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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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116TH MEETING OF THE BLOOD PRODUCTS ADVISORY COMMITTEE

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November 30, 2017
8:00 a.m.

FDA White Oak Campus
Great Room, Building 31
10903 New Hampshire Avenue
Silver Spring, MD 20993

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This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

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M E E T I N G

(8:00 a.m.)

LCDR EMERY: Good morning. I'm Bryan Emery, the Designated Federal Official for today's meeting of the Blood Products Advisory Committee.

Mrs. Joanne Lipkind and Ms. Rosanna Harvey are the Committee Management Specialists, and they can assist you with any needs at the tables located out in the hall.

I would like to welcome all of you to this 116th meeting of the Advisory Committee, held in the FDA White Oak Great Room.

Dr. Christopher Stowell is the acting Blood Products Advisory Committee Chair.

The CBER press media contact is Ms. Megan McSeveney. And if she's here, if you can stand up for everyone. Okay, I don't see her here yet. And Shaylah Burrill is the transcriptionist.

I would like to request that everyone please check your cell phones and pagers to make sure they are turned off or in silent mode. Please also remember to speak directly into the microphone at all times, and please identify yourself to the public and the transcriber. It is helpful for the public and for people attending by webcast and the transcriber.

For members around the table and the audience, coffee, drinks, and snacks are out the doors and to the right of the kiosk.

Members' lunches will be brought to the -- there's a room in the back where the lunches will be brought for you when we break for lunch.

There are restrooms out the doors and to the right, and you go all the way to the end of the hall.

All Committee topics and update discussion needs to be done in the public forum and not in groups during breaks. The FDA and public needs your advice, thoughts, and expertise.

During the voting, Topic II, the BPAC Committee will be seated as a device panel, and the industry representative and the consumer representative will not vote.

The public and industry must stay behind the stanchions and in the audience area. Please do not enter the FDA or BPAC Committee table area. Please wait until the Open Public Hearing designated time to make any remarks, using the center aisle microphone.

Now I'd like to read into the public record the Conflict of Interest Statement for this meeting.

Good morning, everyone. I'm Lieutenant Commander Bryan Emery, the Designated Federal Official for the Blood Products Advisory Committee meeting of the Center for Biologics Evaluation and Research, FDA, and I welcome you all to this 116th meeting of the Blood Products Advisory Committee being convened by the Food and Drug Administration both today, November 30, and tomorrow, December 1, 2017, under the

authority of the Federal Advisory Committee Act of 1972. This meeting is open to the public in its entirety, and all members and consultants are participating in person at this meeting in the open session.

The Committee will discuss this morning, under Topic I, the Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion.

In the afternoon, the Committee will meet in open session to discuss, under Topic II, the Classification of Human Leukocyte Antigen, Human Platelet Antigen, and Human Neutrophil Antigen Devices.

On December 1, 2017, in open session under Topic III, the Committee will discuss the Strategies to Reduce the Risk of Transfusion-Transmitted Zika Virus.

Following Topic III, the Committee will hear two update presentations on the following topics: (1) Transfusion-Transmissible Infections Monitoring System and (2) FDA Summary of the Public Workshop on Tick-Borne Diseases and Blood Safety.

The following information on the status of this Advisory Committee's compliance with Federal ethics and conflict of interest laws including, but not limited to, 18 U.S. Code 208 is being provided to participants at this meeting and to the public. This conflict of interest statement will be available for public viewing at the registration table.

With the exception of the Industry Representative, all participants of the Committee are either special government employees or regular federal government employees from other agencies and are subject to the federal conflict of interest laws and regulations.

Related to the discussion topics at this meeting, all members and consultants of this Committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouse or minor children and, for the purposes of 18 U.S. Code 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S. Code 208, Congress has also authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

However, based on today's agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 U.S. Code 208.

Dr. Christopher Stowell is currently serving as the Acting Chairperson for this 2-day committee meeting. Dr. Stowell is an appointed special government employee, and he also serves as a Temporary Voting Member.

Dr. Judith Baker is currently serving as a Voting Member and the Consumer Representative for this meeting. She is employed by Western States Regional Hemophilia Network in policy. Dr. Baker is appointed as a special government employee and therefore is screened for her financial conflicts of interest and cleared prior to her participation.

Dr. Susan Stramer is currently serving as the Industry Representative to this Committee. Dr. Stramer serves as an Executive Science Officer at the American Red Cross and brings her expertise in transfusion and cellular therapies to the Committee. Industry representatives are not special government employees and do not vote and do not participate in closed sessions.

Dr. Carolyn Gould is an invited speaker for Topic III. Dr. Gould is a regular federal government employee who serves as the Medical Epidemiologist at the Centers for Disease Control and Prevention in Atlanta, Georgia. She was screened and cleared for participation at this meeting.

Dr. Stephen Field and Dr. McDonald are invited guest speakers for Topic I. Dr. Field currently serves as the Medical Director for the Irish Blood Transfusion Service in

Dublin, Ireland. Dr. McDonald is the Head of the National Bacteriology Laboratory of the National Health Service Blood and Transplant in London, UK. As guest speakers, they have been asked to make disclosures related to any affected firms for this meeting.

At this meeting there will be invited regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interests.

FDA encourages all other participants to advise the Committee of any financial relationships that you have with any firms, its products, and if known, its direct competitors.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda but for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

Additionally, I would like to provide the following specific guidance regarding this November 30-December 1, 2017 BPAC meeting.

Please note that each of the topics, namely Topic I, II, and III, of this meeting are determined to be a particular matter of general applicability and, as such, does not focus this discussion on any particular product but instead focuses on the classes of products under discussion.

The presenter/speakers may provide data on products, if any, that will serve only as examples for the Committee to have a scientific discussion.

Please note that this BPAC meeting is not being convened to recommend any action against or approval for any specific product.

This BPAC meeting is not being convened to make specific recommendations that may potentially impact any specific party, entity, individual, or firm in a unique way. Any discussion of individual products will only be to serve as an example of the product class.

This meeting of the BPAC does not involve the approval or disapproval, labeling requirements, postmarketing requirements, or related issues regarding the legal status of any specific products.

This concludes my reading of the Conflicts of Interest Statement for the public record.

At this time I would like to thank you all for your participation, and I now hand over the meeting to the Chair, Dr. Stowell.

DR. STOWELL: Good morning, everybody. Welcome to this meeting of the Blood Products Advisory Committee.

Before we get started, I think we would like to have introductions from the members of the Committee. We will go around the table and start with you, Dr. Stapleton, in the corner. The red oval button.

DR. STAPLETON: Yours is working. Jack Stapleton. I am an infectious disease physician and a professor in the Department of Internal Medicine and Microbiology at the University of Iowa.

DR. SANDBERG: I'm Sonja Sandberg. I'm an applied mathematician, and I teach at Framingham State University in Massachusetts.

MR. REES: I'm Robert Rees. I am the Manager of the Blood Bank Regulatory and Compliance Program for the State of New Jersey.

DR. ORTEL: Tom Ortel. I'm the Chief of Hematology at Duke, and I run the coagulation laboratory in the hospital.

DR. LEITMAN: Susan Leitman, transfusion medicine, NIH.

DR. ESCOBAR: Miguel Escobar, hematologist at the University of Texas in Houston.

DR. DeMARIA: Al DeMaria, Medical Director and State Epidemiologist at the Bureau of Infectious Disease Laboratory Sciences at the Massachusetts Department of Public Health.

DR. BAKER: Judith Baker, Public Health Director for the

Center for Inherited Blood Disorders in Orange, California. I'm with the Federal Hemophilia Treatment Center Network and the Sickle Cell Disease, Pacific Sickle Disease Regional Consortium in the Western States.

LCDR EMERY: I'm Bryan Emery. I'm the public health service officer, and I am the DFO for this meeting.

DR. STOWELL: Chris Stowell. I'm the Director of the Blood Transfusion Service at Mass General and Associate Professor of Pathology at Harvard Medical School.

DR. BASAVARAJU: Sridhar Basavaraju, Director of the Office of Blood, Organ, and Other Tissue Safety at CDC.

DR. KINDZELSKI: Andrei Kindzelski, Program Director of Blood Division, Heart, Lung, and Blood Institute, NIH.

DR. STRONCEK: Dave Stroncek, Chief of the Cell Processing Section, Department of Transfusion Medicine, NIH Clinical Center.

DR. ARDUINO: Matt Arduino. I am Senior Advisor for Environmental Hygiene and Infection Prevention in the Office of the Director of the Division of Healthcare Quality Promotion. I also wear the hat of the Associate Director for Laboratory Science within the division at CDC.

DR. CARROL: I'm Karen Carrol. I am the Director of the Microbiology Laboratory for the Johns Hopkins Hospital.

DR. QUILLEN: Karen Quillen, transfusion medicine and hematology physician, Boston University Medical Center.

DR. STRAMER: Susan Stramer, Vice President of Scientific Affairs at the American Red Cross and also the chair of the AABB Transfusion Transmitted Diseases Committee, and I'm the Industry Rep.

DR. STOWELL: Okay, thank you.

The first topic of several very interesting topics we have over a couple -- the next couple days has to do with additional measures for reducing the risk of bacterial transmission by platelet products, and the first presentation will be by Dr. Haddad from the FDA, who will set the background for us.

DR. HADDAD: Good morning, everyone. My presentation this morning is the Options to Further Reduce the Risk of Bacterial Contamination in Platelets for Transfusion.

I will start with an introduction of the topic, and then I will provide the background on platelet storage and control of bacterial risk. And then I will summarize the recent FDA policy initiatives towards mitigating the risk of bacterial contamination of platelets. And then I will describe the current U.S. practices in bacterial testing. And then I will present the proposed considerations to further reduce the risk of bacterial contamination in apheresis platelets.

Platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component, and this is because platelets are uniquely vulnerable to bacterial outgrowth due to their storage at room temperature.

And this risk of sepsis, although reduced, has persisted despite the interventions currently in place.

Currently, platelets are stored at room temperature for a maximum of either 5 or 7 days depending on the preparation method, storage container, and bacterial risk control measures.

In terms of regulations on controlling the bacterial risk in platelets, under 21 C.F.R. 606.145, blood establishments and transfusion services are required to assure that the risk of bacterial contamination of platelets is adequately controlled. This requirement is currently met by either testing for bacterial contamination at least once or treating with an FDA-approved pathogen reduction device.

For 5-day platelet storage, the bacterial risk control is achieved most commonly through the performance of a culture at least 24 hours after collection, and that's what we refer to as primary testing, or by treatment with an FDA-approved pathogen reduction device within 24 hours after collection.

For extension to 7 days, additional secondary testing, so that would be secondary to the early primary culture, is permitted using a rapid test labeled as a safety measure. And safety measure indicates that testing of platelets proximate to transfusion has shown benefit for detection of contamination not revealed by previous primary bacterial testing.

Extension of dating beyond 5 days does not apply to pathogen-reduced platelets, and this is because the storage of

apheresis platelets treated with an FDA-approved pathogen reduction device is currently limited to 5 days.

Moving on now to the recent FDA policy initiatives to mitigate the risk of bacterial contamination in platelets:

In September 2012 we brought this issue to this Committee, which advised the use of secondary rapid testing on Day 4 and Day 5 transfusions to enhance the safety of 5-day platelets.

In December 2014 we published a draft guidance document with considerations to enhance platelet safety and availability, and it included BPAC's 2012 advice.

In March of 2016 we published a revised draft guidance document on controlling the risk of bacterial contamination of platelets, and it included additional considerations, namely, pathogen reduction in lieu of early culture and secondary testing to ensure the safety of 5-day platelets and extension to 7 days of suitably stored platelets that are secondarily tested with a test labeled as a safety measure.

And in May 2016, the donor eligibility rule, including 21 C.F.R. 606.145, went into effect.

Following the publication of the draft guidance, we received comments, and these will be summarized by my colleague Jennifer Scharpf in the next presentation. And the public comments introduced three proposed alternatives for primary and secondary bacterial testing.

One proposal pertains to 5-day storage of apheresis

platelets, and this is the minimal proportion and sampling volume approach. And two proposals pertain to 7-day platelets, and they are the large volume and delayed sampling approach and the secondary bacterial culture testing on Day 4 following an early primary culture.

In this meeting FDA will ask the Committee whether specific alternative strategies for testing of platelets can provide adequate assurance of bacterial safety for both 5-day and 7-day apheresis platelets.

To inform the discussion, data will be presented on both apheresis and whole blood-derived platelets.

Because the datasets for apheresis platelets are more extensive and 7-day platelets in the U.S. are limited to apheresis platelets, questions for the Committee will focus only on apheresis platelets.

And in the next few slides I will describe the current U.S. practices in bacterial testing.

Bacterial testing of apheresis platelets is performed using either culture-based devices or rapid tests.

For culture-based devices, the detection mechanism is based on the growth of the bacterial organisms, and that can take hours or days. The analytical sensitivity, which is an expression of the limit of detection, is about 1 CFU/mL. And the culture medium can be either aerobic, anaerobic, or both, and culture-based devices can be used for primary or secondary

testing.

The rapid tests are non-culture based devices, and the mechanism of action is through direct detection of specific bacterial components. Their analytical sensitivity varies between 10^3-10^5 CFU/mL depending on the organism and the testing device. And the rapid tests can be used for secondary testing of apheresis platelets.

Focusing now on the culture testing and on the traditional practices for bacterial culture of apheresis platelets: For over a decade, apheresis platelets have been universally screened with a culture-based test, and the sampling of the main collection occurs at least 24 hours after its collection using an 8 mL sampling volume inoculated into an aerobic culture medium.

Numerous studies on apheresis platelet products intended for transfusion have shown that the clinical sensitivity of the primary culture ranged only between 11% and 40% due to the limit of sampling at low bacterial load, what we call the sampling error. So, therefore, on the day of transfusion, a bacterial residual risk persists in spite of the primary culture.

This table has the bacterial detection and sepsis rates of 5-day apheresis platelets tested by the primary culture. The first column has the detection rates, and they range between 1 in 8,900 approximately, to 1 in 3,900. And the rates vary

based on the testing sites and on the apheresis collection platform.

The bacterial detection rate on the day after infusion, as assessed by a culture, is about 1 in 2,400. And the sepsis rate can vary depending on whether the reporting is passive or active. And by passive reporting, we mean that the septic transfusion reaction report was initiated by the clinical team after they have recognized the transfusion-related septic reaction. And active reporting implies a prospective follow-up evaluation of transfused patients, looking for evidence of a transfusion reaction or no reaction.

So by passive reporting, the rate varied between 1 in 59,000 to 1 in 220,000. That's per collection. And by active reporting, one study showed that the rate is about 1 in 10,000 per component.

Now, throughout this presentation, some of the sepsis rates will be expressed by collection, others by component. This is simply based on the fact that these rates were reported as such in the corresponding studies.

I mentioned earlier that the traditional culture testing in the United States is to use only an aerobic medium. However, there are benefits to the addition of an anaerobic culture medium. The anaerobic culture leads to an increase in bacterial detection rate due to sampling of an additional volume from the product. You have growth of the strict

anaerobes that do not grow in an aerobic culture medium.

Also, you can have faster growth of certain facultative aerobes with shorter detection time, and rare fatal and non-fatal septic reactions have been associated with anaerobes missed by the primary aerobic-only culture, which would be detectable by an anaerobic culture medium.

However, there are limitations of an anaerobic culture medium. Anaerobes rarely grow in the aerobic environment of a platelet product. In one recent study, the primary culture testing using concurrent aerobic and anaerobic media showed that the false positive rate of the anaerobic culture medium was 78.9% of the reportedly positive collections.

And of the confirmed contaminated products that were detected by the anaerobic-only culture medium, 60% were contaminated with low virulence, slow-growing organisms, such as the *Propionibacterium*, *Corynebacterium* species, that are detected late, often after the product has been transfused.

Thirty-five percent were contaminated with species that were also identified in other collections in the same study and that grew in the aerobic medium, meaning that the detection by the anaerobic culture medium likely related to an increase in the sampling volume rather than the medium itself. And in this group, *E. coli*, *Staphylococcus*, *Streptococcus*, *Listeria*, and *Gemella* species were identified.

And the remaining organisms, about 5% of them were either

strict anaerobes or facultative anaerobes, and they were the *Haemophilus*, *Peptostreptococcus*, *Lactobacillus*, and *Campylobacter* species.

Moving on now to the practices for rapid testing of apheresis platelets, the optimal sampling time is at least 72 hours after collection, and that's because the sensitivity of rapid testing is lower than that of the culture-based devices. The sampling volume is small, 0.5 to 1 mL, depending on the testing device. The readout is obtained within 20 to 60 minutes, and the rapid testing can be used in transfusion services within 24 hours after infusion as a secondary test.

This slide has the bacterial detection and sepsis rate of 5-day apheresis platelets tested by a secondary rapid test, and these rates have been generated by a study in which about 28,000 apheresis units, found negative by a primary culture, underwent a secondary rapid testing on the day of transfusion, so that could be Day 2 through Day 5, within 4 hours of issuance.

And in the first column you have the confirmed detection rate, and it was about 1 in 3,000. The false positive rate was 0.51%. The false negative rate was equal or greater than 1 in 9,200. And I say equal or greater because in the study, only a subset of the platelets were cultured concurrently with the rapid testing, so the false negative rate could have been higher had all the negative rapid tests been concurrently

cultured.

The last column has the sepsis rates. In this study there was one confirmed septic reaction detected by active reporting, and there was one possible to probable septic reaction detected by passive reporting leading to a septic rate of about 1 in 28,000 to 1 in 14,000.

From this point on, I will focus on the three proposals that we are seeking the Committee's advice on. I will present an overview of these proposals, and then later on we have three speakers who will provide us with a more detailed view of their strategy as they have applied them in their respective institutions.

And the first one pertains to 5-day platelets, and it was the minimal proportional sampling volume approach. The predominant sampling practice for culture-based bacterial testing of platelets is to sample a fixed volume from the apheresis collection, regardless of its collection volume.

A new concept of minimal proportional sampling volume has been recently described whereby the sampling volume is increased proportionally to the apheresis collection volume in order to enhance the detection of bacterially contaminated platelets by decreasing the sampling error and to ensure the safety of 5-day platelets from bacterial contamination without secondary testing.

So this concept has been applied in a blood collection

system in which apheresis platelets were collected during two study periods, A and B, using the same apheresis collection platform. And the bacterial testing methodology was identical in the two periods, except for the sampling volume. In Period A, the volume was 8 to 10 mL, which represents between 1.1% to 2.7% of the collection volume. And in Period B, the sampling volume was the minimal 3.8 proportional sampling volume.

In the next slide I will present the detection rates, comparing Period A and Period B at the center, and in this slide I define the terms used in the next slide, following an initial positive instrument signal after the inoculated bottles have been placed in the incubator.

A true positive is defined as growth of the same organism from the culture bottle and the platelet component and/or from the patient.

A false positive is when you have no growth from the culture bottle, and the platelet component is negative or unavailable for confirmatory testing.

Discordant negative is when you have growth of the organism from the culture bottle, but the platelet component is negative.

And indeterminate corresponds to growth of organism from the culture bottle, but the platelet component is unavailable for confirmatory testing.

So these are the rates, Period A versus Period B, and these data were based on a recent publication from the center that has not just implemented, but conceived, this approach: Blood Systems. And one of the co-authors of the paper is with us today, Dr. Vassallo, and later on he will be presenting in more detail his experience with this approach.

So the tested collections were 188,000 in Period A versus Period B, 159,000. I'm sorry, I skipped a slide. So these are the rates in Period A versus Period B, and the number of tested collections were 188, as I mentioned, in Period A; 159,000 in Period B. And the true positive rate practically doubled in Period B, 1.83 versus 0.9 in Period A, per 10,000 collections.

However, the false positive rate quadrupled in Period B versus Period A, 15.05 versus 3.66 per 10,000 collections. The discordant negative rate decreased in Period B compared to Period A, 3.13 versus 2.14 per 10,000 collections. And the indeterminate rate increased from 0.37 to 0.63 per 10,000 collections in Period B.

The last row corresponds to the collections discarded and potentially harmful discarded, because the machine gave an initial positive signal, and with an initial positive signal, the collections are discarded, you don't wait for a confirmatory test, and potentially harmful because the unit either turned out to be contaminated or potentially contaminated; and in this category for the true positive,

discordant negative, and indeterminate collections, and in Period B, there was a slight increase compared to Period A, 4.6 compared to 4.4 per 10,000 collections.

Looking now at the septic reactions, the number of collections associated with septic reactions, there was one such collection in Period A and one collection in Period B. However, the collection in Period A was split in two components, and the two contaminated splits went to different patients, leading to two septic reactions. So considering a septic split rate of about 1.8% at that institution, the septic rate per component was 1 in about 169,000 in Period A and 1 in about 286,000 for Period B.

The advantages of the minimal proportional sampling volume for 5-day platelets is that it's a single culture conducted at the blood collection center; it doubled the bacterial detection rate, and it would obviate the need for secondary testing at the transfusion service.

The main drawbacks, and based on statements by the author in their publication, the MP as the approach requires upward adjustment of target settings for platelet collection to compensate for increased sample volume and to maintain the apheresis collection split rates. There was an increase in the false positive rate leading to the discard of otherwise suitable products, and the clinical benefits are not yet demonstrated by comparison to the previous strategy at that

institution.

So this is a recap of the bacterial detection and sepsis rates of 5-day apheresis platelets tested by the primary culture. The second column has the rates that I described earlier, corresponding to the traditional practices, and the last column has the data from using the minimal proportional sampling volume that I just described.

Now, here I have the data side by side, and there's an important caveat when you're comparing the rates obtained from two different centers because you have differences in the donor population, differences in the underlying contamination rate, differences in the screening processes, collection procedures, not to mention the definition of septic transfusion reaction, whether the reporting is passive or active. But nonetheless, it's always informative to place the outcomes of a specific strategy within the broad context of the available data, and that's what we're doing here.

So in terms of the bacterial detection rate at sampling time, the rates for the MP as the strategy fell within the broad range of the traditional practices.

In terms of bacterial detection on the day of transfusion, this was not available for the MP as the strategy because the platelets were not cultured on the day of transfusion.

And in terms of the sepsis rate for the MP as the strategy, again, it was 1 in 159,000, falling again within the

range of the traditional practices under comparable conditions, meaning per collection and by passive reporting.

