you vaccinate them and they can spread it?

DR. ALTER: Oh, yes, if they are already infected at the time you vaccinate them, you are not having any--your disease stats are not going to change.

DR. SANDLER: Sure, so the economics of this in the hospitals--our health clinic at Georgetown does not screen people before they vaccinate them. It's just a hell of a lot cheaper. Just vaccinate them and roll on and they're going to show up as donors if they are carriers and they will be positive.

DR. EPSTEIN: I want to comment on Dr. Sayers' point about false-positives. At least,

in this study, there were 21 false-positives out of about 600,000 screened, which is an extraordinarily low false-positive rate, of the order of 1 in 30,000. Even if it were a fewfold higher, as is often seen when you go to the field from a controlled trial, it is still a very low false-positive rate.

Now, of course, it is added on to other false-positive rates, but it pales in significance compared to anti-core, for example.

DR. BRECHER: One possibility is to turf this to our Subcommittee on Emerging Threats.

Mark.

MR. SKINNER: Let me answer the question this way. I mean, within the hemophiliac community, we do have a very aggressive vaccination program for hepatitis B and we do test before we vaccinate. It extends to our families and others. We have been very successful. We are a target population.

I guess I would have to answer this question, I mean, relative to what. If I were

answering the question, what is the public health benefit of this relative to putting these kinds of dollars into increasing surveillance? I would say the health benefit is small. I think that really is the only way that we can answer the question is, it is relativity, which really is the same thing we are talking about, you know, risk versus cost. It has to be this versus doing nothing; this versus doing something else if we had the money to spend it; this versus enhancing something else.

If I was faced with the choice of spending the money on this to get the marginal return versus spending that money on the programs that the CDC talked about, I believe the public health benefit would be much greater on what the CDC is doing than doing this, based on where we are with both today.

DR. BRECHER: I think that seems to be the sense of the committee; that the public health sector will be better served by allocations of monies in other areas, rather than additional tests.

DR. ALTER: I agree. You could even--I

don't know exactly how far you want to go, but you could even say by strengthening the high risk adult immunization program, something like that. It depends on how far you want to go.

DR. BRECHER: Well, we can say immunization program. We don't even have to be specific. But the health care sector would be better served by strengthening the CDC immunization program. You pick where it needs to go.

Karen.

MS. LIPTON: I would just be reluctant--if we are really talking about recipients, presumably the people who are at high risk are not in our centers anyhow. So, I would just say expanding the program generally, being better than focusing--unless you are going to say, we are going to focus next on 20 to 30 year olds, which is fine. But I think targeting people who aren't supposed to be blood donors doesn't really do anything vis-a-vis the blood recipient population.

DR. ALTER: I agree. I'm not quite--I mean, I'm hoping that what you're talking about is

general public health benefit that will, in the end, benefit the recipients as well, but not to expand vaccination into a low--obviously, it is well on its way. So, we are really talking about adults.

DR. BRECHER: It may be recipients. Maybe that would be another group you need to target, people who are likely to get a lot of transfusions.

DR. ALTER: Well, except we do reserve vaccine for people at high risk at this time. I think you would have to go address the Advisory Committee on Immunization Practices about the risk in this population. This is not a high risk population. Now, you're talking about a low risk versus no risk.

I think you need to address--I think you need to take that into account. This is a low risk. I'm not saying we should dismiss it, but it is a low risk and we vaccinate around high risk, at least, with hepatitis B vaccine in adults. So, I think you need to take that into consideration.

DR. BRECHER: Jay.

DR. EPSTEIN: Well, in trying to understand the question, it has been suggested that the same questions were asked of the BPAC, but that is not actually true. The BPAC was asked some scientific questions, more or less along the lines of the validity of the data. The BPAC was asked the quantitative question, if you will. What is the yield?

Really what the PHS Advisory Committee is being asked is whether the benefits are worth the cost. That is not an FDA question. It's a public health question or it is a departmental question. I think that Paul Holland focused for us where the critical issue lies. He basically said in simplistic terms, the yield is comparable to hepatitis C, but the chronic sequelae are less.

I think what you heard Mike Busch tell you is that, if you try to look at that in objective terms, there are about one-sixth the quality adjusted life here, save for infections prevented, for hepatitis B compared to hepatitis C. So, one way of looking at this is to ask ourselves the

question and, of course, it's not the only way and you could dismiss this.

One way of looking at it is to ask ourselves, if we thought it rational, indeed, urgent to apply minipool NAT with all its limitations to screening the blood supply for hepatitis C, how would we use that as a benchmark to look at the HBV question? I would say, again, in simple terms, one would expect the additive costs to be roughly comparable. In other words, it is another non-multiplexed, an AT test. It is stand alone NAT. It's like adding NAT in the first place, but that the individual health benefits, roughly speaking, are one one-sixth, if you are willing to look at it in terms of qualities.

Now, I think what Paul also said is that, it is his personal view not to look at it in qualities. I'm taking that by implication from his statement that, at least, at Sacramento Blood Center, a decision was made to continue testing after the IND study, well, under IND, following closure of the study, because they felt that any

infection prevented, is an infection prevented and there are potentially adverse consequences, which no one disputes.

So, the issue really comes down to whether you are willing to look at that phenomenon quantitatively or not. So, to me, there is a clear dimension of this question which is, do the benefits warrant the costs, looking carefully at what those benefits really are. Then I think that, again, to my way of thinking, it is entirely legitimate for this committee to look at our public health system as a whole and where we allocate resources and comment.

I'm not at all uncomfortable with the committee commenting on vaccination programs where they might be targeted, potential expansion pass risk groups, with all the caveats that Miriam pointed out. I think that is part of the issue. But I think we shouldn't overlook the core question on risks and benefits or costs and benefits.

DR. BRECHER: Karen.

MS. LIPTON: So, given what you just said,

Jay, I agree with your statement, additive costs being equal. If you look at it from the quality adjusted life years, the benefit--although I don't know that I would say to the individual, because that quality is really not an individual issue. It is a big issue.

I think that would make me uncomfortable in and of itself. What gives me some comfort in taking that position is also to say that, we know there are increased sensitivity tests coming along and new things, plus the opportunity to relook at this question if we get to individual NAT. That is what allows me to move in that direction, to make that statement.

Then also, I very much believe in the statement about, if we are really talking about the public health and where we are spending dollars that, again, I cannot get over how effective vaccine has been in terms of if we are really trying to eradicate hepatitis B.

DR. BRECHER: Jerry.

DR. SANDLER: If we are to respond about

the costs of putting this in, I would very much like to have some statement that explained that every blood safety initiative in the last few years has been the burden of the hospitals for two years. That is to say that, the CMS mechanism will not make an adjustment to pick up this cost until two years after it has been put in there.

So, someone is going to make a decision about I think it is worth spending the money and you spend the money for two years until I catch up to you.

I think in some, perhaps, more diplomatic language, we point out that it would be very nice, if she wants to buy something, she can pay for it.

DR. BRECHER: Okay, Harvey and then Larry.

DR. KLEIN: I just wanted to comment that, first, I really agreed with the way Jay summarized the answer to this question, but I would like to additionally say in answering it, if we are to really recommend that we look at getting a multiplexed, direct assay of viruses that can be automated and, hopefully, at reasonable cost on

individual units, because that is, in fact, the bottom line from everything we have seen, even though single unit does not solve all problems.

If you are going to look at a gold standard for testing, you want a sensitive, direct test of the virus on individual units in a multiplexed form.

DR. BRECHER: Larry.

MR. ALLEN: I keep hearing this word high risk. Whatever the donor pool population is today, there is an acknowledged push for more minorities to become more donors. This is going to change this equation. I think we need to acknowledge that.

DR. BRECHER: Yes, that is a valid point.

So, what is the committee's pleasure? We need to respond to this question.

One possibility is what I have already suggested. It would be something like in regard to the introduction of minipool HBV NAT for blood donations, the committee feels the public health would be better served by expanding the hepatitis B

immunization program. We might put in there that as currently configured for the minipool assays or leave the door open for something in the future.

Gerry.

DR. HOLMBERG: I think it is a good point that Dr. Klein made. You might want to consider that in your recommendation also, because that is an additional place where additional resources may be spot on doing more, getting more of those procedures in place, the multiplexing.