So I'm moving on now to the second proposal which pertains to 7-day apheresis platelets, and the first one is the large volume and delayed sampling for 7-day apheresis platelets. The extension of storage up to 7 days under this strategy is based on a single culture using a large volume and delayed sampling. And the large sampling volume equals volume that is larger than the traditional 8 to 10 mL sample. And delayed sampling means sampling later than 24 to 36 hours after collection. And this allows bacteria already present in the collection to proliferate further prior to sampling.

And a combined approach of large volume and delayed sampling would be expected to increase the sensitivity for bacterial detection. And such a strategy has been adopted by Hema-Quebec in Canada and by the National Health Service Blood and Transplant in the UK.

So, in 2015, Hema-Quebec implemented a large volume/delayed sampling approach for testing both apheresis and pooled platelets. The large volume consists of 20 mL split evenly between aerobic and anaerobic culture media, and the delayed sampling occurs at least 48 hours after collection.

So these are the bacterial detection and sepsis rates for platelets at Hema-Quebec before and after the implementation of large volume/delayed sampling, and these data on the slide were

kindly provided by Dr. Gilles Delage from Hema-Quebec.

So the LVDS strategy at Hema-Quebec was implemented in 2015. In the previous period between 2005 and 2014, the traditional practices of bacterial testing were applied and the platelets were stored for 5 days. If we look at the third column, the bacterial detection rate at sampling time, we see that with the new strategy the detection rate almost quadrupled, and that's for the combined apheresis and the pooled whole blood-derived platelets. For the apheresis platelet only, the detection rate was 0.032%. It was lower than for the pooled product.

In terms of the residual bacterial rate after outdate, so that would be outdate after 5 days for the previous strategy and after 7 days for the new strategy, and we see that with the LVDS strategy there were zero contaminations detected after 7-day outdate out of about 2,800 units tested. So, obviously, that's a good result. However, we have a numerator of zero and the denominator is small, so with this small number, it's difficult to make a meaningful comparison to the previous rate.

And in terms of septic transfusion reaction rate with the new strategy, again, zero septic reaction out of about 80,000 components transfused. Again, that's a good outcome. But, again, looking at the numerators, zero with the new strategy and one in the previous strategy, and with this denominator, it's difficult to ascertain that the rates are different.

Now, moving on to the implementation of the LVDS strategy for 7 days at the NHSBT, in 2011, NHSBT introduced screening of all platelet components for bacteria using a large volume/delayed sampling approach. The large volume consisted of 16 mL split evenly between aerobic and anaerobic culture media, representing about 7% of the volume of the apheresis unit. Delayed sampling occurred between 36 and 48 hours after collection, and after a 6-hour incubation period, negative-to-date results qualify the product for 7-day storage.

And these are the bacterial detection and sepsis rates for platelets at NHSBT before and after the implementation of the large volume/delayed sampling. And these data were derived from a recent publication from NHSBT and Dr. McDonald, who is the main author on this paper, and he's with us this morning, and he will be presenting his strategy, and he will give us an update on the data since the publication of this paper.

So this strategy was applied at the NHSBT in 2011. Prior to that, there was no upfront bacterial screening, and the platelets were stored for 5 days. With the new strategy, so that's the third column, the true positive rates are of about 1.2 million collections tested. The true positive rate was about 1 in 3,000, and that's combined apheresis and pooled. And the false positive rate was about 1 in 500.

The bacterial detection rate after the outdate, so that's again after 5 days for the previous strategy and 7 days for the

large volume/delayed sampling strategy, with the new strategy, again, after 7-day outdate there were no contaminations detected after testing about 2,500 units tested. But here again, we have a numerator of zero, a small denominator, difficult to make the comparison to the previous rate.

In terms of septic reaction rate, in the previous period there were 10 septic transfusion reactions reported in about a million collected units. That's a rate of about 1 in 100,000 collections. With the new strategy, there was one septic transfusion reaction in a Day 6 pooled product out of about 1.2 million collections, so that's approximately a tenfold reduction in the septic reaction rate with the new strategy compared to the old strategy, and that's a meaningful reduction.

In the last column you will see that the numerators have two components. The first component is actually the septic transfusion reaction number in the previous column plus numbers that have -- that are marked by stars, and these numbers correspond to units that were discarded upon visual inspection due to suspected -- and subsequently to affirm bacterial contamination.

So the last column represents the risk of contamination proximate to transfusion, and it corresponds to the false negative rate of the LVDS strategy. And we can see that with the new strategy there was about a four to fivefold decrease in

that risk.

And this slide corresponds to the rates but limited to apheresis components at NHSBT. So the true positive rate was slightly lower than for the combined pools. That's because the apheresis rate was lower than for the pooled product. The false positive rate was about similar to the combined.

In terms of bacterial detection rate after 7-day outdate, the paper did not break down the results by apheresis or pools. However, as I mentioned earlier, there were zero detections out of a combined 4,500 units tested, and about 77% were apheresis.

In terms of septic reaction rate, there were none associated with apheresis platelets out of about 1 million collections. And the false negative rate of the early culture base on those three units that were interdicted upon visual inspection was about 1 in 320,000.

So the advantages of the large volume and delayed sampling is that this is a single bacterial test conducted at the blood collection center. It increases the bacterial detection rate. It enhances availability of platelets with 7-day dating. And there were no septic reactions associated with transfusion of close to a million apheresis units and one septic reaction after the transfusion of about 1.25 million combined apheresis and pooled whole blood-derived platelets. And it would obviate the need for secondary testing.

The drawbacks of the large volume/delayed sampling is that

with increased sampling volume, there is loss of therapeutic cellular product. There is an increase in the number of culture bottles to be processed because of the increase of the sampling volume. There is a significant false positive rate leading to discard of otherwise suitable products. And there is a delay in sampling, which entails transfusing all the platelets.

Now, moving on to the last proposal, and this is the second proposal pertaining to 7-day platelets, and the rationale for this proposal is -- which is based on secondary culture on Day 4 of platelets that were cultured early on with the primary culture, the rationale is that platelet transfusion-associated septic reactions and related fatalities rise on Days 4 and 5 due to the proliferation of bacteria during storage. And a secondary culture on Day 4 would be expected to identify contaminated units missed by the early culture.

In 2005 the Irish Blood Transfusion Service implemented a strategy of re-culturing on Day 4 platelets that were negative by primary early culture and intended to be extended to 7 days.

For the early culture, the sampling volume was about 7.5 mL inoculated into each of an aerobic and anaerobic culture medium, and the sampling time for apheresis platelets was at least 13 hours after collection, and for whole blood-derived pooled platelets, at least 30 hours after collection. And for

the Day 4 culture, the sampling volume was identical to the early culture.

And these are the rates of the bacterial detection and sepsis rates for 7-day platelets at the Irish Blood Transfusion Service between 2005 and 2016, and these data were generously provided by Dr. Stephen Field, who is the Medical Director at IBTS and who is with us this morning, and he will give us more details about his strategy.

So in terms of the primary culture true positive rate, that's the second column, for the combined apheresis and whole blood-derived pool, about 172,000 units were tested by primary culture for a positive rate of about 1 in 2,000. About 40% of those units were retested on Day 4 for an additional pickup rate almost of a third of the rate of the early pickup. And after 7-day outdate, about 2,800 units were tested with zero confirmed contaminations, and the septic reaction rate from 7-day platelets were about zero or zero in about 65,000 components.

For apheresis, about 106,000 units were tested for a detection rate of about 1 in 3,600. About half of those units were retested on Day 4 for an additional pickup rate, again, of about a third of the detection rate of the primary early culture. And at outdate, there were zero contaminations out of about 2,100 units tested and no septic reaction after the transfusion of about 50,000 components.

The advantages and drawback of the Day 4 secondary culture:

The advantage is that you have an improved availability of platelets with extension to 7 days. It consists of a single secondary test that would obviate the potential need to repeat the secondary rapid test every 24 hours for 7-day extension. And there were no reported septic transfusion reactions.

The drawback is that, in the U.S., the Day 4 culture would be performed by the transfusion service unless the platelet unit is shipped back to a cooperating testing center.

So this slide is a recap of the bacterial detection and sepsis rates of 7-day platelets, Day 4 secondary culture versus primary large volume/delayed sampling, and you're looking at two rates, the bacterial detection after 7-day outdate and the sepsis rate. For the outdate rate, and looking at the combined apheresis and pools at the Irish Blood Transfusion Service, of 2,800 units tested at the outdate, there were zero confirmed contaminations. At Quebec, again, zero out of about 2,800, and in the UK, zero out of a combined 4,500 approximately.

For the apheresis at the Irish Blood Transfusion Service, zero out of about 2,100; in Quebec, zero out of about 2,200; and in the UK, the combined was not available.

And in terms of sepsis rate for the combined apheresis pool at the Irish Blood Transfusion Service, zero out of about 65,000 components; in Quebec, zero out of 80,000 components;

and in the UK, one septic reaction out of about 1.2 million collections.

For apheresis platelets, the Irish Blood Transfusion Service, zero out of about 50,000 components; in Quebec, zero out of 66,000 components; and in the UK, zero out of about a million collections.

This slide has the false negative and sepsis rates following secondary rapid testing, and you have already seen some of the data earlier in my presentation. And as a reminder, this is the study in which about 28,000 apheresis units found negative by the primary culture underwent secondary rapid testing on the day of transfusion within 24 hours of issuance. And as I mentioned earlier, the rapid testing is used in the United States to improve the safety of 5-day platelets and also to extend dating from Day 5 to Day 7 by increments of 24 hours.

Now, there are no data on rapid testing of Day 6 and Day 7 with concurrent culture. Some data from Hitchcock-Dartmouth exists on Day 6, on Day 7, but these were not conducted with concurrent culture, so the false negative rate could not be established, and they had no true positive detected.

So, essentially, we have data on Day 2 through Day 5, and what I showed you earlier are the columns in -- the data in Columns 1 and 3 corresponding to the rapid test false negative rate on the day of transfusion, so that's combined Day 2

through Day 5 within 24 hours of issuance, and also the sepsis rate, that's Column 3, again, combined Days 2 through Day 5.

What I have added are the false negative rate limited to Day 5 transfusion within 24 hours of issuance, and this amounted to a rate of equal or greater than 1 in 2,800, and the sepsis rate, again limited to Day 5 transfusion, that's the last column, which amounted to 1 in 8,500 to 1 in 4,200. And, obviously, we would expect that the rates on Day 5 would be the highest than with the combined days of transfusion.

So, in summary, bacterial contamination of platelets remains a public health concern. The FDA's March 2016 draft guidance document proposed the use of secondary testing to improve 5-day dated platelet safety and extend storage to 7 days and also the use of pathogen reduction without secondary testing for 5-day platelets.

This morning we have presented to the Committee additional considerations: for 5-day platelets, the use of a minimal proportional sampling volume without secondary testing. And for extension to 7 days, two proposals: the use of large volume and delayed sampling without secondary testing and secondary testing by culture on Day 4 for platelets previously tested by a primary culture.

So the questions to the Committee are as follows:

Do the available data support 5-day storage of apheresis platelets without secondary testing if platelets are cultured

no sooner than 36 hours post-collection with a sampling volume of at least 3.8% of the collection?

And Question 2: Do the available data support the following measures to extend dating to Day 7?

a. Culture of apheresis platelets sampled no sooner than 48 hours after collection using a test volume of at least 7% without secondary testing; and

b. Repeat culture on Day 4 of apheresis platelets previously tested by a primary culture.

And the rest of my slides have the list of the references. And I thank you for your attention, and I will take questions later on in the session.

DR. STOWELL: Thank you, Dr. Haddad.

We're going to hold our questions for the FDA speakers until after the break, so please make a note of your questions now for later.

Meanwhile, we'll move on, and Jennifer Scharpf will do the next presentation for us to summarize the public commentary that they received from their draft guidance documents.

LCDR EMERY: While the slides are being loaded, I wanted to make a quick public service announcement. A wallet has been found and is held at security in Building 1, and please check to see if your wallet is missing, and if you are, you can go pick it up from security in Building 1. Thank you.

MS. SCHARPF: Okay, good morning. My name is Jennifer

Scharpf. I'm the Associate Director for Policy in the Office of Blood Research and Review in CBER, and this morning I will be presenting a Summary of Public Comments on FDA's March 2016 Draft Guidance for Industry on Bacterial Risk Control Strategies for Platelets for Transfusion.

FDA has established requirements for the control of bacterial contamination of platelets. 21 C.F.R. 606.145(a) states that "Blood establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA-approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose."

The preamble to the final rule, which became effective in May of 2016, explains that transfusion services may rely on the steps taken by blood collection establishments to meet this requirement. However, if the blood establishment did not take steps to control risk, the transfusion service must do so. Further, the preamble states that the requirement can be met by either pathogen reduction or bacterial testing of platelets.

So FDA issued a draft guidance in March of 2016 on bacterial risk control strategies. The guidance replaced the December 2014 guidance on the same topic. The guidance applies to blood collection establishments and transfusion services and provides FDA's draft recommendations for controlling the risk of bacterial contamination under the regulations and for

allowing the use of secondary testing of platelets to extend the platelet dating period.

While the guidance provided recommendations for all platelet types, for brevity I will summarize the recommendation for apheresis platelets only.

To ensure the safety of platelets stored for 5 days, the draft guidance recommends the following: to pathogen reduce platelets using an FDA-cleared device or to perform primary testing using a culture-based device, which would permit storage through Day 3, and then perform secondary testing using a rapid test or culture-based device, which would then permit storage through Day 4 and Day 5.

To extend the storage of platelets through Day 7, the guidance recommends the following: to perform secondary testing on pathogen reduced or previously cultured platelets with a rapid or culture-based bacterial detection device cleared by FDA as a safety measure, and these platelets must be collected in a 7-day storage container.

However, it is important to note that pathogen reduction storage systems to ensure platelet efficacy through Day 7 are not available, and culture-based devices labeled as a safety measure are also not available at this time. Therefore, some of the strategies recommended in the guidance would not be available with the current technology.

Also, the guidance states that transfusion services that

perform testing to extend dating beyond Day 5 must register with FDA as a manufacturer. Otherwise, transfusion services that do not routinely collect or process blood components are exempt from the requirements to register with FDA.

So the draft guidance, as I mentioned, was published on March 15th, 2016, and comments were submitted to a public docket. Today I'll present a high-level summary of the comments, but all of the comments may be accessed on the regulations.gov website at the link provided on the slide.

FDA received a total of 16 comments when the comment period closed on June 13th of 2016, and in January of 2017, FDA announced its intention to issue a final guidance. Subsequently, eight supplemental comments were submitted to FDA from May through July of 2017, and many of the comments requested that the FDA docket be reopened. After consideration of these comments, FDA announced its intention to issue a revised draft guidance for public comment in 2018. And, of course, we'll consider the recommendations of this Committee and the public comments received prior to issuing the next draft.

The comments in the draft guidance may be categorized as follows:

- Platelet inventory loss associated with secondary testing on Day 4 and Day 5, with the use of pathogen reduction technology and with the use of rapid tests;

- The impact on transfusion services;
- Alternative strategies;
- Bacterial detection rates;
- Specific methods; and
- Implementation time frame.

So we received numerous comments on platelet inventory loss that may result from secondary testing on Day 4 or Day 5 of shelf life, and comments included the following:

If hospitals elect not to conduct secondary testing, platelets will have a 3-day shelf life and may adversely affect availability and harm patients.

Secondary testing may disrupt the ability of blood collectors to enter into consignment arrangements with hospitals to accept returns of Day 4 and Day 5 platelets for distribution to other hospitals.

Further, that the consignment model maximizes use of platelets by minimizing outdating, and without consignment, the outdating of platelets could lead to severe shortages and inhibit particularly the ability of remote hospitals to keep an emergency supply of platelets on hand.

Another comment stated that hospitals may rely on collectors to perform secondary testing and reissue platelets within 24 hours of outdate. Under this scenario, platelets would be in frequent transport rather than in hospital inventory.

And, finally, a comment suggested that a risk assessment should be conducted to assess the risks versus benefits of the recommended safety interventions.

Commenters also addressed potential loss of platelets during the manufacture of pathogen-reduced platelets, stating that significant platelet inventory loss may be associated with pathogen reduction technology; that widespread adoption of pathogen reduction could contribute to platelet shortages because of stringent criteria for platelet content and volume of single and double collections. Further, triple collections are not eligible for pathogen reduction.

Early implementers of pathogen reduction technology reported being able to qualify a maximum of 75 to 85% of single platelet collections and 40 to 45% of double collections. And one blood center estimated that because of the device requirements, they would be able to pathogen reduce only 32% of their platelet inventory.

Other comments focus on the loss of platelets associated with the use of the FDA-cleared rapid test, specifically that the relatively high false positive rate observed with the use of the device would limit the availability of platelets in inventory.

The second category of comments addressed the impact of the draft recommendations on transfusion services. One of the supplemental comments received earlier this year stated that

the concerns from transfusion services were not well represented in the initial comments submitted to the docket because they were unprepared for FDA's recommendations.

Other comments noted that transfusion services have traditionally relied on blood establishments to address FDA's manufacturing and safety recommendations; that many hospitals lack the operational structure to support complex processes like testing and relabeling of platelets; and that personnel, training, equipment, and information technology adjustments required for compliance can result in major expenditures.

Other comments noted that recommendations for secondary testing adversely affect smaller healthcare entities, not only because of cost but because technical personnel would not become proficient with testing because it would be performed infrequently.

Transfusion services also opposed the requirement to register with FDA as manufacturers if they extend dating of platelets beyond Day 5.

And several comments noted that purchase of pathogen reduced platelets will be costly to hospitals, and one commenter estimated the cost will be an additional $100 to $120 per platelet unit.

Commenters suggested alternative strategies to control the risk of bacterial contamination from those recommended in the guidance. Several commenters noted that FDA should consider

multiple options to protect platelets from bacterial contamination.

Numerous commenters advocated for alternative strategies to obviate the need for pathogen reduction or secondary testing of platelets; to sample larger volume, specifically, the proportionate 3.8 sample volume that's used by BSI; to split required volume over aerobic and anaerobic bottles; to delay primary culture and use larger volume to extend dating to Day 7, comparable to the UK and Hema-Quebec approach; and also, to perform primary culture and culture at Day 4 to extend dating to 7 days, similar to the Irish Blood Transfusion Service approach.

And one commenter stated that the use of delayed sampling and larger volume techniques, in the absence of secondary testing, should be permitted only after sensitivity and specificity is established in well-controlled population studies.

So we received several comments specific to differing bacterial detection rates associated with currently approved technology. One study demonstrated that true positive bacterial detection test results differed significantly among two apheresis separation devices at two large blood collection centers.

Comments noted that the sensitivity of FDA-approved culture-based bacterial devices is not equivalent and that

sensitivity of bacterial screening is more related to the volume sampled and that studies suggest performing the rapid test within 4 to 12 hours of transfusion is more appropriate than within the 24 hours of transfusion, as specified in the labeling of the FDA-cleared rapid test.

Several comments noted that FDA should consider the following methods to control the risk of bacterial contamination:

Pathogen reduction technology should be the preferred approach because it reduces the risk of bacterial contamination as well as viruses and other transfusion-transmitted infections.

The extension to 7-day storage for pathogen-reduced platelets, without the need for secondary testing, should be permitted because the safety of pathogen-reduced platelets has been demonstrated.

One commenter advocated for secondary testing on Day 3 of storage in addition to testing at Days 4 and 5 using the rapid test, and that testing of single whole blood-derived platelet units should be permitted using the rapid test cleared for testing post-storage whole blood-derived platelet pools.

And the final set of comments requested FDA consider an appropriate time frame for issuance of a final guidance and implementation of the recommendations.

One individual commented that FDA should finalize the

guidance without delay to ensure the safety of platelets, while others advocated for FDA to delay issuing a final guidance.

One comment specifically stated that considering the number of unavailable technologies and the uncertainty about supply impact, a decision by FDA to finalize the guidance is premature.

Numerous commenters stressed that adequate time between issuance of a final guidance and its implementation date is needed; that changes in blood establishment computer systems and quality systems require an extended timeline; and that an 18-month implementation timeline is preferred to the 12-month that was recommended in the draft guidance.

Others noted that the limited number of manufacturers of pathogen reduction devices and secondary rapid tests may not be able to provide an adequate number of devices for nationwide implementation.

And others commented that FDA should delay implementation until pathogen reduction technology is available for all apheresis technologies.

And that concludes my summary of the comments on the draft guidance, and I thank you very much for your attention.

DR. STOWELL: Thank you.

Our next speaker is Dr. Vassallo, who is from Blood Systems, who will be talking about one of these bacterial screening approaches taken by his system.

DR. VASSALLO: Thank you for the opportunity to come and speak today. I appreciate the invitation. I'm Ralph Vassallo, the Chief Medical and Scientific Officer of Blood Systems, and my disclosures are on file.

I'll remind you who Blood Systems is, or BSI. BSI started as United Blood Systems primarily in the western part of the United States and over the years has expanded to add 10 member partners. Those blood centers are all listed up here, as well as an affiliate in San Bernardino. We serve over a thousand hospitals, and these are located in 28 states with 4,800 employees collecting about 1.5 million-some whole blood donations and the rest up to about 1.6 million of apheresis collections.

So I tried to frame this in a way that really makes sense to look at the problem holistically. We know that if you look at the literature, it says that the septic transfusion reaction rate is about 1 in 100,000. Of course, this is passively reported. Red Cross has these data, and it's a little less than 1 in 100,000. They have some data on -- as reported, some data on whole blood-derived platelets that are claimed to be similar. Others have looked at the rate and suggested slightly higher than that for whole blood-derived platelets.

But, interestingly, when you look at a study conducted at University Hospitals Case Medical Center and reported in *Blood* in 2016, they had active surveillance, and what they did was

they cultured units as they went out of the -- as they left the transfusion service before they were transfused and were therefore able to retrospectively look at who had gotten a contaminated platelet.

And when you look at the periods in here, where they had -- let's see if I can do this, I'm going to do it here, if you don't mind -- that hole, if you will, in active reporting, there were absolutely no passive reports, and in fact, the one passive report circled here occurred when the group was only culturing Day 4 and 5 platelets, and this indeed was an infected Day 3 platelet. If you look at the active periods, the number of reports are much higher, and in fact, there is a tenfold increase in reporting. So passively reported, 30 per million, and actively reported, 263 per million.