DR. BRECHER: I have given Rich that verbiage. She is going to type it in so we can look at it. We have two--well, he does that. I just want to bring up that, we have two other items that we are going to have to address before we leave or lose our prom.

One is this question of the 20 percent copay that the hemophiliac patients and other users of plasma derivatives have to pay. There is one resolution suggestion from Larry in that regard. I have heard it from several of the other committee members.

One possibility for this, rather than coming up with a specific resolution now, is to send this to the Reimbursement Committee to try to address, with the thought that we would bring this back at the next committee in a big way; that we would spend a lot of time on the--I think it is called the donut, the problem of the copay for these products.

Jerry.

DR. SANDLER: If I understand correctly, the copay issue is something that has been through Congress and we advised the secretary of health. I'm not sure that we have the right address. What can the secretary of health do if it is mandated by Congress, other than sending us a letter saying, I'll readdress your letter to the party that is responsible for this.

MR. SKINNER: Well, I think you raise a good point and I'm fully supportive of the concept behind what Larry is talking about. The copay issue is an issue that has to be addressed. There actually are several ways to do it. We can try to

resurrect or to perpetuate the existing system, which allowed for a differential that allowed those providers to be able to afford to write off the patients. Now, we are faced with the situation where they are going to deny picking up those patients, because they can't afford to write off the copay.

So, in terms of what CMS could do is, they could raise that incremental adhesional reimbursement rate, which I think is five cents, to allow them to have a margin against which they could write off. I think that, perhaps, is within their jurisdiction. Perhaps, it is within the current--or there is the complete solution, which is seeking congressional change or a carve out for the copay for hemophilia products.

DR. BRECHER: So, I think this has some nuances that, I think, deserve some in-depth discussion. So, I would like to send this to the subcommittee as one of its tasks and we will bring this back at the next meeting.

Mark?

MR. SKINNER: I can be agreeable with that if there really is an absolute guarantee that we will spend serious time with it and we do it early in the meeting, so we are not facing a lost quorum.

DR. BRECHER: We could do it first.

Merlyn.

DR. SAYERS: John Walsh had to leave, but he asked me to say that he felt that this deserved more of the attention of the committee than we have now. He was also hopeful that this particular statement might become more comprehensive if the committee was able to devote more time to it.

DR. BRECHER: So, I think it sounds like essentially this is a topic that needs to be addressed; that we have not spent adequate time on it at this meeting. We will plan on spending a considerable amount of time on the question at the next meeting.

Karen.

MS. LIPTON: Just a quick question. I am trying to review all those conflict of interest things. We are not permitted to lobby Congress,

right? I think we should sort of clarify what our potential role can be in this.

DR. BRECHER: Our charge is to advise the assistant secretary.

MS. LIPTON: Do you know, Jerry?

We don't have to resolve it now, but before we start down any road, let's be very clear about what we can and cannot do.

DR. HOLMBERG: You are a special government employee and, therefore, you cannot lobby Congress.

MR. SKINNER: My understanding is, we could make a recommendation to the secretary that they, perhaps, include it in their legislative recommendations to the President in order that the President would include it to Congress or whatever, a statutory change to cover this. I mean, we could make a recommendation for legislative change, but it would have to go through the secretary to Congress. We just don't have the ability to take it directly to Congress.

DR. BRECHER: Okay, we will table this

discussion, with the intent that we will bring it back for a more expanded discussion at the next meeting.

Let's get back to the hepatitis B issue and then the question of the Trial A Resolution that was passed yesterday. There has been a question brought up about that. So, I want to revisit that for just a minute after this.

The proposed wording in regard to the introduction of minipool is "as currently conceived" or currently configured, I think would be better, HBV NAT for blood donations, the committee feels the public health will be better served by expanding the hepatitis B immunization program.

Is that the sense of the committee? Is that where we were going?

DR. KLEIN: Than what, "better served" than what?

DR. HEATON: My concern is this treats this as a zero sum game.

DR. KLEIN: Yes.

DR. HEATON: We might be better off by phrasing this from the perspective that, in terms of value per dollar, more cases of hepatitis B could be prevented by immunization than might be prevented by minipool NAT. I don't think we should view this from a zero sum perspective, but more as a cost-benefit issue.

DR. BRECHER: A bigger bang for the buck.