And I may have misspoken. The study reported in *Blood* in 2016 looked at 51,440 units that left the University Hospitals Case Medical Center from 2007 to 2013, and indeed, of those, there were 20 contaminated units, but 5 resulted in septic transfusion reactions for a rate of 1 in 10,300. So active reporting, as we see in both of their time periods, was 10 times more sensitive.

If we take the number of 1 in 10,000 of septic transfusion reactions resulting from platelet transfusion, and these platelets, we must say, are both -- both technologies for apheresis and include whole blood-derived platelets from PRP

and the pre-storage pooling Acrodose. There were two million transfusions in 2015, according to the AABB survey. So if you take that 1 in 10,000 rate, we're talking about 200 patients affected annually.

Looking at University Hospitals' data, the study from 2008, reported by Mike Jacobs, showed that of the contaminated units that people received, 35% of them had a septic transfusion reaction. And when they looked at the next period from 2007 to 2013, 25%, 5 out of the 20 units that were contaminated, resulted in a septic transfusion reaction.

The fatality rate here is somewhere between 10 and 20%. So that translates, in those 200 patients, to 20 to 40 deaths, and the rest of these individuals with significant morbidity, which is absolutely unacceptable and something needs to be done.

But the important point here is that the cure cannot be worse than the disease. We have to be very careful that we don't affect availability, because if you think about it, a 1 or 2% decrease in availability, even if only 1% of people who don't get a platelet result in significant morbidity and mortality means we'd be affecting 200 to 400 individuals negatively. So as I said, the cure cannot be worse than the disease. We have to be very careful as to what we implement.

People are familiar with this graph. You may not be familiar with the equation upon which it's derived, but this is

the Poisson distribution-based graph -- function that shows when you have different percentages of your bag sampled, what the likely detection rate will be. And within the relevant range of contamination of 1 to 65 CFU/mL, you can see that going from 8 mL -- and this was from a paper that Peter Tomasulo published in 2012 -- that there's a doubling within the relevant range, going from the 8 mL sample to the scheme that BSI has introduced in 2012, and that is a minimum 3.8% sample volume.

Now, we know that BacT/ALERT has a 1 to 10 CFU/mL detection rate, and if you look, the 1 to 26 CFU per bag is really less than 0.25, so therefore the more you culture, the more likely you are to pick this up. And like a poor storyteller, I will reveal who done it. We predicted a doubling based on this graph of what we would pick up in inoculation and therefore remove from the potential population of transfused platelets, and indeed, that's exactly what we saw.

So we're now left with looking at different techniques, so we're looking -- I'm going to talk about the BSI. The next two speakers will talk about the UK and the Irish Blood Transfusion Service schemas to interdict more platelets up front that are infected.

But when we start to compare things, as Salim said, it's very difficult because what we're really trying to reduce is

the residual risk of septic transfusion reactions, and that's very difficult to get at because, as we mentioned, 25% plus of people who get a contaminated unit have a septic transfusion reaction, but not all of them, and it's dependent upon a confluence of 10^3 to 10^7 bacteria of particular virulence, lesser to greater virulence.

And, of course, it has to be in a susceptible host because each of us, every day, clear bacteremia from brushing our teeth, going to the bathroom. And, of course, a lot of the patients that we serve are on antibiotics. So not every patient that gets a contaminated unit is going to have a septic transfusion reaction, so that's really the sine qua non of what we're trying to get at.

The problem is it's very difficult because, as we saw with active versus passive reporting, there are issues, there are issues in recognition in that *Blood* 2016 study. All five of the passive -- of the actively reported septic transfusion reactions were not recognized by the clinical team, one of which was a quite striking reaction and it was not recognized. And what happens often is these reactions, especially in platelets nowadays that we're screening and taking out most of the virulent organisms up front, these can be delayed, and it can be delayed from 6 to 24 hours, not in a classic 6-hour period that clinical teams are looking.

When you look also, there are near-miss reports, so Salim

did add some near misses in there, but of course, our system is designed to take those out. So, really, I think what's fair is to not look at your near misses but look at your actual hits. But the problem is it's very difficult to determine those, and indeed, the numbers required are so large that this is not really practical.

When we look at unit contamination, that's our next surrogate down, we presume that at the end of storage, if we reduce in some manner the number of contaminated units by whatever mechanism is used, pathogen reduction excepted, then we would expect that, of course, the number of septic transfusion reactions would go down, and that's a reasonable expectation. In fact, it could be even greater depending upon what technique is used in order to interdict some of these units. If you're interdicting the higher content, more virulent organisms, you may actually decrease septic transfusion reactions more than expected.

The problem with these is they're very expensive, and they require very large numbers because the event rates are very low, and indeed, all studies to date have been underpowered for making significant comparisons.

In addition, when you look at some of the studies, some studies -- and I'll describe ours shortly -- actually investigated co-components, they went after transfused co-components and looked at those patients. And other studies,

like the PASSPORT study, did not. They simply relied upon passive reports. So these studies are very difficult to conduct but also difficult to interpret.

The next level that we talk about, and we've heard about this from Salim and you've read these papers, is looking at interdiction rates up front in your primary culture. So if indeed we're looking at enhanced primary culture, with or without a delay in the sample inoculation, we're going to begin naturally to compare collectors, and I would state, as Salim did, that indeed it is very difficult to do so because we're starting with different contamination numbers. You start with a different fraction of contaminated units, we start with differing levels of contamination in those units, and if you're looking within a single organization, which is probably more robust, there could be changes in other practices besides one that you've instituted. Say you go from 8 mL culture to a 3.8% minimum, there could be differences in the comparator periods.

So when we look at why it might be different, it could be the donors. Do you have donors who are outside workers and therefore in contact with soil? Are you using different technologies? And we will see, and many of you are aware, that there were differences reported recently in the apheresis technologies.

Are you using additive solution or plasma? A triple platelet takes longer to collect, and it processes more blood

and therefore may have a higher rate of contamination. All arm preps are not created equal, and staff turnover affects the staff's skill level. All of our collections are now sample diverted, but when you look historically, some of the studies were not. And, of course, when you look at whole blood-derived, there's a difference between the European buffy coats and the U.S. PRP.

In my experience, I have not seen a single contaminant that I could definitely point to that occurred during manufacturing. Does it occur? It probably does, but it's probably rare. It's most of these other donor- and collection-related factors that make this difficult to interpret.

Also, when you read the papers, are they sampling from the mother bag, or are they sampling each and every split?

What is the volume, the delay, aerobic versus anaerobic bottle use? In the UK study, when they used multiple bottles, as soon as the BacT/ALERT rang, they pulled out all of the bottles and didn't give the other bottles a chance to ring. So if you're seeing mostly anaerobic bottles coming up first, would the aerobic bottle, had it continued to incubate, have eventually rang as well, an hour or two later perhaps?

How do you inoculate? Do you inoculate under a hood? How old is your unit, and how often are you opening the BacT to put in bottles when you look at false negative rates?

And then, of course, as Salim also mentioned, what do you

call an initial positive where the bottle grows a strange organism, the patient grows a strange organism, and you didn't have a chance to culture the platelet because it was thrown away? Well, there's a probable true hit. But what if it's coag-negative staph and you don't do molecular testing? Is that an indeterminate, or is that a true hit?

So it's difficult to interpret these studies, but I must say that within-center comparisons are much more robust than across-center comparisons.

So the delayed large culture volume options are here. All of these have been done on the Trima platform. United Blood Services is one of the member centers within Blood Systems, along with Inland Northwest Blood Center, Blood Centers of the Pacific, and Life Blood Memphis, that are on the ePROGESA blood establishment computer system and that are doing this sampling.

We collect 10 to 28 mL per collection, per donation, in contradistinction to Hema-Quebec, which does 20 mL per collection, but their collections do not include triples, and NHSBT, which does 16 to 48 mL per collection depending upon whether it's a single, double, or triple. UBS is the only one that uses anaerobic-only bottles. The other two use aerobic and anaerobic.

The percent of volume cultured is here, the timing is there. We inoculate at 24, Hema-Quebec at 48, and NHSBT and also Canadian Blood Services that uses the same model as NHSBT

inoculates at 36 hours. The only difference between Canadian Blood Services and NHSBT is that Canadian Blood Services samples from the mother bag, NHSBT from each of the splits.

Of course, the difference, the major difference, is the 7-day dating, and it's an incredibly important difference when you start to delay your culture volume.

So these are numbers that we'll delve into in more detail, but in a comparative form, even though it's fraught with difficulty, when you look at the passive septic transfusion rate from all three of these studies, BSI's is 3.5 per million, Hema-Quebec has transfused about 80,000 units in total, about 60-some-thousand that were apheresis that have had no reactions, and of the 960-some-thousand that NHSBT reported in the paper, there were zero septic transfusion reactions reported in the apheresis platelets.

When you look at the true positive rate, the upfront interdiction rate was 183 per million at UBS, 225 per million at Hema-Quebec, and 140 per million at NHSBT, which you'll notice that the latter two, Hema-Quebec and NHSBT, because they're using anaerobic bottles, are picking up a very large number of *P. acnes*. *Propionibacterium* has rarely been reported to cause problems. But typically, it grows late and it grows after an uneventful transfusion and the patient has negative blood cultures.

So excluding these relatively non-pathogenic organisms,

you see the numbers look remarkably similar. None of these numbers, either in the septic transfusion reaction rate that are passively reported or the true positive interdiction rate, are statistically significantly different.

What's the contribution of the delay in sampling? Well, the only data that I'm aware of that very nicely show this are from Hema-Quebec. They increased their sample volume from 10 to 20 mL in October of '14 and 1 year later introduced the delay. That allows you to look at their pre-period where their BacT true positive rates went from 1.1 million to a 20 mL collection, 3.7 -- I'm sorry, per 10,000, 3.7 per 10,000, and then the delay, which is a 336% increase. But the delay only increased that rate by another 5%. So it appears that the delay did not do very much, and that's unfortunately very deceptive because most of what was picked up was, of course, *P. acnes*.

So when you take *P. acnes* out, now the rates go from 1.1 per 10,000 to 1.5 per 10,000, only a 31% increase with the sample volume, and then with the delay, another 52% increase. So one gets the sense that both the volume and the delay are important in terms of increasing safety.

With this delay, it's a 24-hour additional delay, but a 7-day platelet gives you 2 more days, so functionally an additional day on the platelet, and their outdate rates dropped dramatically. So a 7-day outdate is key to having a viable

option here with this delay technology.

This is BSI's algorithm, and you see anywhere from 10 to 28 mL are inoculated in one to three bottles. Although the data are several years old for the percentage of units within each volume band, this is still true today, that only about 1% of the platelets we collect end up going into one bottle. The vast majority are in two or three bottles.

What you notice when you look at the totals on the bottom is a 2.4-fold increase in the number of bottles that were used. Obviously, more bottles is going to lead to a higher false positive rate, and indeed, the false positive rate rose more than fourfold because of two things: (1) more bottles and (2) more bottles means more opening and closing of the door, which results in false positives.

As was mentioned, there is an impact on split rate because we are pulling out a significant volume from our platelets. Now, from my perspective at headquarters in Scottsdale, we were able to "easily," if you will, ameliorate the impact on the split rate. When you talk to the recruitment and collections folks that had to make significant changes, it was not that easy, but it was doable.

So we talked about study results. Well, when we went from 8 mL to 3.8% relative volume, we also did a culture study at the end, and what happened was, of the expired units on Day 5, we asked hospitals to send them back, and we would culture both

the ones that came back and the ones on our shelves at expiration, 2 days later on Day 7. We got about 60% of the platelets that had expired cultured, and there were four implicated collections. Three of them were double products; the third was a triple product.

The first grew a *Leclercia* both in the BacT bottle that was used on Day 7 and in the platelet itself. And the second bag was a red cell and did not grow anything. The second unit grew a coag-negative staph, both from bottle and bag, on Day 7, but the other unit had outdated and was thrown away.

The third unit, coag-negative staph, both bottle and bag, and the second unit had been transfused. When we contacted the hospital, the patient had been asymptomatic, but on blood culturing, the patient had coag-negative staph. Unfortunately, molecular testing was not done to see if it was the same coag-negative staph.

The last collection was a triple. Two units were on our shelf for testing at expiration. One unit, the BacT alarmed; the other, it did not. Unfortunately, what happened at the center was they threw away the wrong unit and cultured the one that had the negative BacT bottle. So that positive coag-negative staph bottle, we did not have the product cultured, and that became an indeterminate. Contacted the hospital because the third unit had been transfused and the patient had had a flora septic transfusion reaction that was not

recognized. He did have coag-negative staph in his blood culture, and indeed this obviously not recognized was not reported.

So we ended up with three true positives, one indeterminate, and two patients presumably infected with the same organism that grew at least from the bottle and in one case from the bag.

When you look at the rates on the next table down, that's anywhere from 3 to 6 of the 8,000 Trima units that were looked at in this study that were cultured, and the rates vary between 373 per million to 746 per million residual risk.

When you begin to compare this externally to the PASSPORT study that did a surveillance of about 6,000 units, their rate was 662 per million, and they were predominantly Trima and Spectra with a little bit of Amicus. And, of course, that number is not statistically significantly different either from the true positive indeterminate value of 498 per million or counting the patients as well, which PASSPORT did not count patients, of 746 per million.

When you try to look at what Verax does, it's difficult to tease the paper apart. We've mentioned it several times in the preceding talk; 27,600 units were tested, but of those, the subset that were cultured was about 10,300. Of those 10,300 units, not all of them were on Day 5 because, remember, we're talking Day 7 cultures for BSI, Day 8 cultures for PASSPORT.

So if one presumes that of the entire 27,600 that were involved in the Verax study, that 31% of the entire number were Day 5 units, assuming that a subset that were cultured had approximately the same, you'd come up with a rate, a residual contamination rate on Day 5 of 620 per million, again, not statistically significantly different from our results as well.

However, when you look at this, the lack of statistical significance does not mean there is no difference. So this is really an inadequately powered study, as was PASSPORT, as was the Verax study, to draw any significant conclusions.

We're not comparing apples and oranges. As my colleague Hany Kamel says, it is a fruit salad. So it makes it very difficult to interpret these results. So, again, we are left with looking at upfront interdiction rates.

So these are the data reported in the study this year in *Transfusion*, comparing -- and Salim has highlighted these, comparing the Period 1 where 8 mL was inoculated in 188,000 Trima units and in Period 2 where we go to 3.8% were inoculated in about 159,000 Trima units. You can see that our initial reactives did double. Our true positive rate also doubled. The false positive rate more than quadrupled.

Discordant negative, and that means something grew from the bottle but the platelet itself was negative, that rate stayed the same. It actually dropped a little.

And the indeterminates, which are the bottle grows

something but the unit has been transfused or is not available, has expired and is not available for -- or otherwise unavailable for culture, so that doubled as well. But although doubling, you can see the magnitude there, an increase of 26 per million really doesn't affect most of the other rates.

So if we look now at the septic transfusion reaction, there were two septic transfusion reactions, as Salim reported, in Period 1, one in Period 2. But these are per donation, so we have to adjust them for units, and it would be the approximate split rate in both periods was 1.8. So adjusted to units, so we're all speaking in the same units now, it is 5.9 septic transfusion reactions per million units transfused versus, in the post-period, 3.5.

We have subsequently expanded the experience through September of 2017. You'll notice that Period 2 there, in the paper, only extended to September of '16. There have been no additional septic transfusion reactions, but obviously more units, there are more than 380-some-thousand units through September of '16, so now the rate is 2.4 per million.

When you contrast that, if you would, with the UK experience where, in 960,000 Trima platelets, they've had no septic transfusion reactions, but none of these rates are statistically significantly different, at least the 3.5, the 2.4, and the zero are not, and the 5.9 in Period 1 and 3.5 in Period 2 are not statistically significantly different either.

When you look at the true positive rate at NHSBT, it's 217 per million. Different ways of expressing this. It's a little easier, I think, to see when you have a number that you can look at and intuit what it means. But interestingly, when you take out *P. acnes*, it's there, it's 140 per million. So, again, these numbers look very, very similar and are not statistically significantly different, even the 217 versus the 182 per million that we see at BSI with 3.8% sampling.

So we didn't just go from 8 mL to 3.8%. What actually happened was we started with a 4 mL culture, and in 2008 we went to 8 mL. In 2012, as an intermediate step before doing the 3.8% culture, what we did was we put 9 mL in an aerobic bottle for singles and 19 mL in two aerobic bottles for doubles or triples. So there was an interim step there.

And what is interesting is, if you look on the bottom, our rate of true positive early interdictions, a 24-hour-plus sampling in Trima, from 4 to 8 mL didn't do very much. From 8 to essentially approximately 16 mL also was not statistically significantly different. It was only when we got up to the 3.8%, which on average was 21 mL per unit, did we see a statistically significant difference, and you see that here.

We had Amicus in our armamentarium at the time, and due to contracting issues, we phased out Amicus and are now 100% Trima. So we don't have very large Amicus numbers, but even so, although the numbers in and of themselves from 4 to 8 to

essentially 16 mL grew, they're not statistically different from each other along the Amicus line, but notice how quickly it goes up. But they are statistically significantly different from Trima lines, from the rates of interdiction. We had reported that before and showed a 2.8% increased odds of having a true positive interdiction with Amicus versus Trima but were unable to substantiate whether that carried through to septic transfusion reactions because we only had a very small number.

However, this year Red Cross reported their experience with a million and a half Amicus and 675,000 Trima and saw the same odds ratio of 2.3; the absolute rates, 252 per million for Amicus interdictions and 112 per million for Trima, looked very much like BSI's. But they were able, with a very large number of units, to look at passive interdiction -- I'm sorry, passive septic transfusion reactions rates, and those, in fact, were also increased in Amicus 3.8-fold over Trima.

So all platelets are not created equal, and one assumes that your earlier interdiction rate leads to higher septic transfusion rate down the line, and indeed, that is the case.

Back to our experience: When we look at the 2.8% in our Trima, one of the organisms that were picked up, there were 29 true positives; not unexpectedly, 79% of these are gram positive and 21% gram negative. Of those 29 units, 80% of them the BacT alarmed within 18 hours. In fact, almost equally distributed between the first 12 and the next 6. And of the

21% that alarmed after 18, none of these were transfused to a patient.

Of these 29, 12 bottles, 12 of the sets because, as I mentioned, 99% of our units are cultured in two or three bottles, so all of these 29 showed up in two- or three-bottle sets, and they were statistically distributed amongst the bottles, as one would expect for two or three bottles. So anywhere from 24 to 41% of these would not have been picked up had we not increased the sample volume and cultured in multiple bottles.

So to close out here with the next two slides, there are three safety enhancements that have been proposed. The first is obviously pathogen reduction. It's a good technology, and in lots of transfusion reports from Europe there have been no reported septic transfusion reactions that have been substantiated, as one might expect with a technology that's likely to get most pathogens expected for sporulating organisms and ones that within 24 hours grow to exceedingly high levels.

The problem with pathogen reduction is, of course, the availability of platelets. So in our largest center, our usual collections, 3% of our apheresis collections were eligible for treatment without having to do anything to our collection, our collection parameters. Three percent.

In the centers that have introduced pathogen reduction, we can get that up to 60 to 75% eligibility. So it is possible.

And the 75% eligibility is when we are treating -- when we're taking triples and breaking them down into either three singles or a single and two doubles for treatment, but we don't think we're likely to get above 80% for apheresis. That leaves us and our customers with a mixed supply of pathogen reduced versus non-pathogen reduced, and that's a difficulty for our hospitals.

The point-of-issue tests, they require one or more tests anywhere from Day 3 through Day 6. These are difficult for hospitals to implement, and as you'll see, I think, on the next slide, I think it's very difficult for us to implement as well. It does involve cost, and it involves a significant false positive rate of 0.51%. That's in contradistinction to our false positive rate of about 0.16%.

The third option is enhanced primary culture, and one can enhance either by volume alone or volume and delay. NHSBT and CBS, their protocol is a 36-hour delay; Hema-Quebec, a 48-hour delay. BSI currently does a 24-hour delay, and we think that the increased interdiction, certainly in studies when you look at a different type of intervention, when you look at changing your technology and what that would do to your septic transfusion reaction rate, we think that our increase in interdiction also will reduce the septic transfusion reaction rate to allow 5-day storage.

Now, to allow 7-day storage, obviously, we're going to

need to enhance that to some degree, and that involves a sample delay of 36 or 48 hours.

What we have to look at, as I said as I started the talk, holistically is the impact on blood availability, on operations, and upon total cost. So when we look at donor replacement, the seasonal recruitment shortfalls are even more challenging. So even a small decrement overall in, say, a 1% average, well, during the summer and then holidays that 1% could be strikingly more, and there could be patients who go without needed platelets if we're not very careful.

We would need any change that is addressing these 200 unacceptable septic transfusion reactions that are occurring every year, and up to 40 deaths, very few of which end up being reported to FDA.

We need to have a longer shelf life if we're going to have this option of delayed primary culture.

We need low false positive rates when we talk about point-of-issue or enhanced culture.

We want to minimize additional equipment, we want to minimize the procedural changes that our hospitals and our blood centers have to implement and, of course, the increase in labor.

So when you look, we think that pathogen inactivation technology and point of testing are not as user friendly either to the hospitals or to the blood centers. But frankly,

pathogen reduction is the most user friendly to the patient, right, because the risk is markedly reduced.

And I think that that's where we need to go to eventually, but until we get there, is it 3, is it 5, is it 7 years before we're able to treat all of our platelets, before we're able to do that in a cost-effective manner? What do we do in the interim? And I think that both point-of-issue and enhanced sample volume, primary culture, are ways to get us to a safer blood supply, but maintaining the adequacy of the blood supply as well and not placing patients or really physicians and hospitals at jeopardy of giving -- deciding which patient gets a pathogen-reduced safer product and which patient does not.

We are certainly, as an organization, gearing up for pathogen reduction demand because a lot of hospitals are able to incorporate this into their cost structure. But, of course, we can't provide 100%; no blood center can provide 100% pathogen reduced anywhere within the next, at least, 3 years and perhaps even longer.

So we are looking at point-of-issue testing. Point-of-issue testing is not really practical for our many hospitals. We have small hospitals that keep platelets on their shelf at all times but transfuse 10% of them. If we have a 3-day platelet and they can't do point-of-issue testing, sending it back to the blood center is not really a good option, because when it goes out again, it has functionally 16 hours or less,

by the time it hits a hospital, of shelf life.

What about our own transfusion service? We might have to look at point-of-issue testing, but we think enhanced culture would obviate the need for all of that and allow a relatively transparent method for us to address bacterial contamination mitigation for our hospitals. It's been used safely, as you'll hear in the next two talks, and there's a building evidence base for its efficacy, and I think the largest evidence base for that is the UK, and you'll hear that from Carl.

So with that, I think I am done, and we'll hold questions until the end session. Thanks.

DR. STOWELL: Thank you.

Our next speaker is Dr. McDonald from the National Health Service Blood and Transplant service in the UK, and he'll describe their experience.

DR. McDONALD: Well, thank you much to the organizers, the FDA, for the invite to present at this meeting the work of NHSBT. It's always a pleasure to visit the United States and see old friends and colleagues. And I'm really going to present obviously not only bacterial screening, but I would say at this point that I'll start off with also other interventions we've put in place to get where we have got today regarding platelet components.

So in my presentation I'm going to give you the impact of bacterial transmissions with some more mortality rates

worldwide; why platelet components are the greatest risk of transmission as opposed to red cells; the NHSBT strategy for reducing the risk of bacterial transmissions; the impact of diversion in donor arm disinfection, which I think are very important as to what is bacterial screening; the NHSBT protocol for bacterial screening and the NHSBT results on bacterial screening; the added value of bacterial screening and future developments in that field.

So starting off with mortality figures worldwide, starting off where we are today, United States, 2005-2015, 38 deaths reported to the FDA.

In France, 1994-2015, 36 deaths reported to the French hemovigilance system, which is potentially the best in the world. It's a mandatory reporting, very, very strict regulated system.

In Germany, 1997 to 2014, 14 deaths reported in the German hemovigilance system.

In the UK, in 1994, we know there were three deaths. This is pre-SHOT; SHOT stands for Serious Hazards of Transfusion, which is the United Kingdom's surveillance system. So in the UK, 1996-2016, 11 deaths reported in the SHOT.

So, obviously, bacteria is a significant problem, and platelet components are the greatest risk. Data from this country, again, from the FDA, 2005-2015, platelet components comprised 87%, 33 of 38 cases of the fatalities, bacterial

fatalities.

UK, 1996-2016, platelet components comprised 84%, 37 of those 44 cases.

Now, this is a contaminated unit with bacteria, *Klebsiella oxytoca*. Now regrettably, not all units are this transparently clear of being contaminated, and this is why you need to do bacterial screening. There are millions and millions of bacteria present, but also you can have units that have 10^{12} bacteria in it, and they look perfectly normal.

So the NHSBT strategy to reduce the risk of bacterial transmissions, and this is really based on our early work in which we tested time-expired red cells and platelet components. We discovered what our contamination rate was. Twenty years or so, we had no idea what that rate was, no idea what the contamination went up to, roughly about 1 in 250 for platelet components.

So we looked at -- on that evidence, we found that skin contaminants were the major cause of contamination, so we looked at improved donor arm disinfection method, and we currently use the ChloraPrep method, which is 2% chlorhexidine and 7% alcohol, 3% application with that disinfectant -- I'm sorry, a 30-second application with 30-second drying time. That has actually been adopted now in the UK as the standard for catheter infection in hospitals on the basis of some of our results.

We also looked at diversion, and diversion is the rerouting of the first initial 20 or 30 mL of blood away from the collection bank into a side arm, which dramatically reduced the risk of contamination.

And we also looked at bacterial screening with various devices, rapid devices and also culture devices such as the BacT/ALERT system.

So intervention is introduced, improved donor arm disinfection was introduced nationally in 2007. Now 2007, it actually was in 2006 with only one site in England that was not using the ChloraPrep system. Diversions implemented in 2003, and in combination, in our paper, relatively values, we predicted a 7% reduction in contamination, and that is actually what we saw in reality.

So after the implementation, we improved donor arm disinfection and diversions. In 2006-2010, we had seven contamination incidents in platelet components. We had 10 patients affected; we had three deaths and five near misses, and the five near misses comprised of four *Serratia* -- *Staphylococcus aureus*, I should say, and one *Raoultella planticola*, which is a *Klebsiella* genus always classified now into another genus.

It looks like donor arm disinfection and diversions don't work very well because you actually had an increase in reports in this period. They work very well, and other blood services

actually published on the fact that they work very, very well indeed, but what we had was we had an increase in reports. It became mandatory for hospitals to report any transfusion reactions due to the implementation of a EU Directive in blood banks.

Also, our regulators, the MHRA, Medicines and Healthcare products Regulatory Agency, then began to inspect the hospitals themselves, the hospital blood banks, and that also stimulated reporting cases back to us with increasing awareness.

So based on those results, it was decided to implement bacterial screening. The NHSBT board, in January 2010, sat and made a decision to implement bacterial screening in 12 months. It was rolled down in February 2011, and by July 2011, all components were screened.

So a large amount of work to be done in a very, very short time. We used the BacT/ALERT system, and this was done for a tendering process, and that was chosen as the system of choice. Back in 2001-2002 we actually had published on use of the system for platelet concentrate screening.

Our regulators then asked us to do a retrospective validation of the implementation, which involved 16 bacterial species in replicates of 10 in PAS, platelet additive solution, and in plasma. So we did a very thorough validation retrospectively.

We also received a letter from our regulators saying this

is the last time we're asking to do a retrospective validation. All validations need to be up front. We're also now required to validate any system put in place by ourselves, and we're inspected to a pharmaceutical standard, and we have a license to supply blood to hospitals.

I'm just going to show you a couple of slides of the facilities within NHSBT for bacterial screening. Key point here, we have a cabinet here for inoculation with bottles. This is to reduce exogenous contamination. The bottles are disinfected with alcohol, and it's important to allow the alcohol to dry for the disinfectant to work. Then they're inoculated. There are various systems in place, barcode labeling and verification of stages to ensure the bottles are sampled. And we actually weigh the pack at the end of the process and record the volume to ensure it actually has been sampled. So we have a very rigorous process.

The BacT/ALERT system in place in our facility and the whole thing here, and we actually have the platelet components within the screening facility.

Now, our protocol, which is the key point: We very bravely, at the time, decided to go for one test and extend shelf life for 7 days. Now, platelet components, be it apheresis or pooled, are held for 36 to 48 hours after collection. Platelet components are then sampled and tested. We do aerobic and anaerobic culture, and we put 8 mL into each

culture bottle. And we also test every split from the apheresis unit. We do not test the mother bag, which I think is a key point.

Now, the units are held for 6 hours, and the reason for this is an issue with our computer system; this is the first time we can get a result from the BacT/ALERT systems. They're released with a 7-day shelf life, monitored for the component shelf life, and all positives are recalled.

If the unit has been transfused, we then inform the hospital that they possibly have a potentially contaminated unit, they monitor the patient, and when we get the reference laboratory result, which my laboratory undertakes, we inform the hospital.

So what happened with bacterial screening and results? Now, we were rather anxious about this. We were going to -- very rapid implementation, and I was quite wary of what we were going to get in the initial couple of months. We're going to get a high contamination rate, and we're only going to detect skin flora. So I was very worried about it, to start with.

And this is what we actually got. These are quarterly bacterial screening rates, initial reactive rate in blue and confirmed positive rate in red. So when we started off, we had a 3% initial reactive rate.

And I should cite this point. When a bottle triggers positive on our system, and that's any bottle, the aerobic,

anaerobic, all the other bottles will be withdrawn, so bear that in mind for what I'm going to say about anaerobic bottles. But it also means all the platelets for that donation are dead. They're going to be discarded, as are the red cells with pool platelets -- plasma. So we're losing 3% of our platelet supply at this point, which obviously was not sustainable. So we very rapidly put in corrective action to reduce that initial reactive rate.

Now, the Australian Red Cross saw an initial reactive rate, when they implemented screening, of about 1.06%. Ours was somewhat larger than that and quite alarming. But we've done a lot of hard work, we put some corrective action in place, and that was really starting off with retraining the staff of your new procedures. A number of staff performing the work are actually bacteriologists, so rapid retraining was undertaken regarding disinfection of the tops of the bottles, etc.

We also had a problem with the siting of the instruments within our facility. They were placed near air conditioning systems, blowing cold air onto them, into sunlight, etc. That was resolved. We also saw an issue with electrical interference of the system, so line conditions were put in place to get rid of that. And we also noticed an issue with the anaerobic bottle, that we had a substantial amount of false positives for the anaerobic bottle, particularly after the

incubator drawer had been shut for 24 hours.

Now, this was also noted by the Irish Blood Service, who came up with a loading pattern to resolve this issue, and by loading only 30 bottles into an incubator drawer and then closing that drawer for 48 hours, that resolved that issue.

So with that corrective action in place, we have driven the initial reactive rate down to about 0.3%, which we believe, at the moment, is the limit of the system. So we are losing 0.3% of our platelet supply with bacterial screening currently. This is somewhat inherent in the -- our computer system, the way it functions. There's no way we can retest the positive units, which we would do in our laboratory.

When we screen stem cells, we take the bottles off the machine and we gram stain them and we subculture them onto plates, and then we reload the bottles, and we save the stem cells because obviously they're very extremely valuable products.

So we've driven the initial reactive rate down. Note that the confirmed positive rate is consistent throughout the screening period, about 0.03%.

Now, this table shows initial reactive rate and confirmed positive rates in the same reported period, 2011-2017, and all the data I'm going to present has the same reporting rate.

This column here, we have the type of product, apheresis or pooled, the number tested, the initial reactive rate, and

the confirmed positive rate.

So apheresis, 1.2 million-plus apheresis units screened, 0.33% initial reactive rate and confirmed positive rate, 0.02%. With pooled, we have approximately over half a million screened, initial reactive rate 0.25 and a confirmed positive rate of 0.07.

So, in total, we now have 1.8 million-plus platelet components screened, and obviously, just past Christmas, we'll be pretty near 2 million, an initial reactive rate of 0.31% and a confirmed positive rate of 0.04.

Apheresis donations are collected by the Trima system exclusively. They are in plasma; they are not in PAS. Our pool platelets were in plasma to start with, and they are now in PAS. We have seen no increase in initial reactive rate between PAS and plasma once we made the change, though our surveillance team is keeping an eye on this and there may be a difference in the potentially pathogenic streptococci we are detecting with PAS rather than plasma.

We've also done some growth kinetic studies in our laboratory with PAS and plasma, and some organisms grow slightly quicker in PAS and some grow slightly quicker in plasma. And some just go the same in both. So it really depends; it's organism specific. Some of them are marked differences, but most of them are only small differences in growth kinetics.

Note that we have a difference between apheresis and pooled: apheresis, 0.02% confirmed positive rate, and pooled, 0.07. And this is potentially due to the number of donors we have. The venipunctures: pooled, we have four donors involved, and apheresis, there's only one donor.

Now, if you look at studies done by other workers, some agree with what we have said, Murphy et al. Others disagree. Schrentzmar (ph.) et al. disagrees and found the complete opposite. So it really depends on your process and your blood and various other things that are going on within your blood service.

Now I'm going to talk about the initial reactivity by bottle type. So in this column we have the bottle type here, and here we have the initial reactive percentage of those initial reactives, and also this column here, we have the false positivity.

So the anaerobic bottle, we got 73.8% of our initial reactives, aerobic bottle 21.3%, and both bottles 4.8%. But with the anaerobic bottle, we got a false positive rate of 7.9%, aerobic bottle 21.7, and both 0.4. So we have a high false positive rate with the anaerobic bottle.

Sensitivity-wise, we got 65% of our initial reactives for the anaerobic bottle compared to only 7% with the aerobic bottle and both bottles 28%. So the anaerobic bottle is very sensitive but not very specific. We got 30 species from the

anaerobic bottle only, compared to 16 from the aerobic bottle only, and both bottles we got 34 species. So a sensitive bottle, but not specific.

We did say in our paper that if you had to choose one bottle, potentially maybe you would go for the anaerobic bottle. But our data, as has been said, is skewed because we remove -- once a bottle goes positive, we remove the bottle. It certainly comes up quicker most of the time in the anaerobic bottle.

So our confirmed positives, we got 666, and by confirmed positive, I mean we've got the same organism in the initial reactive bottles in the pack. So 666 confirmed positives, of which 640 are gram positive and 26 are gram negatives. Roughly about 60% of the initial reactives we only found in the index pack. Another 30% we found in the index pack and the red cells, and 8% we confirmed on the red cells only, as the other packs weren't available.

So these are our confirmed positive organisms. In 640 gram positives, 26 gram negatives, the majority of the organisms we have detected are skin contaminants, with *Propionibacterium* species being the largest. So about 75% are skin flora, with about 16% being oropharyngeal and roughly about 9% being gut organisms or environmental.

I should say at this point, *Propionibacterium acnes*, *Propionibacterium*, we're not caught in an immediate transfusion

reaction. Potentially, it causes endocarditis, back issues. I really don't think it's a good idea to transfuse any viable bacteria into a patient. So I think it is good that we're picking this up. It also gives you an indication about, to mention, how good your disinfection actually is.

Now, this table here shows you the gram-positive organisms we think are particularly pathogenic, particularly, you know, we've done extremely well in detecting these. We've got *Streptococcus dysgalactiae*, 24 of those, but we got very rapid detection times, 2 to 19 hours and 32 components contaminated; *Staphylococcus aureus*, 17.

And bear this in mind what I'm about to say for near misses. So we've got 17 *Staph aureus* we've actually detected, 22 to 21 hours detection rate, 21 contaminated units. *Strep pneumoniae*, 12 detected in 10 to 13 hours, 16 components. *Streptococcus agalactiae*, six detected, 6 to 16 hours, five components contested.

And we got *Listeria monocytogenes*, and this has been reported by other blood services such as the American Red Cross. We've got donors walking around who are simply quite happy with *Listeria* in the bloodstream, which is somewhat surprising, but we are actually testing, screening healthy individuals the majority of the time. That's quite an interesting finding. Four of those, 14- to 20-hour detection times, five components detected. *Bacillus cereus* from the

environment, two detected, 11 to 14 hours, two components contaminated. So we got, pathogenic-wise, 65 organisms, 81 units contaminated.

Moving on to the gram negatives, and these ones are particularly dangerous because these are rapid-growing organisms which will form endotoxin. So we got *E. coli*, *Serratia marcescens*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis, Pseudomonas aeruginosa*, and *Campylobacter lari*.

Now, very rapid detection for all with the exception of *Campylobacter lari*, which I think is the second detected in the world. But all of these are gram positives, and the gram negatives we detected, which we found were particularly pathogenic, none of these left the NHSBT. They were all returned to us without leaving the service. So with the gram negatives, 22 organisms and 37 contaminated components.

This table shows you the number of splits contaminated in confirmed positive apheresis donations. So this is when we've got all the splits back for that donation. So for the doubles, in this column we have the splits per donation, the number of splits were positive per investigation. One only was positive. Two or three in the case of triples. So the doubles, we've got approximately 50% of the contamination was only found in one of the splits. With the triples, 50% in only one split, 90% approximately in two splits, and 31% in three splits. And the

ones where it was found in the three splits and the doubles, in both, potentially, are bacteremia individuals.

This really justifies us screening all the splits from the mother bag, and mother bags are split within 3 to 4 hours. With our testing protocol, we have to test the splits. We also are testing the splits, which increases our testing volume, which increases our sensitivity.

So now I'm going to run through near misses. We have one transmission to date, with 1.8 million platelet components, and that was a *Staphylococcus aureus*. Four near misses, three *Staph aureus* and one *Serratia marcescens*. I'm going to run through them now.

The first one, we got no clumps visible in apheresis donation with two splits. Large clumps were reported in Pack 2 by Hospital A. Pack 1 issued to Hospital B but not transfused; no clumps were present. Both units received by ourselves, and when they got back to us, the pack that didn't have any splits -- sorry, any clumps, had clumps in, and the one that did have clumps had no clumps in. So we've got a clot forming cycle and then the clot breaking up.

So they were positive on the BacT/ALERT system -- so heavily contaminated; a*ureus* was detected. Investigation of the donor found *Staph aureus* colonization, and the strain type and the platelet component and the donor isolate were indistinguishable.

This is a picture from the -- so you've got millions of bacteria present in the bag, and what you've got is this clotting cycle of clots being formed, breaking up, and the clots are formed by -- from being activated by coagulase enzymes from the origin, forming a clot, then it's broken up by *Staphylococcus* kinases breaking down the clot and dispersing the organism.

In none of the three *Staph aureus* near misses did we retain the bottles. We don't actually know if the bottles were actually sampled, so we don't know that in these cases.

So the fourth near miss, which is a *Serratia marcescens* near miss, apheresis unit with two splits. Clumps observed in Split 1 by our stockholding unit. Packs sent back to us, screening bottles sent to NBL. This is Pack 1, and we got the lovely clots in here. And Pack 2, there's nothing at all. So on testing, the gram from Pack 1 gram-negative, from Pack 2 there's nothing present at all. On the BacT/ALERT system, clotted Pack 1, positive after 3.7 hours; un-clotted Pack 2, negative on the BacT/ALERT, so no bacteria present in that bag.

And we got *Serratia marcescens* from Pack 1. And these bottles were retained, and it took us a lot of work to actually maintain -- to get actually the bottles to be retained. So these were inoculated using -- visibly and inoculate the bottles. In comparison, inoculated/un-inoculated. So you can visibly see if they're inoculated or not.

So BacT/ALERT bottle gram stained, negative with both packs. BacT/ALERT bottles were subcultured into other BacT/ALERT bottles, and there was nothing in there at all. So no organisms present, and nothing present on re-subculturing the bottles.

We then inoculated the screened bottles in the near-miss incident. We have *Serratia marcescens*, the one actually from the incident, and they weren't positive. So the bottles worked, so nothing wrong with the bottles, but obviously, there's nothing in the bottles to trigger the bottles positive.

So we conclude with this incident, it's not a BacT/ALERT failure. Insufficient sampling or bacteria present at the time of sampling. Now, highly dubious, this.

And I'm about to show you, on the next slide, contamination post-screening, I think is a possibility. I think we need to think about that.

So this is the growth study. We've got bacterial concentration on the y-axis, and on the x-axis we have time in hours. And there are 10 organisms per bag, not per mL, spiked into a platelet component within plasma, which is what our apheresis units are in, and by 36 hours we've got over 10^7 organisms present with this organism. And at 48 hours we've got over 10^9.

So I think it's highly unlikely it didn't grow sufficient numbers in a bag to actually trigger the bottles positive. And

we have tested -- detected five *Serratia marcescens* in screening as we've tested -- detected 17 *Staph aureus* in the three that were missed.

So moving on to our one transmission, which was reported to SHOT, pooled platelet unit transfused into an acute myeloid leukemia patient. After 50 minutes the patient became agitated and suffered rigors, tachycardia, and pyrexia. Her temperature rose to 38.7 degrees C, then overnight to 40 degrees C. The patient grew *Staphylococcus aureus*.

The patient unit was received by NBL. The unit was leaking in an open port sealed with a cath needle. So the bag was a bit a mess, to be honest. The remaining contents, 3 mL, appeared cloudy. Gram stain showed heavy contamination with gram-positive cocci, and this is the actual organism in our picture of the gram. It's a nice picture of the great light clumps there, classical *Staphylococcus*. BacT/ALERT cultures were positive in 3.8 hours.

Staphylococcus aureus was strain-typed to match the patient isolate. All four associated red cell units were cultured by NBL, National Bacteriological Laboratory, and remained negative after 7 days incubation. Two of the four donors investigated, both had *Staph aureus* in multiple sites. Strain typing of the first donor associated showed a distinct strain but no match. The second donor investigated was closely related SPAR type and matching DNA fingerprint. So it was a

confirmed positive, and it's been reported to SHOT.

I'm just going to say, very briefly, the added value of bacterial screening. Bacterial screening gives you an idea of what's actually going on out there in your population, but also healthcare benefit regarding *Streptococcus bovis*, which is linked to bowel cancer. We had four donors who had onsets of bowel cancer, which were then reported back to their GPs and then followed up, obviously saving the healthcare system substantial amounts of money. And we had incidents with *Streptococcus constellatus* of people who have dental gum issues from the organisms.

Moving on to bacterial screening, I'll give you a feel about what is going on with your actual processes. If you got pseudomonads, you got a poor hygiene issue in your processing facilities. And if you get extensive amounts of staphylococci, you got an inadequate donor arm disinfection method, or it's not being carried out correctly in accordance with a standard operating procedure.

So in the future for bacterial screening, there's a new generation BacT/ALERT system, the VIRTUO. We've looked at this in our laboratory, as has Michael Jacobs in a joint study looking at sensitivity studies for the VIRTUO system. It gives superior performance to the 3D BacT/ALERT system, faster detection times by 2 to 3 hours, potentially lower false positive rates because the bottles are automatically loaded

into the system, it scans the barcodes, loads the bottles themselves. So it's hopefully going to reduce this false positive rate, which is key to us because we're losing product over this. It also has some very nice features in its automated calibration of the machine. It takes digital images of the machine. It also checks if you've actually inoculated the bottles, which are key points.

So we've had one transmission over 1.8 million platelet components screened. We've seen approximately 90% reduction in clinical cases of bacterial transmissions prior to screening.

There are four near misses, three with *Staphylococcus aureus* and one with *Serratia marcescens*.

There was a false negative rate of 1 in 360,000; 0.0003%.

And we test our targets by platelet components, which have the bacteria screened, and we test them by the BacT/ALERT method, as in the screening method, and they are tested between Day 8 and 11. We now have one confirmed positive in over 6,000 targets by platelets.

This was a *Strep pneumo;* it was tested at Day 8 and came up very rapidly with the BacT/ALERT system, which shows you that obviously the screening system is extremely good but not infallible.

So the success of NHSBT bacterial screening is actually due to quite a few things: delayed sampling, high-volume tests between 5 to 7% of our platelet components, the screening of

the apheresis splits, and the use of a two-bottle aerobic/anaerobic system.