Jerry.

DR. SANDLER: I think it would be helpful to have some sort of an introduction that explains that, contrary to issues that we faced in the past with regard to blood safety, specifically, the HIV and the hepatitis C issue, this hepatitis B problem has a preventative strategy that was not available, namely, vaccination. Therefore, and then go on.

I think that we are all going down the path that we have been down before and this is not the same path.

DR. BRECHER: Okay, would you repeat your opening statement so that we can get that into the computer?

Jay.

DR. EPSTEIN: Well, I have been trying to gin up a preamble. It includes what Jerry is saying.

Whereas, the HBV risk from transfusion now exceeds that from HIV and HCV; whereas, HBV minipool NAT, as currently configured, has limited ability to reduce risks of HBV post-transfusion compared with ID NAT technology that is under development; whereas, the average clinical morbidity of HBV infection is significantly less than that of HIV and HCV, but donor screening would incur comparable costs and, whereas, vaccination is a known effective prevention strategy for HBV, the committee x, y, z.

DR. SANDLER: The only--where the HIV vaccination is a known preventative strategy for HBV--parens or however--but is not available for HIV and HCV. I think that would be something more direct.

DR. BRECHER: Okay, so that is going to be typed in so we can look at it in just a second.

We still have to do the Trial A. Merlyn, you want to maybe just talk us through the Trial A question? I have a copy here if you don't have yours.

DR. SAYERS: I apologize for bringing this up again, but I was looking over it last night. That Trial A recommendation starts out with, the committee reviewed the available transfusion-related, acute lung injury data. I think that is a more ambitious assessment of what we did. We listened to one presentation. We heard Steve review the Canadian meeting.

I wondered, if the committee or the survivors were to pardon us leaving out "we reviewed the available transfusion-related, acute lung injury data" and just say the committee reviewed transfusion-related, acute lung injury data. I think when we say "available," it makes it sound as if what we did was much more embracing than what we did. So, I would like to leave out available there.

When we say we did not find sufficient

scientific evidence, I wonder if we really need to include "sufficient," because it implies that we found some evidence to recommend an intervention, but it hadn't reached the density prompting us to act.

So, I would ask the committee to consider rewording that, "did not find scientific evidence to recommend." Then we also said a "specific intervention." I don't know that we need the word "specific," because the implication is that we might have entertained some non-specific ones. So, I would just like to say, "recommend an intervention at this time."

So, we leave out "available." We take out "sufficient" and we take out "specific."

DR. BRECHER: It would save a lot of trees.

Jerry.

DR. SANDLER: You are going to need a vote. I make a motion that we accept the revised language for the previously voted upon policy or document.

DR. BRECHER: I'm sorry. Karen?

MS. LIPTON: I am sort of troubled by saying we didn't see any scientific evidence. We saw some evidence. We just don't know what it meant.

DR. BRECHER: Well, we aren't saying that we did not find scientific evidence. We are just not--we are just eliminating the word "sufficient." We did review transfusion, acute lung injury. I think these are relatively--

MS. LIPTON: So, we saw no evidence to recommend. I don't know that that is true.

DR. SAYERS: Well then, we should have done something.

MS. LIPTON: I think there was some evidence. I just don't think it--we felt we had the full scope and it wasn't conclusive. Maybe I'm wrong, but I--

DR. BRECHER: So, you are advocating retaining the word sufficient?

DR. BIANCO: Instead of sufficient, I just came up with the word conclusive. Why not

conclusive evidence that would give it--

DR. BRECHER: Or overwhelming evidence?

DR. KLEIN: No, I don't think that you always need conclusive evidence.

MS. LIPTON: No.

DR. KLEIN: You may need compelling evidence, perhaps, but certainly not conclusive. If you wait for conclusive, we would be waiting a long time for a lot of things.

DR. BIANCO: So, compelling, I will accept compelling.

MS. LIPTON: Does compelling work for you, Merlyn?

DR. SAYERS: These are just suggestions. I mean, we did not find evidence to act.

DR. BRECHER: I think compelling would probably meet everyone's needs.

Okay, so there are three suggestions. We are going to eliminate the word "available" and substitute the word compelling instead of sufficient in front of scientific evidence and drop specific, because we did not talk about

non-specifics.