So I will conclude that bacterial screening within NHSBT has been proven to be an extremely successful risk reduction intervention. We are having, at the moment, and we hope it will stay that way, only one transmission in over 1 million platelet components, which is fantastic and a very good safety mark. All this work is published in our paper in *Transfusion*.

And I'd just like to say thank you to Jennifer Allen, Kate Aplin, Su Brailsford, Richard de Ritis, Rachael Morrison, Tyrone Pitt, Mariza Vasconcelos, and Tracy Ward for helping me put the presentation together, and all the hard work with bacterial screening. So thank you.

DR. STOWELL: Thank you very much.

Our last presentation for this part of the session is from Dr. Field from the Irish Blood Transfusion Service.

DR. FIELD: Good morning, and thank you once again for inviting me to address this meeting. I am presenting this paper really on behalf of my colleagues, Dr. Niamh O'Flaherty and Danny Curran, who do the actual work at the Irish Blood Transfusion Service. I come also with the experience of having been the Medical Director of the Welsh Blood Service prior to my appointment in March at the Irish Blood Transfusion Service, which also has 10 years experience of bacterial culturing of platelets.

A little bit about the Irish Blood Transfusion Service, just to open up. It's a statutory body established in 1965, responsible for the national blood supply of Ireland. That's the Republic of Ireland, remembering there is also part of Ireland which is still part of the UK, which is Northern Ireland, which is separate. Okay, so we're regulated by the Health Products Regulatory Authority under terms of the European Blood Directives, and we report directly to the government Department of Health. And those are just pictures of our building.

A little bit about Ireland itself: a population of 4.7 million, increasing since 2011; birth rate falling since the peak of 2009. And just a map of Ireland showing the major cities: 1.1 million living in Dublin, and then we've got the other major city, I think, the Republic of Cork down in the south, of 200,000 and then there's Limerick and Galway, which also have appreciable populations. So a different situation to the UK and the U.S., really, in terms of the major densely populated cities.

Just an idea of the immigrant populations are just given there as well: The population is largely Irish. Only 17% of residents not born in the UK, born in Ireland rather.

Just the number of whole blood donations, just to give you an idea. It's like anywhere else in the world, red cell transfusions are decreasing, and we've gone down from 136,000

to 129,000 in 2016. Funny enough, a slight increase in 2017.

And the national statistics, just to show you where our donors come from. I'm not going to dwell too long on this, but you can see the varied age of our donors, and the number of donors slightly increased from 2015 to '16, and the number of donors, of whole blood donors, comes from 81,000 donors giving 128,000 donations, so not very many donations per person.

And just to give you an idea of the donation per thousand of the population, as you can see, it varies from region to region. I'm not going to dwell too much on that.

And we get on to the important subject now, platelet production. Okay, pools are 54,000 -- sorry, 5,408 in 2016. The red are those that can be issued, and the blue are those that we produced in total.

The MRTCs are Bantry and Cork down in the south. So we have the two centers basically producing platelets. And you'll note that the great majority of platelets are from apheresis. Our current policy is to produce 80% of our platelets from apheresis, largely as a variance -- risk reduction measure, which is under review because of the production of pooled platelets in plasma, which reduces that particular risk. So we will be reducing our apheresis platelets into the future. But as it stands at the moment, we are holding between 75 and 80% of our platelets from apheresis. The pools are pools of four donors made by buffy coat method.

Okay, our rates of apheresis donors in singles, doubles, and triples: That's pretty self-explanatory.

And the issues, just to show the condition to many hospitals, many of those in the Dublin area, St. James's, St. Vincent's, Beaumont. The bottom of the graph that's out of the ring is St. James's Hospital, which is our largest user, and the others show different hospitals with others coming in at 5,978. But that's probably 21 hospitals with less than 100 donations of platelets used per year.

Just to show the laboratory components, laboratories consisting of processing, labeling, sampling for platelets and bacterial screening. We'll be looking at the bits in blue in particular.

Just pictures of the processes: We've been using the OrbiSac System to produce our pooled platelets, but we've now moved on to the Terumo TACSI system, and that's coming into production now. And we do put our platelets into approximately 65% PAS, platelet additive solution.

I'm not going to dwell on that one, just to say we're going to move on to our process of sampling.

Okay, so the collection is Day 0; pooled production at Day 1; apheresis sample, Day 1, which is 24 hours after collection post-donation. It's actually approximately between 12 and 24 hours depending on the actual time of collection during Day 0. Pooled platelets are sampled on Day 2 and

incubated until midnight of Day 5, in other words, for the period of the shelf life. So we have a 5-day initial shelf life on all of our platelets.

Then we give a little bit of information about the pre-culture preparation, donations stored overnight at 22. Apheresis, each split dose is recombined to produce -- prior to sampling, to make one sample. Pools are sampled the day after the pool is made.

Sample volume is roughly 16 mL on initial screen, 8 mL into each of the two types of bottles, aerobic/anaerobic, and 3% of a double dose of an apheresis donation is approximately 484 mL or 5%.

Okay. A pooled platelet volume is 5% of a pooled platelet volume of approximately 294 mL. There's no hold period after testing or loading the bottles. That's one thing I will look at because I do believe you should perhaps wait for the 6 hours for the first results to come through.

Just to give you some ideas of the -- of pictures of the laboratory. You've seen this in the other presentations. It's all done under hoods and with an aseptic technique, as possible. And again, we're using the BacT/ALERT system.

Okay, now supplementary testing: Apheresis, a second sample is taken on Day 4. Now, these are only the products that remain in stock within the Irish Blood Transfusion Service. We do not record any product from the hospitals. So

they have a 5-day life, and they would expire on Day 5, and that would be that. But any platelets which we happen to see are issued will then be subject to do culture on Day 4. Okay, and that's the process. And again, it's very similar.

Right. What happens when we have a positive detection by the BacT/ALERT system? Okay, gram stain, subculture bottle, and organism identification are conducted at a collocated hospital, which happens to be St. James's Hospital, right next to our center in Dublin. Recall of the implicated unit and quarantine of associated products. Hospital blood bank contacted. Physician is contacted if product is infused. Recipient samples are advised. Follow-up recorded and onward reporting, if necessary, onward reporting to our local hemovigilance system. Testing, 10 mL of platelet or red cells if available, incubated for 7 days and re-sampled a segment, what's 1 mL after 7 days of initial culture negative.

Okay, confirmed positives on BacT/ALERT: An organism isolated from BacT/ALERT is also cultured from platelet or associated product or recipient. These are just the definitions now.

Unconfirmed positive, a positive flag on BacT/ALERT: Organism isolated, but other components are not available for further testing, or negative culture results are obtained on testing of platelet or other components.

False positive is a positive signal from bottle, but

subculture of bottle or associated product is negative.

Right. So a septic transfusion is suspected, and that's a transfusion of a temperature greater than 1.5 degrees centigrade, high potential rigors. IBTS medical staff are advised, advised blood culture, specialist infection advice, and antibiotic therapy. Donor review and follow-up notification of the severe adverse events or reaction to the National Haemovigilance Office.

Right. These are the numbers. Okay, so this is for apheresis platelets in the period of 2005 to 2016. So just over 106,000 donations, 46 unconfirmed positives, the unconfirmed positive rate being 0.043. Confirmed positives was 29, which is 0.027% with a confidence limit shown under. So the total positive rate, confirmed plus unconfirmed, is 0.07%.

Day 4, 51,000 approximately; 15 unconfirmed positives, 0.029%; 5 confirmed positives, and that's 0.0097; and again, a confidence limit shown, and the 0.039 for the total.

So if we were to culture them on Day 5 as expired platelets, as we do post-dated, we did 6,395, 14 unconfirmed positives, 2 confirmed positives, 0.031 and 0.25. And the bacterial risk rate, therefore, is 0 in 2,169.

Right. Okay, the pooled platelets. So at Day 2, the initial 65,000, 39 unconfirmed; that's 0.059%. Fifty-eight confirmed; that's 0.088. And the total is 0.139 positives.

At Day 4, 16,000, 9 unconfirmed positives, 7 confirmed

positives; that's 0.043, the combined total of 0.0485. Okay, so the bacterial detection rate on Day 4 is 1 in 2,300.

Five-day expired, 1,961 cultured, 3 unconfirmed positives, of which 1 was confirmed, and that's 0.051. That's 0.2% total.

And again, 7-day expired, 631, of which nought were positive, unconfirmed or confirmed, with nothing. So the bacterial risk rate is 0 per 631. So septic reactions reported for 65,619 whole blood-derived platelets collected.

Right. Just a list of some of the organisms. I think you've seen these lists with the other presenters. It's a very similar array of organisms, *P. acnes* being the major one once again, and that's skin flora-type organisms being in the major group at the top there.

However, there are some nasties as well: gram-positive pathogenic *Staph aureus*, six; S*trep dysgalactiae*, five. Plus there's others I've listed: one *Listeria* and *E. coli*, *Klebsiella oxytoca* and *Proteus mirabilis,* and that anaerobe at the bottom, *Bacteroides theta* -- that's a mouthful, that one, but you can read it for yourself.

(Laughter.)

DR. FIELD: My Greek's not very good.

Right, a very busy slide just showing, again, all of these organisms with the time to detection: Again, the apheresis with *Listeria* was 18 hours, which is a bit of a concern. And again, *Staph aureus* at 14.4 down there. And 12.24 for another

Staph aureus. But most of them were clearly under 10 hours. A *Strep infantarius* of 11.27. So you see there's not always being absolutely rapid growing, and some of them do take a little longer.

And I do recall a case from my days at the Welsh Blood Service where we had issued an organism, a platelet, and just rescued it almost from the patient's bedside, which had a *Klebsiella* in it, which was a little bit of a later grower. So not everything comes up as rapidly as we would like, and I think that's the message.

Okay, this is just to illustrate the time to detection. As you can see there, the graph starts with those with the lower figures. The ones with stars are the apheresis. Okay, and you could see from the different colors from the -- the different organisms, you can just see it, as I've said verbally, it varies quite some time, and you can see that at least two of those were infused.

Okay, organisms not detected. Again, coag-neg staph, *Staph aureus*, *Strep infantarius*, *Kocuria*, and of course *P. acnes* once again.

And confirmed Day 4 cultures, again, those particular organisms, again, *P. acnes* being the major contributor.

Okay, culture results by apheresis splits. So isolate from Day -- that should be Day 1 initial culture. *Listeria*, a single split positive; there was a single *Staph aureus*, it was

a single dose; and the *Proteus*, three out of three.

Isolate from Day 4, both splits for the *Strep infantarius;* coag-neg staph, only Split Number 2; *Strep aureus*, both. Sorry, *Staph aureus, Staph aureus* was 2 and 3. And *S. capitis*, a single.

All right, a little bit about some of the cases: This *Strep dysgalactiae* was 9.36 in both bottles, was a pooled platelet in PAS, infused prior to recall. Red cells also grew *Streptococcus*, but the red cells had not been issued. There's nil of note from the health questionnaire, that's what the HLQ is, on the day of donation. It's a regular donor. Nil of note from subsequent medical review. Twelve previous donations. Satisfactory donor arm cultures. This was the quality control measure on the culturing of a donor arm on three particular occasions. The recipient was in his thirties, a new diagnosis of AML, received the unit whilst on those particular antibiotics for neutropenic sepsis; wasn't exactly the best patient to be getting any septic units.

A team was contacted by IBTS on the 2nd of October and advised the microbiology opinion with reference to further antimicrobials and blood cultures. More than five sets of blood cultures were taken between those dates, and none were positive. Added vancomycin and tazo, whatever it is, TZP, escalated to meropenem as part of the sepsis protocol anyway at the hospital. And the source of the sepsis deemed to be chest,

not transfusion, and reported to NHO as an SAE. Confirmed contamination of product, not as a TTI.

This *Proteus mirabilis* was a *Strep* apheresis donation in 2005. It was a triple. It was tested in August of 2005. Issued and infused the 31st of August and flagged on the 1st of September. For whatever reason, only one bottle incubated prior to introduction of the two-bottle testing, which was later in 2005. All three splits were positive, culture presumptive *P. mirabilis* with the classical swarming on the plate. The donor had given 156 donations, normal white cell count and blood pressure on the day of donation; follow-up information was unavailable. Unfortunately, this was one of the cases that our notes got lost in the archives somewhere. The patient was a cardiac artery bypass patient who tolerated the infusion well. No apparent septic reaction, but notes are minimal. So the patient got away with it.

Right. Interval donation started in March 2005. Bacterial screening results were negative. So the donor pool flags at 9.36 hours, both bottles. Note same interval to positivity. Products were issued to a pediatric hospital. Not infused on this occasion. Red cells negative. Retest. No donor identified. However, one of the donors also contributed to the pool.

Permanent deferral initiated, and a telephone conversation with the donor did not reveal any significant information. And

arm cultures taken. CFU count pre- and post-cleaning, 300 versus 0 CFUs post. But further identification was not undertaken. No blood cultures, so likely heavily colonized if two products contaminated in 2 years. This was actually the *Strep dysgalactiae* case.

Okay, interdiction of *Staph aureus* contaminated apheresis donation. Not detected on initial screen, but a sharp-eyed person in the issues laboratory didn't like the cloudiness and unusual orange discoloration of the product, which you can see there. They're not as obvious as Carl's example, so I think there's really a sharp-eyed person that picked this up. So the pack was sent back to IBTS for investigation, retested, and positive flag up to 3.84 hours with a gram-positive cocci.

Okay, this is a donor who had *Staph aureus*, a regular platelet donor, systematically well, but on examination had this beard rash and folliculitis, which is demonstrated there in the picture, said to be exacerbated by shaving, which he doesn't look as if he does that often.

(Laughter.)

DR. FIELD: Okay. And said to be exacerbated over the last 12 months prior to this thing. A nasal swab showed *Staphylococcus lugdunensis*, and chin and venipunctures, site swabs, all nil of note, although there is that whatever the STAE is, I can't tell you, on ref. laboratory report, and was referred to GP. Donor was deferred pending resolution of

symptoms and condition of skin. Sorry, STAE means *Staph epidermidis*.

Strep bovis subspecies *infantarius*. Apheresis donation, two split doses. Split 1 issued to pediatric hospital, recalled successfully. Split 2 remained in house. Both splits positive for *S. infantarius.* Donor, 54 previous donations. When contacted, "well," no weight loss. Nil else documented. GP contacted in light of association between organism and endocarditis or colon cancer, albeit the risk is lower than in the other *S. bovis* subgroup. IBTS advised and consideration given to blood culture, echo, colonoscopy. IBTS attempts at follow-up with GP were unsuccessful. Donor did not return to donate.

Okay, I just want to recall another case which I had in Wales just prior to my thing. We had a donor who had visited the dentist but not declared it, and he grew a *Strep parasanguinis* in his culture, an apheresis donor. Recalled the donor, retested him, and he still had the *Strep parasanguinis* circulating. We then advised him to see his GP, with strong advice to the GP to ask for an echocardiogram. The donor had the echocardiogram and active subacute bacterial endocarditis and was submitted to treatment.

About 2 months later we had a second case of *Streptococcus parasanguinis* from a donor that admitted to vigorously brushing his tongue, and we went through the same process but without

the same result. His echocardiogram was negative. So not all cases will come to the same conclusion.

Right. Another case from Ireland: A donor had a swollen elbow the previous month. GP review: no follow-up or treatment deemed necessary and appeared to be eligible to donate in October; felt well. Association with *S. bovis*, bacteremia-endocarditis and osteoarticular infections has been described. Should this donor have been deferred pending information or investigation?

So, again, I think what we're trying to say here is that perhaps our initial screening of donors is just as an important stage in looking at all of these cases of potential bacterial contaminations.

Right. Again, another case: *E. coli,* pooled platelets, confirmed on retest. Sensitive to ciprofloxacin and gentamicin and amoxicillin. Red cells in stock. Recultured, no growth. Therefore, no donor identified. Nil of note on the questionnaire. All four donors, because it was a pool, were contacted. Apart from mild sore throat in one donor, nil of note.

And the questions we normally ask on our questionnaire are:

- Any fever, chills, flu-like symptoms, headache, skin rash, infection, acne, venipuncture, and assessment of venipuncture site as well?

- Any dental manipulation?
- Any urinary tract symptoms?
- Any contacts, travel, pets, animals, occupation?
- Any recent antibiotics?

So those are things we do ask.

Okay, so our remaining significant pathogens. Okay, I think the table says it all. No apparent clinical symptoms in those particular cases, or donor not identified from the pool in those particular cases.

P. acnes: I think we talked about this at length already today. Again, a case where the donor questionnaire showed shoulder pain, and Carl mentioned the back symptoms in one particular -- as one particular sequela of *P. acnes,* so perhaps we should pay more attention to that. Uneventful transfusion to an attendee in the hematology day ward, normal vital signs after 1 hour. Patient contacted at home: well; no issue.

So as we tend to say, *P. acnes* doesn't really generally cause any problems, but as Carl was cautioning, there are cases where it can. So perhaps we shouldn't take it too lightly. And this just gives examples of other cases, which I won't go any further on.

And again, *P. acnes* can go on. I think you've got the slides, and I think you can read through those; that's fine.

And just the last thing is the false BacT/ALERT alert signals. Just to show our experience over the years in

Ireland, we had ever-increasing rates of false positives and then a few interventions such as designated incubators for each day of the week, avoid loading incubator 3 days thereafter, try to load in batches, allocate drawers for later loading of bottles, and minimize interruption to monitoring.

And just to say that earlier this year we had an incident where we were testing our contingency electricity supply, and we switched off the mains and switched it over to generator, and on the return of generator to mains, it tripped the switch, and it was done on a Saturday afternoon, which I think was a big mistake, and it tripped the switch on the BacT/ALERT. And so we had a huge problem, and once we reinitiated the power, because of the interruption, a whole lot of bottles coming out false positive, and we had to risk-assess a way through that in order to -- along with lots of subcultures, I might tell you, to ensure that we didn't have anything truly septic. We couldn't afford to throw away our platelet supply. So just a word of caution about protecting your equipment whilst you're doing these cultures, from any outside influences.

Right. Again, just to summarize, 65,619 pooled platelets are screened. Detection rate based on Day 4 culture: 1 in 2,300. Bacterial residual risk based on screening of 7-day expired platelets: There's nil in 631. Majority of significant pathogens isolated were detected in pooled platelets; that's 12 out of 17.

Even though sampled 1 day later than apheresis, all but one -- that's *Proteus* in 2005 -- of the contaminated products were infused, were detected in pools, *P. acnes* times three and *S. dysgalactiae*. Reflects proportionally a higher sampling volume, more sensitive than test or the influence of PAS. And that's the other question that needs to be answered, does PAS actually influence the growth of bacteria or not?

Then the apheresis platelets, 106,337. Detection rate based on Day 4 culture. Roughly 51,041 donations, which is 1 in 10,208. Bacterial residual risk based on testing a sample of expired Day 7 donations was 0 in 2,169.

Right. Now, the majority of significant pathogens are picked up on initial test. However, there is a value in a second Day 4 test. The facilities, extension of shelf life to 7 days with an extra margin of safety. Opportunity for organisms to grow, e.g., interdiction of the *Staph* whatever-it-was, contaminated platelets and two other contaminated products. Pathogens with potentially adverse outcomes were detected and not infused; *Staph infantarius*. Even if platelets already issued, opportunity to recall red cells if there's a positive flag. Day 4 monitors the sensitivity of the initial test.

However, IBTS will consider the one test 7-day strategy. Evidence suggests it's also safe and the testing cost-saving advantages.

We will also consider pathogen inactivation in the future. We have had one look at one system. I think, for commercial reasons, I won't say which one it is, but we were not satisfied with it. I'll say we dropped that particular project, but we will have another look in the near future at pathogen inactivation.

And again, a question arises at the timing of doing the pathogen inactivation and whether we can afford to drop platelet bacterial culturing or not.

I just want to acknowledge the input into all of the work at IBTS. And my predecessor, Dr. Willie Murphy, I'm sure, is known to many of you, and he kind of pioneered this work in Ireland, and I have thanks to him. And, of course, to Niamh O'Flaherty and Danny Curran, who actually did the work and just gave it to me, as probably an inadequate presenter, to present their work.

Thank you very much. Niamh is actually on holiday in South Africa, that's why she's not able to be here, but otherwise she would've been. Thank you.

DR. STOWELL: Thank you, Dr. Field.

We're running just a little bit ahead, but what I'd like to do is to take our break a little bit early and also come back early. We have a number of people who want to speak during the open hearing portion of this, and also we will have questions, I'm sure, for the speakers who just finished

presenting. So I suggest we would be -- it's just a couple minutes before 11:00 and that we be back here by 11:10. Thank you.

(Off the record at 10:57 a.m.)

(On the record at 11:15 a.m.)

DR. STOWELL: Okay, so at this point we would like to open up the discussion to the members of the Committee to see if you've got questions for any of the people who just presented earlier this morning. So this would be questions for Dr. Haddad, Ms. Scharpf, Drs. Vassallo, McDonald, and Field.

Dr. Basavaraju.

DR. BASAVARAJU: So my question for FDA would be whether the new culture interventions, whether you're going to -- does this include anaerobic as well, or just aerobic?

DR. HADDAD: So I had some slides in my presentation, you know, discussing the benefits and the disadvantages of including an anaerobic bottle. So, obviously, including anaerobes will detect strict anaerobes, and there have been a few of those cases, recently some *Clostridium* cases.

This has to be weighed against some of the drawbacks of using the anaerobic bottle, which is increase in false positive that can lead to the discard of otherwise suitable product, especially, for example, HLA-matched platelets, ABL-matched platelets, fresh platelets, especially in maybe transfusion services, that they don't have a high -- frequent platelet

transfusions, and a false positive would be deleterious to those transfusion services.

So it's an issue of platelet availability as well, and has to be -- we will weigh, you know, all the pluses and minuses, and we will, of course, wait for the input of the Committee before making any final decision.

DR. STOWELL: Dr. Escobar.

DR. ESCOBAR: Yeah, for Dr. Haddad, since you're up there, so in the United States right now, all the laboratories are doing the anaerobic culture because --

DR. HADDAD: The aerobic, the aerobic.

DR. ESCOBAR: You know, because there's still reports of -- fatal reports and morbidity from anaerobes bacteria.

DR. HADDAD: Sure.

DR. ESCOBAR: Anaerobe bacteria. So they are not all doing anaerobic right now?

DR. HADDAD: No, the overwhelming majority, they do only the aerobic.

DR. ESCOBAR: So there was underreporting probably of maybe possibly reactions that are due to anaerobes that are not being detected?

DR. HADDAD: Possibly. I mean, the underreporting is certain regarding all septic transfusion reactions, and certainly, we may be missing some anaerobes as well.

DR. STOWELL: Dr. Leitman.

DR. LEITMAN: Dr. Haddad, I have a question on your questions to our Committee, because they're fairly specific, and the first question has to do with platelets cultured no sooner than 36 hours for a minimum sampling volume --

DR. HADDAD: Correct.

DR. LEITMAN: -- system, but we didn't see data on that. The data we saw from BSI was more than 24 hours, so I don't know how to answer more than 36 hours if I didn't see data on that.

DR. HADDAD: The data from BSI is actually 24 to 36 hours, and we opted to go for the 36 hours to add, you know, a level of safety.

DR. LEITMAN: The same applies to Question Number 2, which is the delayed sampling, larger volume, and it's again in 2a, no sooner than 48, but the studies we saw from the UK were 36 to 48.

DR. HADDAD: Yeah, that's correct. I mean --

DR. LEITMAN: So it would be safer than what we saw perhaps, but we didn't see data on that actually.

DR. HADDAD: Correct. The data they have, you know, spanned 36 to 48 hours, so we thought to go with the upper range in terms of delayed sampling to ensure even better safety.

DR. STRAMER: Thank you. I have the same question as Susan Leitman did regarding, at least, the 7% because Carl

reported 5 to 7% of their volume. So it's difficult. It's difficult when the ranges, whether it's time or percent culture, are different than what the presenters showed, to responsibly vote on a question. It should be really limited to the data that we're presented.

DR. HADDAD: Well, you know, Dr. McDonald's data, the 5% were pertained to the pools and the 7% pertained to the apheresis. So the proposal that we have pertained to apheresis platelets, and that's why we went to the 7%.

DR. STAPLETON: This is more of a microbiological question, I suppose, but do you have any evidence on the bacteria that grew slowly, if they were nutritionally deficient or slowly replicating, or was it due to the low inoculum?

DR. HADDAD: You know, we don't have the microbiological data on the slow growers, you know, but whether the slow grower or the fast grower, you know, you have the sampling error at the beginning because you are sampling a limited volume from a large collection and you have the Poisson distribution issue.

DR. ESCOBAR: Is there any benefit of doing testing after Day 4, let's say Day 5, 6, or 7? I mean, the Irish data seemed like no, they don't detect anything.

DR. HADDAD: Um-hum. Sure.

DR. ESCOBAR: Is there any benefit of doing testing further out than 4 days?

DR. HADDAD: Yeah, yeah. Sure, there's enormous benefit

because then you get an opportunity for the bacteria to grow. And usually, around Day 4 the bacteria reaches a steady state, so the bacteria load would be much higher, and it would be much easier to detect those contaminations. Obviously, if you go beyond the 4, if you do Day 5, Day 6, if it's a culture, then you need some time to obtain the result, and it would be less practical with a culture. But with a rapid test, it's done, it's being done, testing on Day 5, 6.

DR. ESCOBAR: I know you recommended to do testing on Day 4.

DR. HADDAD: For the cultures?

DR. ESCOBAR: For the cultures.

DR. HADDAD: Yeah. So that's our recommendation, is to do a culture on Day 4.

DR. ESCOBAR: Okay.

DR. HADDAD: To extend to Day 7.

DR. ESCOBAR: Now, if the recommendation is made, let's say, to get a larger volume to do the testing, what did that imply in regards to the effectiveness of those platelets? You know, for that individual, you're removing a certain number of platelets.

DR. HADDAD: Sure, yeah.

DR. ESCOBAR: Does that mean that the individual is going to require, then, more units, which could certainly become an issue?

DR. HADDAD: You know, as I mentioned in my slide, one of the downsides of the large volume sampling is that you would, you know, decrease the potency of the product. Now, this can be addressed by increasing the volume of the platelet collection at the beginning. And then, also, another issue is, you know, now with platelet dosing, with the platelet study, you know, maybe patients need less platelets than they currently do to maintain the hemostasis.

DR. QUILLEN: I'm referring to Dr. McDonald's paper where their method says they sampled 16 mL. Could we ask Dr. McDonald whether that is the method, or is it really a percentage of the volume?

DR. McDONALD: What we do, we put 8 mL into each bottle. You take slightly more out of the bag than 16 mL, but what goes into the bottles, which is the key point, is 8 mL.

(Off microphone comment.)

DR. McDONALD: Yeah.

DR. QUILLEN: -- on volume inoculated and not percentage of the product?

DR. McDONALD: No, no, no, no. We're not that technical. We don't have the systems put in place that's weighing the bottles. We wanted a nice, quick, easy, clean system to use, so we went for 8 mL.

DR. QUILLEN: Thank you.

DR. LEITMAN: That seems to be a confusing point. So the

article says that the mean volume of the splits was 243 mL, and 16 mL is 7% of 243. So there didn't appear to be a target; it was a post facto calculation of what percent 16 mL was in their mean volume.

Can I ask a question of Drs. McDonald and Field? And it's not related to the questions to the Committee, but it was striking to me that in the UK there's a 6-hour hold to release after placement into culture, and if I understood Dr. Field correctly, there's no hold in Ireland. Yet, although the majority of organisms come up in 4 to 6 hours, a substantial minority take 10 to 20 hours, requiring urgent emergency phone calls to transfusion facilities. So I believe the standard in the U.S. is a 12-hour hold. How did they come about with a 0- to 6-hour hold?

DR. McDONALD: Okay, right. Can I just start off with the UK? The United Kingdom consists of England, Scotland, Wales, Northern Ireland. We are England, NHSBT. Blood transfusion-wise, it's a national blood service of England.

They are different countries. They're all bacterial screening, but they're all using different protocols at the moment. So we are the largest country population-wise, and most of the reports going to SHOT come from England. Six-hour hold is in there because of our computer system, because that's the first time it can receive results. It's not actually -- we didn't work out we're going to do a 6-hour hold, but it's

prudent in a way that it's in there for 6. So I think it's best to hold them because it saves recalling the units. But they're actually within NHSBT, the units, 12 hours before they go to the hospitals anyway.

So we've already got a 12-hour hold in essence, but technically, the first result that goes to the machine, they can be released if it's urgently required clinically in 6 hours. Yeah, okay.

DR. FIELD: As I said, this is something I need to be reviewing. Being in the post for 6 months and having reviewed this data, I think it's something we do need to be looking at.

But in mitigation, we do issue our platelets from the oldest to the youngest, oldest first, and therefore many of the units that do come up would still be in stock at the IBTS, and there's also the time it takes for them to get from us and then to the inventory in the various hospitals, bearing in mind they largely go to the Dublin area, so that's relatively quick.

But those going further afield takes many hours. So if anything were to come up, we would pick it up quickly. But I do agree, that is a weakness in our system, and that's something we did pick up in Wales, where we did have that near miss, and therefore it's something that I think we do need to review in Ireland. Thank you.

DR. STRAMER: As long as we're comparing the English and the Irish systems, another striking difference were the rates

of initial reactives between the two systems, 0.33% from Carl's data and 0.07% from Stephen Field's data from the Irish.

So it probably has to do with staff training or issues related to the laboratory itself, but it is interesting that in the Irish system they did drive down the false positive or initial reactive rate to lower rates than we saw in the English system. So I don't know if Dr. Field or Dr. McDonald want to comment on that.

DR. FIELD: I think in fairness to say the Irish system is considerably smaller than the English one, and that our platelets would be collected largely in the metropolitan areas of Dublin and Cork and therefore quite easily get in to be tested appropriately and made within the particular pooled platelets, made within the requisite 24 hours from delivery, from collection. Therefore, I think the chance is there of -- the lag periods are such that you would get less. You can control the system in terms of getting less false positives through the measures I mentioned in the talk, keeping the incubator closed, having specific allocation of incubators for specific days, and not opening them for 48 hours. Those sort of measures, I think, have really made our rates a lot, lot lower.

And Carl will answer for himself, but I think the large number of platelets being produced in the UK from a larger array of centers will create a much more difficult situation to

control that, which I think they have done to a degree, but not to the same.

DR. McDONALD: Okay, I agree with what Stephen is saying, we have much larger numbers. If you look at the UK -- and obviously, the Republic of Ireland is a separate country -- London, we have a population greater than Scotland, Wales, or Northern Ireland. We could supply all those countries probably relatively easily.

We test a large number of platelets now in three sites very, very rapidly, time constraints these people are under to do other jobs as well. I would say the Irish -- the Republic of Ireland blood service deserves a lot credit for doing a lot of work on this and getting their rates down. So they have worked on this, but we use their loading patent. So I think it's the numbers involved. It's much easier. In our laboratory, when we screen stem cells, whole blood, obviously very precious units, we don't see any of these problems because we have trained staff and microbiologists screening these units, using good aseptic techniques putting them into machines.

We've got processing staff doing these, screening very large numbers, which I think is why we've got a higher positive rate, and I think 0.3% is where -- the best we could at the moment.

VIRTUO probably offers us an alternative that we can get

the rates down with, which we obviously would like. And obviously, it's hurting us losing product, both for the patients and obviously financially as well.

DR. STRAMER: Thank you, but my point is it can be done.

DR. STOWELL: Does anyone know if this VIRTUO system is available in the United States? Has it been licensed here for use? This new version of the BACTEC that either Dr. Field or Dr. McDonald mentioned.

DR. HADDAD: No, it's not. No, it's not.

DR. McDONALD: I can speak for bioMerieux here. I can just explain what we have done in Europe. For us to use that product in Europe, it needs to be CE marked as a product we can use. It's not CE marked yet. I believe bioMerieux are going to CE mark the product the early part of next -- early quarter of next year. Then we can potentially use that product.

At the moment it's not available. It's available in Europe for the clinical market because these systems are not built for blood transfusion, they're built for the clinical market, which is much larger than our own market here. But it will be available.

And potentially, it looks good for mass throughput samples. But I honestly can't say if specificity will be any better than what we've got now because I don't know. All I could say is the sensitivity is equivalent, and the termination times are better with the BacT/ALERT.

DR. HADDAD: This system has not been cleared yet in the United States. This system, the VIRTUO, has not been cleared yet by FDA.

DR. QUILLEN: I have an unrelated question. I think Dr. Field mentioned that in Ireland, donors are asked about the history of dental manipulation. Are they deferred? And what's the time frame of this dental work that they would get deferred for?

DR. FIELD: It's the more invasive dental work, root canals, extractions, and things like that, which could cause a bacteremia, and it's a couple of days, if I recall correctly, that we would defer. But certainly, not normal dental scaling and stuff like that, no.

DR. STOWELL: Any additional questions for our speakers?

DR. STRAMER: A question for all speakers. What do you do with your positive donors? Are they deferred, are they put into surveillance? I know the answer from the English system, but I'd be curious to have the question maybe, so that all of the Committee is aware of what happens to a positive donor.

DR. FIELD: In Ireland they're deferred. We do as much investigation as we can on them. We do believe we have a duty of care to the donor in order to try and identify a clinical problem, but we do defer them, yes.

DR. STRAMER: All donors, regardless of bacterial species?

DR. FIELD: Yeah. Well, the *P. acnes* I don't think we

would defer, but it's the more significant pathological species that we would defer.

DR. STRAMER: Thank you.

DR. VASSALLO: At BSI we're basically doing the same as Red Cross; we're very similar. It depends on the species. So something that's bloodborne is likely to defer the donor, or something that's skin contaminate, if you look at the arm and evaluate that and make sure that there's nothing obvious like severe pitting, they're not deferred. We have very few second hits, however, much fewer than I saw when I was at Red Cross.

DR. McDONALD: So just to let everybody know, in England it depends on which organism it is. So we sit down together as a team, we discuss the case. Sometimes we get the donor back and test them. So it really depends on the organism. But obviously, potentially pathogenic ones would be deferred; we don't want them back. And we have advocated where the donors come back and we detected them twice, and then they would be removed from the panel as well, because the risk is too great, yeah.

DR. ARDUINO: So this is going back to the anaerobic bottle, so a question here. While it improves sensitivity, what do you give up on specificity in your -- in both the UK and Ireland, if you're doing both bottles?

DR. McDONALD: We don't really know because most of our false positives, 79% are coming from the anaerobic bottle. But

the thing is, once the bottle goes positive, both bottles are removed. So would the other one come up? We don't know. Probably unlikely, but I think it is an issue; bioMerieux has told us there's an issue with the bottle.

It needs a rewrite of the algorithm, and obviously, they're going to phase out the 3D BacT/ALERT systems and replace them with VIRTUO and their new algorithm in VIRTUO. So, no. You know, to be honest, you're going to lose product with it, if that's your system. But in our paper we proposed a method of -- most of these bottles are positive, and if you have a rapid test, you can determine if there's any bacteria present in that bottle.

We do this in our laboratory with gram staining, putting them on plates and putting the bottles back on the system. You can potentially save that product. And we were doing an evaluation for the MALDI-TOF system, matrix-assisted laser desorption/ionization for identification for doing -- mainly for stem cells, getting the bottles off the system and determining which bacterium was in that.

What's important for the patient is waiting. But you could use the fact we discovered at least 10^5 bacteria in the bottles. So the rapid systems that are out there commercially would detect that number of bacteria in the bottle, and then you could save that platelet unit and reload the bottle. So potentially, you could actually obviate that by doing a quick

rapid test, which I think, in a way, is maybe more appropriate to do those tests on those bottles to save that product and the culture is more sensitive.

DR. STRAMER: Just to respond to the question. Any time you add a second bottle, you're going to increase your false positive rate. Even with the aerobic bottles, as you could see from Dr. Vassallo's data, they had -- during Period 1 they had 366 false positives, and then with the addition of further aerobic bottles to get to the 3.8%, they had 1,500 false positives. So I mean, it is not only dependent on the medium, but dependent on the fact that you're doing additional culture.

DR. FIELD: I guess, from the Irish perspective, the reason we really do two bottles is because we're very risk averse. We just want to be sure that we pick up everything. That's really the only real reason. I think we do get more false positives as a result of doing that, and we are not issuing more product because of it. But I think, essentially, it's just because we have a really risk-averse approach to this. And when we had our little outage with the power supply, we really considered the anaerobic bottle to be very important in trying to resuscitate the situation.

DR. McDONALD: Can I just add to that? We have had a *Clostridium* transmission prior to bacterial screening, which was fatal. So we have liability for any of our components, so we are open to litigation, which has been quite costly in the

past, and we would look, should we say, compromised if we did not do anaerobic culture after having this transmission.

DR. BASAVARAJU: So if you extend the life of a platelet to 7 days, does that additional available platelet balance out with what you would lose by false positives, do you think, Susan?

DR. STRAMER: Well, if you're asking me, from data generated with 7 days either through the PASSPORT study or through the UK's system, for what Carl has presented for outdates, at least at the ISBT and Copenhagen this year and what Hema-Quebec presents, is that the 7 days is balanced by reduction in outdates. So the additional, let's say, cost for the system pays for itself because you're outdating far fewer platelets. So, to answer, the false positive balance is out because of reduced outdates; I can't answer that directly, but outdates is a big part of the equation.

DR. QUILLEN: I just want to clarify something from the English data to make sure I understand this. So I would like input from the infectious disease and microbiology experts here. What I heard from the English data is out of the confirmed positive cases, 65% were detected in the anaerobic bottle only.

So I assume they weren't all *Clostridium;* therefore, some of this could be oral flora detected on the anaerobic bottle only. And is this something that we should be thinking about

in our deliberations?

DR. McDONALD: I wouldn't get too hung up about the fact it was anaerobic, and I think you're getting hung up in it. True anaerobes you wouldn't detect; they'd all be dead in the blood products. It's just an anaerobic environment, so these are not strictly anaerobes. You class as anaerobic organisms, but the anaerobic bottle is particularly good at picking up a broad spectrum of organisms but has --

DR. QUILLEN: Actually, my question --

DR. McDONALD: -- poor specificity. Yeah, so it picks up. So we got 30 species of bacteria only detected in the anaerobic bottle, compared to 16 only in the aerobic bottle, with 34 in both bottles.

Yeah, so it's got a broad species range, and I think we're getting a little bit hung up because if you do classical anaerobic testing in broth bottles, it would be five electrolyte broth, and you can pick up aerobes in there as well. It's the layer on the top that's anaerobic. And also, for example, *Propionibacterium acnes*.

BacT/ALERT works by agitating the bottles. You actually get a much rapid detection of *Propionibacterium acnes* if you don't agitate the bottles; you just put them in the incubator. So I think we're getting a little bit hung up on the word anaerobe, to a degree, because you're not going to restrict true anaerobes in this environment, and you have to ask how

does a Clostridia grow in a platelet bag that breathes?

DR. QUILLEN: I actually was trying to argue for the sensitivity of the anaerobic bottle --

DR. McDONALD: Yeah.

DR. QUILLEN: -- for all the reasons they are not strict anaerobes. That was actually the --

DR. McDONALD: Yeah, yeah. Yeah, sensitivity is good because there's a broad range of organisms.

DR. QUILLEN: Yeah. Thank you.

DR. McDONALD: But I'm telling you now, beware, because it has a false -- high false positive rate as well.

DR. STOWELL: Other questions?

(No response.)

DR. STOWELL: Very good. If not, then, I think it's time for us to proceed with the open hearing. We have a relatively large number of people who want to speak and I am -- have to read to you these particular announcements.

And please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the

Committee of any financial relationship that you may have with any firms, their products, and if known, their direct competitors. For example, this financial disclosure information may include the firms who may have made payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The first person who is teed up here to present is Dr. Michael Jacobs from Case Western.

LCDR EMERY: If all the open public speakers can give their presentation from the center aisle, and there is a microphone there, we will have a handheld device that you will be able to control your slides.

DR. JACOBS: Thank you, Mr. Chairman. As you can see, I am Michael Jacobs. I'm Professor of Pathology and Medicine, Case Western Reserve University, and Director of Clinical Microbiology, University Hospitals Case Medical Center in Cleveland.

The next slide shows my --

LCDR EMERY: Excuse me, Doctor, if you could speak closer to the microphone --

DR. JACOBS: Oh, okay.

LCDR EMERY: -- so everyone can hear, I'd appreciate it. Thank you, sir.

DR. JACOBS: And I'm not sure how this slide device is working. These are my disclosures. Can you hear me now?

I've had research support or honoraria from Verax, Paul Gambrah, Hema Systems, Immunetics, GenPrime, Fenwal, Charles River Labs, and bioMerieux; consultant for Biosense Technologies, Limtech, Blood Systems. I'm a member of the bacterial contamination task forces of AABB and ISBT. And I have received no financial support for this presentation.

Next, this summarizes what we are here for, and I've listed at the bottom what, to me, are the issues, the potential safety and enhancements. We can optimize primary testing. We can mandate secondary testing, and that's an issue not being directly addressed by this Committee, but it was addressed by the previous Committee in 2012, and there were definite recommendations to mandate secondary testing on Day 4 and Day 5 platelets and then finally to use pathogen reduction technology.

Next, my objectives are three: To show that the gold standard for determination of bacterial contamination rates of platelets at actual time of use is culture, and you can either do this as a term of use or hard date, and that the utility of interventions must be documented by such culture.

The second point, which was being discussed extensively by several of the speakers, is to show that septic transfusion reactions detected by passive surveillance reliant on reactions being appropriately recognized, investigated, and reported to suppliers are greatly underreported by a factor of five to tenfold.

And, thirdly, to discuss evidence showing that detection of bacterial contamination by primary testing is limited and is more dependent on time of testing than volume tested, and this addresses one of the issues that one of your Committee members just mentioned.

These are the data sources; they're most of the same data sources that previous speakers have used. A couple of others. And I've also used statistical calculations to compare all of these using the same statistical methods.

So my first objective, to show that the gold standard is culture, is addressed by the next slide. These are our bacterial contamination rates. We've been culturing platelets, sometimes all platelets; other periods, no platelets. From 1991 and during this time period, over 25 years, we've picked up 80 bacterially contaminated platelets, and we use approximately 0.5% of the U.S. platelet supply.

We use an embarrassingly simple detection method. We take an aliquot of platelets at time of use. We plate 0.1 mL onto one blood agar plate. We incubate this aerobically for up to

48 hours. If growth is detected, we retain the initial aliquot at 4 degrees centigrade and repeat the culture, and if there's sufficient growth on the initial plate, we do serial tinfoil dilutions to obtain quantitation. And many of you will have recognized that lack of quantitation in many of the studies presented is a big limiting factor. You don't know how many organisms were present in these transfusions.

This shows our results to date, assuming we don't have any more next month. We've had 80 contaminated platelets. You'll notice, from 2001 to 2003, we did not have any. We did not have any reports of septic reactions, and the reason we didn't have any positive platelets is because we did not culture them during this time period. When primary testing was introduced in 2004, we reinstituted culture, and since then, we've had a lot of contaminated units.

You'll also see something interesting and for which I have no explanation, and that is for the period of 2012 onwards, we have had a decrease in our contamination rate. Our usage per year has been pretty constant, and something changed after 2011, and it wasn't a change in testing methods, it wasn't a change in diversion; I don't know what the reason for that change is, but we've seen a change.

The next slide shows a summary of our results. Before we started culturing, we saw approximately 400 contaminated units per million, and most of the data I'm going to show you is

looking at rates per million so that you can compare all results and use a very standard method of comparing them.

So here you can see before culture was introduced, we were seeing 400 contaminated units per million. After 2004 we were seeing exactly the same number. As far as whole blood-derived units, when they were pooled at issue we were seeing 2,600 per million. After pre-pooling, this rate fell to under 200 per million. So we're actually in a situation where pre-pooled platelets are actually safer than apheresis platelets.

The next slide shows a summary of our results and these are the exact same figures, but what I've shown here are I divided this up into different time periods, and you can see here, 2007 to 2017, I've used this time period because this was the time period where the volume used for BacT/ALERT was increased to 8 to 10 mL versus our other supplier, which continued to use 3 to 4 mL.