So, all those in favor?

DR. SAYERS: Aye.

[A show of hands]

DR. BRECHER: Okay, all those opposed?

[No response]

DR. SAYERS: Thanks.

DR. BRECHER: Any abstentions?

[No response]

DR. BRECHER: Okay, so we will make those three changes.

Okay, let's look at all the whereases.

MS. LIPTON: Comparable costs to what? Comparable cost to HCV? The third, it has to be comparable to something.

DR. EPSTEIN: Oh.

MS. LIPTON: It was comparable to HCV, correct, Jay?

DR. EPSTEIN: Yes, comparable to HIV and HCV.

MS. LIPTON: It was both, to both?

DR. EPSTEIN: Well, you have one multiplex

test and two non-multiplexed tests. It is compared to another NAT test.

DR. HEATON: To other NAT tests?

DR. EPSTEIN: Right.

MS. LIPTON: To other NAT tests?

DR. KLEIN: That would be fine.

Just for better English it would be, would incur a cost comparable to other NAT tests.

MS. LIPTON: Okay, should we just transpose comparable and cost and then just take the s off of costs.

DR. HEATON: I would also like to propose a change to the final recommendation and insert after "the committee feels" the section "for comparable expenditure of health care dollars, the general public health would be better served." I want to make the point that this is not a zero sum game and that we are making a relative value judgment. So, I propose that after "the committee," we would insert "the committee feels that for comparable expenditure of health care dollars, the general public health." Expenditure

of health care dollars and then "the general public health."

DR. KLEIN: If I could ask that you might change "feel" to believe.

DR. BRECHER: Mark.

MR. SKINNER: I wanted to go back to Harvey's comment about whether there should be a second recommendation. It is kind of implied in the beginning, but it is not stated, about encouraging research into the multiplex assays on single unit donations, if we should add that. Maybe Harvey can phrase it better than I can.

DR. KLEIN: This would be after, perhaps, a final thing that the committee believes that we should pursue, multiplexed assay to detect direct detection of these viruses on individual units, something to that effect.

MR. SKINNER: Maybe not we should pursue, but the secretary should pursue a resource--resources should be committed to develop or pursue.

DR. KLEIN: Yes.

DR. BRECHER: Sort of encourage research?

DR. KLEIN: Um-hum.

DR. SAYERS: Well, could we eliminate "clinical" in "clinical morbidity" and eliminate "known" in "known effective?"

DR. BRECHER: The development of multiplexed NAT. It is sort of like when you go out to the movies, to the multiplex.

[Laughter]

DR. EPSTEIN: It may not be NAT.

DR. BRECHER: Right, it may not be NAT.

DR. KLEIN: I think we should just stick to multiplex, direct viral testing. It may not even be viral, but multiplex direct pathogen testing on single donations.

DR. BRECHER: Very good.

MS. LIPTON: I believe he said on single donations.

DR. SAYERS: You know, that clinical morbidity could just be morbidity and non-effective could just be effective.

DR. BRECHER: Jay.

DR. EPSTEIN: I think what I would really want to do is available, but that is something that could be contested over the issue of current resources, you know, how available is it. So, perhaps, I'm happy just deleting the word.

DR. SANDLER: [Off microphone] We say, hepatitis B virus post-transfusion, rather than commonly referred to as transfusion-transmitted HBV.

DR. EPSTEIN: Where?

DR. SANDLER: The second--transfusion-transmitted HBV.

DR. BRECHER: And then get rid of post-transfusion.

DR. EPSTEIN: I know I stuck in the acronyms, but do we want to expand MP and ID in the second bullet?

DR. BRECHER: We can do that later.

DR. EPSTEIN: Yes, right.

DR. BRECHER: We will blow them up.

All right, before we think of anything else, are we ready for a vote?

All those in favor?

[A show of hands]

DR. BRECHER: Five, six, seven, eight.

Fortunately, we barely have a quorum. So, this passes.

Okay, we have one abstention and nine in favor. So, that passes. Nine is our quorum.

Do we have any other items that need to be discussed?

[No response]

DR. BRECHER: If not, this meeting is adjourned early.

[Whereupon, the proceedings in the aforementioned matter were adjourned.]