And you can see that our contamination rates, by either system -- and this is the first time I've ever presented this data, I only recently got the numbers from our suppliers -- that there is no difference between 4 mL and 8 mL. Our contamination rates are exactly the same, and we have pretty good numbers: 21,000 and 34,000.

I'm also showing you, just for comparison, what the theoretical rate is if you had 1 in 25,000 to 1 in 50,000 so you can compare the confidence limits to see that you'd have to

have 50,000 with only one to be significantly statistically different from these rates. But the bottom line is this is evidence that volume is not the driving factor in positivity rates for primary testing.

The next slide; the next slide after that. Now, I added some other studies to this, and I want to highlight a few possible studies, depending on how you interpret the data, had between 3 and 600 per million, but with numerators of only 2 or 4.

A study published from Ireland by Dr. Murphy had a numerator of 4. This is our data where we had a numerator of 29, and you can see, we had a much tighter confidence interval. That's where that number of 400 -- but you can see, none of these studies are diverse from each other statistically; they're all comparable.

Also, I've got one study here, and I was the lead author on this, but it was a multicenter study where 27,000 platelets were studied, and 9 were found to be positive. And I take exception to two of the speakers this morning who didn't lift out this fact, that this is the most successful study ever done on preventing transfusion of platelets. They concentrated on the fact that one septic reaction out of this 29,000 was missed and came up with ridiculous figures about how that's such a high sepsis rate, forgetting the fact that we prevented 9 patients from getting sepsis. So please remember this fact,

and I'll have more data on this.

I've also looked at the outdate studies from a Canadian system, Ramirez and Goldman, their group, and their rate was higher. And I think that's probably because they used anaerobe bottles as well.

Also, I'm presenting this data which was presented for the first time at AABB recently by Paul Ness, who's been a strong supporter of our program as well, and he reported that he cultured -- recultured his platelets, this time on Day 3, and found a rate of 300 per million, 5 out of 17,000 platelets were bacterially contaminated.

This is the English data that Dr. McDonald has shown you, and you can see he had an extremely high rate based on outdate cultures, but aerobic and anaerobic of 2,300 per million, which was reduced to 166. The only reservation I have about this is that the numerator is 1, and you can see that this is not statistically significantly different, whether there were 25,000 or 50,000, if your numerator is only 1. So I think this is very encouraging data, and I would encourage Dr. McDonald to increase this number so that we know that this is real.

So, in summary, what point I'm trying to make is that no testing rate was higher than in other studies, while the outdate testing rate was lower but not statistically significantly different.

The next slide shows my second objective to show that

septic transfusion rates based on passive surveillance are unreliable.

And the next slide shows some of the data towards this. This shows the data that we have by quantitation, and you can see here, this is how we came up with the figure that approximately half of contaminated transfusions have greater than 10^5 CFU/mL, and under 10^5, you get no or mild reactions. Greater than 10^5, 50% of them have a reaction varying from moderate to severe.

The next slide, and one after this. Yeah, this summarizes some of the data, and here, again, I'm comparing active surveillance programs, and these are data from Johns Hopkins versus our data; very similar rates, 40 to 50 per million by active surveillance versus most of these other studies whereby passive surveillance you're seeing very low reported rates. And this is, again, the big problem. The next slide summarizes this.

The third evidence that this is time and this is volume is summarized in the next slide. And you can see here, this is your detection limit of your BacT/ALERT bottle, and you're much better off waiting later to get more organisms so that you can pick them up rather than trying to increase the volume, which gives you very limited improvement.

The next slide.

Again, this shows this data in this context.

The next slide.

And to emphasize, this is the PGD test that we referred to several times. It's probably the most successful study for interdiction of contaminated platelets. I think Dr. Ness's data may have superseded this, and it showed that 1 in 3,000 units were prevented from being transfused. So please don't lose sight of this when you make alternative recommendations. And to emphasize this point, the number of doses studied is similar to the number of apheresis transfusions every week. So we can prevent nine patients every week from getting contaminated platelets with high numbers of organisms by implementing a second test.

And my next slide: These are my objectives. Again, I hope I've proven them to you in the very limited time that I've had.

And, in conclusion, at this time there are approximately 400 contaminated apheresis units or 800 per year with 2 million transfusions, an estimated 200 septic reactions per year, and that these bacterial contamination rates can be reduced.

Thank you.

DR. STOWELL: Thank you, Dr. Jacobs.

Our next speaker is Dr. Jessica Jacobson, who is representing the American Association of Blood Banks.

DR. JACOBSON: Thank you. I'm Jessica Jacobson, and I have no disclosures other than AABB paid for my hotel room, and

I'm representing the bacterial contamination workgroup, which is a subgroup of TTD.

Okay. From June 19th to July 21st, we distributed a survey to hospital transfusion services to get a sense of whether hospitals were aware of the draft guidance issued by FDA and to assess whether the hospitals were becoming prepared to implement once it's finalized. We also were interested in determining what educational programs or additional resources our transfusion services might need, if any. We're not going to present that data today.

Okay, so overall, 41.4% of hospital transfusion services responded to our survey: 94% of the hospitals responded that they were knowledgeable regarding the guidance; 75% of the respondents were preparing in some way for implementation of the final guidance; 59% of the hospitals anticipated challenges; most hospitals, 59%, planned to implement or recognize that they might need to implement a combination of risk mitigation strategies.

And when asked which control methods they might choose to implement, 69% of respondents indicated that pathogen inactivation would be part of their plan; 20% of the hospitals indicated that only pathogen inactivation was their plan, and that represents 15% of the transfused platelets in the survey; 45% of respondents planned to use an FDA-cleared rapid test on Day 4 or 5, and 26% of hospitals planned only to transfuse

platelets on Days 1 to 3; 4% of hospitals indicated a plan that only indicated transfusing Day 1 to 3 platelets, and this volume would've been about 1,200 platelets in 2016.

So 437 total hospitals were represented in the database. We did get some duplicate responses from institutions. Obviously, we only counted one of those sets of responses.

The responses came from a variety of sized transfusion services based on their platelet usage. Most of the responses came from, you know, hospitals using four to -- you know, reasonable size numbers of products, although 26% of the hospitals used less than 500 products a year.

So of the total usage of platelets, there were 705,000, roughly, platelets reported as having been used by the respondents in the previous year, in 2016, by single donors and about 87,000 whole blood-derived platelets, and the average pool was five.

So assuming that our transfusion numbers for the respondents were similar to those who responded to the NBC last survey, our respondents represented 39% of platelets transfused in the United States in 2015. And this just shows the remainder of the information. There were actually about just under 2 million platelets transfused in 2015.

Okay, we asked hospitals to report what types of products they routinely stock: 80% of hospitals routinely stock single donor platelets; 20% do not routinely stock any product and

only order platelets for specific patient need; 8% said they stocked pre-pooled Acrodose platelets, 6% pathogen reduced platelets, and only 4% stocked whole blood-derived non-pre-pooled product.

Ninety-eight percent of respondents were aware that there are different strategies that could be used to implement to mitigate the risk, and 94% of respondents were aware of the recommendations.

Thirty-four percent of hospitals planned to implement once the guidance is finalized, using the final date of implementation. Thirty percent said they would implement once final guidance was released but prior to the final date of implementation. Eleven percent had already implemented, 7% planned not to implement, and 18% had responded with "other."

The other implementation plans predominantly relied on 49% saying they were going to do whatever their blood center recommended. Twenty-seven percent also said they were waiting to know what the full final options would be. And the others are much smaller, but some 8% had already implemented.

Okay. We asked hospitals to indicate which options they might choose and to answer all that might apply. So the total number of respondents is going to be greater than 100%.

Sixty-nine percent of hospitals said they planned or would consider implementing pathogen-inactivated platelets. Forty-five percent said they would do a secondary test on Day 4 or 5.

Twenty-six percent said they would only transfuse platelets on Day 1 to 3, thereby not having to do anything additional in the transfusion service. Twenty-six percent said they would use a safety measure test to go to Day 6 and 7. And 4% said they were going to plan to do a culture-based test on Day 4.

So more than half of the respondents, 59%, indicated that they would have to use two or more mitigation methods. The remaining 32% of hospitals that only chose a single mitigation method specified that 20% were going to use single donor platelets that were pathogen inactivated, which would represent a little more than 100,000 PI platelets. Four percent said they would use an FDA-cleared rapid test on Day 4 and 5, which would be 20,000 SDPs. Four percent planed to transfuse platelets on Days 1 to 3. That would be 3%. Three percent planned to use an FDA-cleared rapid test as a safety measure on Days 6 and 7, and that would represent 27,000 single donor platelets. And a tenth of a percent of people planned to perform additional culture-based tests on Day 4, which would be 22,000 platelets.

Nine percent of the responding hospitals didn't select any mitigation, and they were waiting for additional information either from FDA and/or their transfusion services.

And the impact of the choices did vary somewhat by the size of the hospital and the transfusion service, but you saw answers to the questions in all size groups of hospitals,

irrespective of size.

There was a little bit of a difference between hospitals that care for children exclusively versus hospitals that care for adults or all comers, where more hospitals that cared for children, 82%, planned to perform a rapid test on Day 4 or 5, whereas only 42% of the adult hospitals did. And pathogen inactivation of platelets was slightly more commonly desired by adult hospitals at 68% versus 53% of pediatric hospitals. And 25% of adult hospitals planned to only transfuse on Day 1 to 3, whereas only 6% of the pediatric centers thought that was an option.

Fifty-nine percent of hospitals responded that they anticipated having challenges. The single largest challenge, 39% felt cost, whether it was the cost of testing reimbursement or the cost of paying for higher priced products, would be an issue. Twenty-eight percent felt they were going to have problems with inventory concerns and shortages. Twenty-six percent were concerned about staff resources and training.

Twenty-four percent were expecting problems related to blood supplier and what their blood supplier was going to do. Twenty-three percent had IT concerns, whether they were LIS or billing codes or how they were going to manage changing expiration dates. And 22% of hospitals felt that the testing time and the availability for emergencies would be impaired by needing to perform the secondary test.

So, in conclusion, 41% of hospital transfusion services responded to our survey, and they represent 39% of the platelets transfused in the United States. Only 10% of the hospitals produce any of their platelet supply, and 80% routinely stock single donor platelets. The facilities are well aware of the different strategies to mitigate against risk, and they have knowledge of the various recommendations.

Okay, overall, hospitals are preparing to implement the recommendations once the guidance is finalized, using the final implementation date or prior to that final implementation date.

Thirty-two percent of responding hospitals plan only to implement a single mitigation option. Most hospitals plan to implement a combination of options or at least recognize that that was likely to be required of them. Sixty-nine percent of hospitals included purchasing pathogen inactivated platelets as one of their options. Forty-five percent plan to use a rapid test on Day 4 or 5. Twenty-six percent of hospitals plan to extend dating using a safety measure test. And 26% of hospitals would only transfuse platelets on Day 1 to 3.

Fifty-nine percent of hospitals anticipate challenges in meeting the guidance and are heavily reliant on blood centers to provide these products. And based on the number and size of hospitals that indicated they would implement PI platelets, only the demand is expected to be at least 269,000 but may be significantly more than that, depending on what the ultimate

available selections are and how many of those hospitals that chose that PI platelets was part of their mitigation strategy would ultimately be purchasing what percentage of inventory as PI.

Thank you.

DR. STOWELL: Thank you very much.

Our next several speakers, I would like you to keep your comments to about 8 minutes each, please, so that we can get a chance to hear everybody.

The next speaker is Dr. Peter Tomasulo, who is representing bioMerieux.

DR. TOMASULO: My name is Peter Tomasulo. I am receiving financial support from Terumo BCT and from bioMerieux, and bioMerieux paid my way to the meeting.

That's not my slide.

(Laughter.)

DR. STOWELL: Does somebody recognize this slide as being theirs?

DR. TOMASULO: That's Dr. Jacobs's slide, isn't it, Michael?

DR. STOWELL: I don't think so.

(Pause.)

DR. TOMASULO: That's the slide. Okay.

DR. STOWELL: All right.

DR. TOMASULO: FDA has determined that current small

proportion primary screening of platelets with BacT/ALERT and eBDS does not provide bacterial safety for transfusion up to 5 days, and it has recommended pathogen reduction technology for 5-day platelets or secondary testing for 5- or 7-day platelets.

There has been limited implementation of these strategies because of the higher cost, logistic complexity, and variable sensitivity and reduction in the availability of platelets.

The benefits of large proportion sampling are shown on this slide. The first column has apheresis platelets, platelet results reported by Dr. McDonald in *Transfusion* and here this morning. The second column has data from the first column and all the SHOT data for both apheresis and component-lab platelets, as well as the platelets transfused in Scotland, Northern Ireland, and Wales.

The third column has data from Blood Systems that you heard this morning. They are data from the BRAVO paper in 2015, the second period where they used greater than 3% testing, the data from the Kamel paper, and the report that Dr. Vassallo showed up to the present, September of 2017. And the last two columns are two different reports from the American Red Cross.

The results with the NHSBT protocol are significantly better than the results with the ARC protocol. There were fewer septic reactions even though NHSBT stored platelets for 7 days. BSI has demonstrated 5-day platelet safety. Neither BSI

nor NHSBT has reported fatalities due to septic transfusion reactions, but ARC has reported fatalities at the rate of about one per million.

NHSBT inoculates 6.6%, BSI inoculates greater than or equal to 3.8%, and the American Red Cross inoculates an average of 1.7%.

BSI predominantly collects platelets with Trima, NHSBT collects platelets exclusively with Trima, and ARC uses predominantly Amicus in these reports reported here. It is known that Trima platelets cause fewer transfusion reactions than Amicus platelets, and the better results seen in Columns 1 and 2 could be due to the combination of delayed testing, Trima, and large proportion testing. Thus, the question arises: Is it necessary to use large proportion sampling if platelets are being collected with the Trima device?

So this is an aggregate of seven different studies using exclusively Trima platelets. The slide shows that when greater than 3% of the platelet volume is cultured, there is a significant increase in the identification of units, Rows 2 and 3, and a significant decrease in the frequency of septic transfusion reactions, and therefore one would conclude that even with Trima collections, there is a significant benefit to large proportion sampling.

So bioMerieux recommends that FDA approve a specific option for blood establishments to utilize a greater than 3.8%

sample at 24 hours in primary bacterial screening to provide platelets which are safe enough to transfuse up to 5 days without secondary testing.

On this slide there are data from 17 peer-reviewed studies of buffy coat platelets, Trima, and Amicus platelets. We aggregated them to see if we could detect an impact of large proportion and delayed testing, and as you can see, large proportion testing increased the detection of contaminated units and decreased the risks of septic transfusion reactions in Rows 2 and 3.

Delay of primary screen increased the detection of contaminated units and decreased the septic transfusion rate in Rows 4 and 5.

Because all the sites that test more than 36 hours after collection use large proportions, we can't conclude with certainty that delayed testing and large proportion testing independently reduced the rate of septic transfusion reactions. The combination surely does.

BioMerieux also recommends that FDA should provide a specific option for blood establishments to utilize a greater than 3.8% sample at 48 or 72 hours in primary bacterial screening to provide platelets which are safe enough to transfuse up to 7 days without secondary testing. This recommendation, if implemented, will increase the availability of platelets.

Secondary testing and pathogen reduction require additional manufacturing steps which could disrupt hospital and blood center operations. Large proportion and delayed screening can be implemented entirely within the GMP environment of blood centers with minimal change from current operations. It will improve safety and increase the availability of platelets.

I'm done.

(Laughter.)

DR. STOWELL: Thank you.

Our next speaker is Dr. Ana Rosatos (ph.) from Terumo.

DR. ROSATOS: That's not my slide either.

(Laughter.)

DR. ROSATOS: But somebody really wants to present this slide.

(Pause.)

DR. ROSATOS: There we go. So my name is Ana Rosatos. I am an employee of Terumo BCT.

Terumo BCT is committed to advancing the availability of safer blood for transfusion and agrees with the FDA that the current platelet supply would benefit from mitigation to further reduce the risk of septic transfusion reactions.

However, Terumo BCT believes that additional mitigation strategies or pathways should be included in the guidance document to ensure that U.S. blood centers can provide safer

platelets while at the same time meeting the current demand for platelet transfusions.

In 2014 FDA released the first draft of this guidance document specifying both pathogen reduction and point-of-issue testing as acceptable risk mitigation strategies. Almost 3 years later, the industry has seen limited adoption of both mitigation strategies due to technological limitations that prevent universal adoption and jeopardize the availability of platelets in the U.S.

Terumo BCT is asking this Committee and the FDA to include larger volume or proportional volume sampling, as well as delayed sampling during primary culture, which provides significant risk reduction with less cost and impact to the nation's platelet supply.

Next slide, please.

So as described by my predecessors, large volume sampling consists of sampling a larger percentage of the total collect volume. So, for example, a 16 mL sample, which represents roughly 3.6 volume percent, rather than an 8 mL sample, which is 1.8 volume percent, from a 450 mL collection. And then delayed sampling is taking the sample 36 hours post-collection rather than the typical 24 hours. And it's actually the combination of large volume and delayed sampling that supports extending platelet shelf life from 5 days to 7 days.

Next slide, please.

So larger volume plus delayed sampling -- I'm sorry. Larger volume plus delayed sampling and a 7-day shelf life was actually pioneered by Dr. Carl McDonald at NHSBT in 2011. So since that time, we know that Hema-Quebec, as well as Canadian Blood Services and New Zealand Blood Service, have adopted similar models to the NHSBT model. And then Blood Systems here in the U.S. as well as the Australian Red Cross have adopted large volume sampling but take the sample 24 hours post-collection with a 5-day shelf life.

So now data published by BSI and also by Hema-Quebec demonstrate that taking a larger sample volume increases the detection of contaminated units at the time of culture. And so as shown here, you increase or improve your detection by a factor of two, and that removing these contaminated units from the transfusion pool will prevent potential septic transfusion reactions.

The data presented in this next slide is septic transfusion reaction rates. So the rate of septic transfusion reactions in the U.S. has been assumed to be that 1 in 100,000 or 10 reactions per 1 million transfusions. Since the FDA released the guidance document, however, Anne Eder has published data demonstrating that the septic transfusion reaction rate can vary based on the device used to collect the platelets. So the risk of septic transfusion reactions to platelets collected on the Trima Accel automated blood

collection system, with smaller volume sampling, is between two and five reactions per 1 million transfusions. The NHSBT collects exclusively on Trima Accel.

So if you start with a platelet collected on the Trima Accel system, add large volume sampling and delayed sampling, then you can reduce your risk down to less than one in a million or the 0 in 900,000 transfusions that's been presented.

And so this data, we feel, is significant because the NHSBT is a large study and should be taken into consideration.

There has been one septic transfusion reaction reported in the United -- I'm sorry, reported to NHSBT since large volume and delayed sampling was implemented in 2015, and it was associated with a whole blood-derived platelet.

In 2016 there were three near misses found to be contaminated via visual inspection and were returned to NHSBT, and it is difficult to compare these three near-miss events at NHSBT to other studies which did not include an assessment or reports of other near-miss events.

The last slide, please.

So, in summary, large volume and delayed sampling is a cost-effective method that does not significantly impact platelet availability, as was described earlier by Dr. Vassallo. Moreover, it provides a shelf life that is uninterrupted by additional testing after primary culture, which is a logistical advantage and remains invisible to

transfusion services and hospitals.

So in addition to pathogen reduction and point-of-issue testing, Terumo BCT requests that this Committee and the FDA include the following mitigation strategies:

- Large volume sampling 24 hours post-collection with a 5-day shelf life;
- A larger volume sampling 48 hours post-collection with a 7-day shelf life.

Thank you.

DR. STOWELL: Thank you very much.

Our next speaker will be Dr. Richard Benjamin from Cerus.

DR. BENJAMIN: Thank you for the opportunity to address this Committee. I appreciate the time. I'm the Chief Medical Officer of Cerus Corporation. Up until 2 years ago I served as the chief medical officer for a large blood center in this country, where we published data on the world's biggest experience with bacterial culture, and most of my comments will be related to that period of my life and the publications from that time.

I want to review with the Committee why bacterial culture screening -- and how it fails through model, and then I want to review national hemovigilance data from four European countries, looking at bacterial culture and pathogen inactivation.

So with that start, if I can get this to work, let's talk

about our model for bacterial culture. We believe that most platelets collected are, in fact, sterile. A small number, a smaller proportion, contain bacteria but at collection contain very, very low numbers of bacteria, I would guess between 1 and 10 single colony forming units, which is less than one bug per 100 mL. If you take an 8 mL sample or a 50 mL sample, you're not going to detect that bacterium.

So what we do is we wait 24 hours or 48 hours, and what happens is that some of the bugs die and become irrelevant. Other bugs grow rapidly and reach concentrations of more than 1 CFU/mL and are easily detected by initial culture. Let me just click through this. I'm not getting much -- there. Easily detected by initial culture and the next day we need to do a confirmatory culture; the bacteria have grown further, and they're easily confirmed as true positives.

Some of the bacteria have a long lag phase. They might be sitting within white cells or stuck to plastic, and they have a long lag phase or they have very slow growth. And they reach concentrations of about 0.1 CFU/mL.

So your 10 mL sample most of the time will actually pick up one viable bacteria and be positive on the initial culture. And when you come back the next day, they've grown more, and so your confirmatory culture is positive, and it's a true positive. But you will miss a couple that have a sterile 10 mL sample, and you'll have some false negatives, and I would

venture that this is where increasing volume might pick up more initial positives.

What worries me the most are the bugs that don't grow, and we now know that *P. acnes* does this, and we know from the NHSBT data that *Staph aureus* does this. It sits. They don't grow. You have one bug per 100 mL. It doesn't matter if you take a 10 mL sample or 50 mL sample, you're not going to pick this up. They're mostly going to be false negatives. But these are the ones that, on Day 4, 5, and 6, may grow up and cause septic fatalities. That's the data. So mostly false negative.

Now, consider what happens if you do happen to get that one viable bug in your bottle. You get an initial positive. You come back the next day, the bugs haven't grown, so now you have a negative culture. You call that a false positive. In the Red Cross we call that a false positive contamination. Other people call it an unconfirmed positive, or at BSI they call it a discrepant negative. The point is that discrepant negatives are truly contaminated products that are removed from the blood supply and are providing safety to the patient population.

So with that background, let's look at the data with minimal proportional sample volume testing. We heard this morning from Dr. Vassallo that when you move from an 8 to 10 mL sample to greater than 3.8% sampling, you double your true positive rate. That's very nice. But the discordant

negatives, which are also really contaminated, actually went down, and the total number of contaminated products that were removed from the blood supply did not change. Hence, the septic rate did not change. I will venture that there's no data presented that minimal proportional sample volume has increased the safety of the blood supply one iota. Also, it doesn't use anaerobic cultures.

We now have two fatalities and two near misses in the U.S. with *Clostridium perfringens* contamination of platelet -- of apheresis platelet products. We have no protection. I would suggest that this Committee needs to consider whether primary culture testing needs to include an anaerobic bottle. I would venture it does.

Let's move on to national hemovigilance systems. We recently reviewed, in a publication in *Transfusion* online, the UK system, which includes the NHSBT English system over the last 10 years, compiled their data, as well as the Belgian, French, and Swissmedic hemovigilance programs where pathogen inactivation is used.

So let's talk about the UK system, the SHOT UK data. So as Dr. McDonald pointed out, NHSBT is about 85% or 88% of the SHOT data, and you can see their schema here. That's England and a little bit of North Wales. The Northern Irish blood system also uses delayed large volume culture, but they take from the mother bag; they wait 48 hours, not the 36 hours that

the NHSBT does. They also do aerobic and anaerobic cultures. So that's very similar to the Hema-Quebec system that was described above.

The Scottish and the Welsh systems do not delay their primary cultures and so are not relevant, but they are about 10% of their SHOT data. However, the near misses and the septic reactions all occurred, as far as I can tell, over the last 6 years in Northern Ireland or in England.

So let's look at the last 6 years: NHS SHOT-compiled data. There were 1.65 million transfusions. There were 620 suspected septic transfusion reactions. So for every 1 in 2.5 -- sorry, 2,500 transfusions, the doctors reported a septic, a suspected septic reaction. That's a very, very high reporting rate. So vigilance is high.

Most were excluded or ruled out. One was ruled definite sepsis because the same bug, *Staph aureus*, was found in a patient, in a platelet, and in the donor. One was ruled a possible sepsis. The hospital found a *Strep* in the platelet bag and in the patient, the same *Strep*, but were unable to -- the NHSBT were unable to confirm, and they called it a possible sepsis. There were also eight near misses.

I should note that I'm counting the actual bag components that's here, whereas Dr. McDonald tended to count the collections and not their actual products that were available to patients.

When we compare this to the prior 5 years, there was definite sepsis, 13 bags given to 10 patients in the prior 5 years, definite drop in sepsis. There was no change in the near misses, eight and eight. There was also an increase in the indeterminates and possible sepsis. I would venture that the SHOT folks are using more stringent criteria to call sepsis now than they were previously.

Okay, moving on very quickly, national hemovigilance data with INTERCEPT Blood Systems. The Swiss implemented in 2012 and have no septic reactions, definite septic reactions or fatalities since then, a 14-fold decrease. Part of France put INTERCEPT in place and have had no sepsis in 10 years in those places, whereas they continue to have fatalities and sepsis where they were doing nothing. Belgium, one blood center used BacT/ALERT culturing, they had lots of sepsis; the other blood center used INTERCEPT, no sepsis.

We now have 2.4 million platelets transfused worldwide with no definite sepsis or fatalities, and under hemovigilance it's actually now 646,000 because the new data for 2016 in Belgium has been added.

So, to finalize, without culture screening, you have high contamination rates. You add culture screening, you have lower contamination rates. The UK pool was 67%. The U.S. pool was 72%. I would venture they are not different. In those places where they put in PI, they've seen no sepsis.

I would conclude that 7-day storage with delayed large volume culture is not superior to the current system in the U.S. with 5 days when you take into account these near misses.

I would venture, also, that there's little evidence that minimum proportional volume screening improves blood safety one iota.

And finally, the INTERCEPT Blood System provides protection against bacteria, viruses, protozoa, GVHD, and you can release your platelets 2 days earlier than with delayed large volume culture, allowing for the transfusion of fresher platelets.

Thank you.

DR. STOWELL: Thank you.

Our next speaker is Dr. Art Bracey from St. Luke's Health Center.

DR. BRACEY: Thank you. The hour is late, so I'll try to be brief. This is not my slide deck, though.

(Laughter.)

DR. BRACEY: So we've heard a lot, as the slides come up, about the risk and the problems that we face, so I'm going to try to limit the amount of time that I spend on background. Initially, I was going to talk much about -- to some degree about the impact of large volume/delayed culture. You've heard much in that regard. I want to focus, really, on what happens at the hospital level. I am in a transfusion service, and I

want to share with you the experience that we have with using a secondary test in that setting.

If I learn how to work the -- oh, yeah. So my disclosures are shown here.

And just by way of background, I think it's important to raise one other point, and that is, again, as Dr. Benjamin was explaining, the platelets, as we collect and store them, are not sterile products. That is the root issue. Obviously, after 5151, we've taken steps and there have been incremental gains in terms of detecting bacteria, but what's really important in terms of the paradigm of safety is knowing what the outcomes to our patients are.

And so one study that provided a pretty good look at that, as Dr. Jacobs pointed out, was the Verax trial, from the Verax study group, and there the rate of risk following pre-released culture was at 326 per million.

So way back in September 2012 there was a recommendation from this very group that steps would be taken to mitigate risk, and we've heard that patients are suffering. So I think that, you know, at some point we need to get on with it, and we need to make sure that we're protecting those who we serve.

I don't want to talk much about this, so let's -- you've heard much about delayed sampling.

And important, though, is the discussion of hemovigilance, and Dr. Benjamin, again, did a great job of covering the

hemovigilance reports from the SHOT report. But any of you who have been in the clinic knows just how difficult it is to diagnose sepsis. The over-clear case, easy. There are lots of occult cases that we just don't fully understand. So when we talk about the data that we have at hand, it's an incomplete dataset, and I think we need to be mindful of that. We also need to be mindful of the very stringent criteria that are generated in the SHOT report and raise questions about how many cases are falling through that we really yet don't know are affecting patients.

So in our hospital, we felt uncomfortable with, early on, how we were managing our whole blood-derived platelets. We cling to those because we like whole blood-derived platelets. And we began testing with rapid bacterial diagnostics back in 2010, and after hearing the recommendations of the BPAC, we began to test, in a limited way, apheresis products in 2013, and by 2015, we're testing all apheresis products at Day 4 and Day 5. In some, we transfused over that interval about 30,000 doses of platelets and tested a little more than half of those, 16,839.

What you can see is that in terms of the repeat reactive rate, there were not that many positive platelets that we saw. In point of fact, if you're concerned about losses, at least in our facility, it was extraordinarily minimal, 0.15%. So this did not represent a problem for us. We did have one culture

positive, coagulase staph negative, for a confirmed positive rate of about 59 per million.

So there have been concerns about the operational aspects of how one could do this in a busy transfusion service, and we provide complex cardiovascular care, transplants, heart, liver, lung. What we do is we pay careful attention to our platelet inventory. We maintain 15 to 20 doses of platelets at all times, and on average, we have to prepare these batches of tested or secondarily tested platelets about four times a day.

We had one of our residents do a time study in terms of exactly how much time it took to prepare this product and then to equate that to how much time we're spending in our staff over the course of a year. That was 0.68 FTE, which is less than 5% of our full-time equivalent staffing. Given the ability to have other efficiencies such as using automated testing for cross-batching, etc., we were able to implement full testing of secondary testing for bacteria without adding a single FTE.

One of the challenges that we did find, and we certainly are compliant with the labeling, is that virtual pooling, wherein you test whole blood-derived platelets for 24 hours, akin to the way you manage your apheresis platelets, makes it very easy to have products all tested. To date, we have not issued untested, secondarily tested platelets to any of our patients. So we find it to be a very efficient and easy

process.

So with that said, here you see a display of the hospitals that are in our system. The mother hospital is Baylor St. Luke's Medical Center, the more complex hospital. But as of this year, we began to roll this out to other hospitals, and these are hospitals that do not have SBBs. In point of fact, the people working in those labs are often generalists. So at our hospital at the Woodlands, a general care facility, we're providing secondary testing. At a very small hospital, The Vintage Hospital, we're also providing secondary testing.

When I asked, because I've been very concerned that perhaps we're overtaxing our staff, perhaps we made a bad decision, when I ask them, they tell me that in point of fact, it's very easy to get this done. We haven't fully converted our staff -- our facilities as of yet, but the plan is to do that because, again, our experience with using this testing is that it's not that difficult.

So we find, in a nutshell, that rapid bacterial testing or detection is easy to operationalize.

The uptake is possible in smaller facilities where perhaps there's not even a technologist whose focus is simply or strictly blood banking.

In our hands, product loss from testing is minimal and absent sterile products because, clearly, if you have a sterile product or at least a product that's PI, that's the -- you

know, we strive for that. But absent sterile products, mitigation beyond pre-released culture is warranted.

Thank you.

DR. STOWELL: Thank you.

Our next speaker is Dr. Sarah Harm, who's the Medical Director of the Blood Bank at the University of Vermont Medical Center.

Dr. Harm.

DR. HARM: Hi. Thank you for letting me speak today. Disclosures: I received travel expenses from Verax, and I've received speaker honorarium from the American Red Cross.

And I'm here today to present 1-year experience with -- over 1-year experience with Day 6 and Day 7 platelets, and it's a combination from two hospitals, two academic medical centers that have been using this product by using the PGD test, the rapid test, on either Day 4 or Day 5 or Day 6.

So here are the two centers: UVM Medical Center in beautiful Burlington, Vermont. We are 520 beds. We are the only Level 1 trauma center and NICU in the state. We do autologous stem cell transplant, and we transfuse approximately 1,500 apheresis platelet doses per year. We are located 4 hours from our blood supplier, and we batch test all apheresis units on Day 5 and Day 6 with the rapid test.

Dartmouth-Hitchcock Medical Center is in Lebanon, New Hampshire. They are 420 beds. They are a Level 1 trauma

center and NICU. They also do allo stem cell transplants on top of auto. They transfuse approximately 2,500 doses per year. They are 100% apheresis. They collect approximately 40% of their own inventory, and then the rest comes from blood suppliers that are approximately 2 to 4 hours away. And they batch test all units, all apheresis units, on Day 4, Day 5, and Day 6.

And so here's a chart showing the pre-implementation period 12 months before using routine use of Day 6 and Day 7 platelets, and the post-12 months after routine use of Day 6 and Day 7 platelets at each of the hospitals. And you can see there the number of transfused apheresis units: a slight uptick at one hospital, a slight decrease at another hospital. The number of transfused platelets that were transfused after rapid testing was performed increased significantly, obviously, at both centers, and that provides additional patient safety, we believe.

The average number of apheresis units that were transfused per transfused patient did not increase. We are using older platelets now, we're using Day 6 and Day 7 platelets routinely, but that did not reflect in the number of units that went to each patient.

There were no significant changes in the number of transfusion reactions that were reported per 100 apheresis platelet transfusions at either hospital, and no reported

septic transfusion reactions at each hospital.

And there you can see our inpatient admissions and surgical volumes are both increasing, and the average length of stay, which is also an indication of patient safety, did not change significantly between the pre-implementation and the post-implementation period.

We, both hospitals, had no additional needs for FTEs to perform daily rapid testing of our entire apheresis inventory. It is very easy, and both hospitals perform this testing during the off shifts when we have minimal staff available.

At the University of Vermont Medical Center, over those 12 months we screened 762 units, and to do that we used 781 PGE tests. Our false positive rate is less than 1%; there were only six units that had to be discarded. But when you consider our outdate rate is exceedingly higher than that, that is nothing to us. And 19 of the 781 tests performed were performed to either confirm or negate the initial positive PGE test.

Platelet outdate rate decreased by 50% at both hospitals, 5 to 3% at one hospital and 28 to 14% at the other hospital.

And ad hoc ordering, which is a reflection of platelet need beyond a standing order, decreased by 50% at one hospital. It went from over 50%. It went from 21% down to 9% of their inventory was obtained by ad hoc ordering.

And if we get to the root of the original draft guidance,

which was based on patient safety and increasing the patient safety of our platelet transfusions, we really have to talk about the false negative rate of initial culture. And we know that it's there in the USA because we have looked for it, and given data today, we know that the false negative rate is unknown right now using the delayed large volume culture. But we do know there are four near-miss events, as we've heard, and approximately 100 cases of suspected bacterial transmission each year, but they do not meet the strict criteria for the septic transfusion reaction.

So if the goal is really zero tolerance for bacterial contamination in platelet products, then we need to consider that initial culture is not enough.

And there you go, summary: Initial culture alone is not enough, and in our hands, in my hands and in a colleague's hands, rapid testing is an easy and important part of safer platelet transfusions, and rapid testing on Day 4, Day 5, and Day 6 increases the flexibility of the inventory and decreases outdate rates of apheresis platelet products.

Thank you.

DR. STOWELL: Thank you.

Our next speaker is Dr. Neil Krueger from Oxford Immunotec.

DR. KRUEGER: Oh, those are my slides.

(Laughter.)

DR. KRUEGER: So good afternoon. I'm Neil Krueger, and I'm a principal scientist at Oxford Immunotec, which is my full-time employer, and I appreciate the opportunity to address the Committee today. It's been 5 years since the last BPAC meeting on the issue of bacterial contamination platelets, so I'd like to take a few minutes to give the Committee an update on the BacTx platform and how rapid testing in general can become an important part of the draft guidance that will eventually become final to make platelets safer. BacTx was developed over the past 15 years at Immunetics, which was acquired by Oxford in 2016.

So the problem is well known to everyone. Early culture simply misses too many contaminated platelet concentrates. Sampling at 24 hours is problematic. There may be only one or two CFU in the entire platelet concentrate at 24 hours, but these bacteria can grow up to dangerous levels later in the shelf life of platelets. Some bacteria enter log phase very early, and early culture catches most of these. Less than 20% of dangerous -- or excuse me, less than 20% of transfusion-transmitted contaminants fall into this category.

Other strains have an extended prolonged lag phase before entering log phase. Many gram positives fit this category, including *Staphylococcus*. More than 80% of transfusion reactions are in this category.

Before log phase growth, there are too few bacteria to

reliably sample. The PASSPORT study demonstrated that 25 to 50% of contaminated platelet concentrates are missed by early culture.

The problem with early sampling is best exemplified by studies that report only one co-component of double or triple splits being contaminated and other co-components remaining sterile. Thus a sample that contained one-third to one-half of a platelet concentrate can miss the presence of bacteria in the remainder of the unit. So we believe the solution is universal bacterial detection by the BacTx rapid test.

Many invertebrates possess a defense mechanism that triggers a proteolytic enzyme cascade resulting in inactivation of bacteria. The cascade is initiated by the binding of an insect peptidoglycan receptor to a bacterial peptidoglycan. The BacTx assay utilizes this cascade to detect the presence of peptidoglycan, a universal component of bacterial cell walls.

Insect peptidoglycan recognized in proteins have been evolutionarily selected for universal bacterial detection. The survival of the organism depends on peptidoglycan recognition of every bacterial strain. There should be fewer holes in this than others -- that may be the case in other strategies, such as antibiotic cocktails.

Binding of an insect peptidoglycan binding protein to peptidoglycan activates an enzyme cascade which the BacTx assay takes advantage of by adding a chromogen that detects the

activation of the assay that turns from white to bright red.

Seeing that peptidoglycan is an obligate component of all cell walls, this strategy enables BacTx to detect even the rarest strains of bacteria. In fact, hundreds of bacteria strains have been tested with BacTx, and to date, no strain has ever failed to be detected by it.

Brief overview of the BacTx assay system: The system consists of a kit of reagents sufficient for 32 tests plus the BacTx Analyzer, which is an automated platform that minimizes the risk of human error by using barcoded -- barcoding of both the platelet donor IDs and assay tubes and automated results analysis. There is an on-screen result reporting function and also the capacity to download results in an XML file. It has eight channels random access so you can start a few tests, and then if you have more platelets coming in, in a few minutes, you can start a few more. The turnaround time is 40 minutes, so it's obviously much faster than culture testing. It's cost effective, and you would only need to test platelets that go beyond Day 3 under the current draft guidance.

BacTx is FDA cleared for use with random donor platelet pools as well as apheresis platelets. If you're interested in the details and limitations of these claims, please grab one of our handouts outside the conference room.

Very recently Oxford Immunotec has submitted a 510(k) for use of the kit with random donor platelets pre-pooled with the

Acrodose system.

This slide shows the analytical sensitivity of the assay with ATCC strains. The analytical sensitivity of BacTx is in the 10^3 to 10^4 CFU/mL range. The sensitivity is one to two logs lower than titers that have typically been reported to cause morbidity or fatality during platelet transfusions. In addition, BacTx has been tested with clinical isolates as shown on the next slide.

A series of clinical isolates was provided to Immunetics from the collection of Dr. Michael Jacobs at University Hospitals. These isolates came from contaminated platelet units that caused morbidity or fatality and were part of his collection due to the active surveillance studies that he talked about that have been such an important part of understanding bacterial contamination.

All isolates tested were detected with sensitivity analogous to similar ATCC strains. This study demonstrates detection of clinical isolates from actual contaminated units with high sensitivity. Thus, we believe that near point-of-transfusion rapid testing should decrease the frequency of adverse transfusion reactions, and in fact, Dr. Verax has -- or Dr. Jacobs's Verax study demonstrates that quite clearly.

Finally, to briefly address the specificity of the BacTx assay, the specificity reported in our 510(k) clinical study was 99.8% in a collection of more than 400 sterile apheresis

units. This specificity is comparable to what has been reported in some BacT/ALERT 3D studies, such as the one cited in the slide. So it is not necessarily the case that use of a rapid test will dramatically increase platelet units being thrown away unnecessarily.

In conclusion, Oxford Immunotec believes that the BacTx assay, in combination with the pending FDA guidance on bacterial contamination in platelets, will result in an effective approach to improving patient safety while allowing a cost-effective way to significantly reduce the risk of bacterial contamination.

Thank you again for the opportunity to update the Committee.

DR. STOWELL: Thank you, Dr. Krueger.

Our last speaker is Dr. Louis Katz from the American Red Cross and America's Blood Center.

DR. KATZ: One correction. I'm not from the Cross. My name is Dr. Louie Katz. I'm the Chief Medical Officer and Acting Chief Executive Officer of America's Blood Centers. This statement is, indeed, the consensus of my organization and the American Red Cross. My only conflict of interest is that I am paid by Terumo to chair two of their data safety monitoring boards for trials of their pathogen reduction platform.

ABC and the Red Cross are responsible for more than 90% of blood collection and distribution in the United States, and we

appreciate the opportunity to present this statement as the FDA considers revisions to the draft guidance. This statement is intended to update FDA on the current thinking of our organizations. We believe these comments will assist FDA in evaluating the multiplicity of effective approaches that are available to enhance the safety of the blood supply and ultimately the care and safety of the patients we serve.

Despite the current interventions which interdict, at most, 30 to 50% of bacterially contaminated platelet units, transfusion-transmitted sepsis remains the most common infectious cause of recipient fatalities reported to FDA. Currently, around five fatalities per year are recognized and reported, but the surveillance is passive, and the clinical burden is believed to be substantially greater. Hence, our organizations support a need to enhance bacterial safety of transfused platelets using measures beyond the current approach of initial bacterial culture performed on apheresis platelets at approximately 24 hours after collection.

We strongly endorse the availability of multiple options to achieve this goal based on operational considerations in collection facilities and hospitals across the U.S. that affect their ability to implement one or more of the allowable interventions.

The options currently available to achieve this goal include enhancing the sensitivity of testing for bacteria and

the use of pathogen inactivation. The data support the conclusion that pathogen inactivation is the intervention that will provide the maximum bacterial safety for platelet products.

While PI using an FDA-licensed technology is being implemented throughout the U.S., current demand exceeds supply, and the capacity to produce PI platelets is not sufficient for their universal use. Reasons limiting availability include the restrictive guardbands for qualifying apheresis products as eligible for pathogen inactivation and the lack of a licensed system for triple apheresis products or whole blood-derived platelets.

A contributing factor is the length of time it has taken FDA to review and approve blood center license applications allowing for interstate shipment of pathogen-inactivated platelets. Thus far, the only approved license applications took 1 year or more to be approved by FDA, and older completed submissions still await decisions by the Agency.

In addition, FDA has made changes to validation and QC data requirements while submissions have been in progress, and such long review cycles should not be necessary given that the format for each center submission has been largely standardized, and the processes under review already have been in common use in blood center component manufacturing for other indications.

A number of process changes to increase the percentage of products eligible for pathogen inactivation have been proposed, guided by the PI sponsor and being standardized between blood centers. However, each of these requires another round of submissions and FDA review, further delaying the ability to increase the supply of pathogen-inactivated platelets.

In order to overcome these limitations to the PI platelet supply, we urge FDA to do its part in pursuing a goal of extending the guardbands, approving triple collections for treatment, and most importantly, making the regulatory process more conducive to timely implementation of this technology.

We have discussed the clinical efficacy of the U.S. licensed PI platelets and understand the limits of the data. Robust data on their effectiveness are derived largely from hematology oncology patients, and patients with active hemorrhage from trauma or other conditions may be underrepresented. We are, however, encouraged by evolving hemovigilance data, especially from the European Union, that are not suggestive of material issues with the product, but surveillance clearly must continue.

With regard to enhanced sensitivity testing for bacteria, we favor making multiple approaches available, including point-of-care tests on Day 4 and beyond, reculturing during the shelf life of the product, and delayed primary culturing at 36 to 48 hours with higher input volumes using both aerobic and

anaerobic bottles. Data are available for each of these approaches to support increased bacterial safety relative to the current intervention using early culture alone. An alternative approach involving increased platelet culture volume in approximately 24 hours after collection, combined with use of both aerobic and anaerobic bottles, may increase sensitivity and should be considered as well.

Although these enhanced testing options can be implemented with 5-day platelets, they become much more realistic with extension of platelet dating, platelet storage to 7 days. This is particularly true with regards to both reculture during storage and the delayed primary, high-volume culture option, which each result in an additional loss of ½ to 1 day of the cumulative shelf life unless product expiration is extended to 7 days.

Currently, the FDA has proposed that 7-day dating be restricted to the use of tests that have a safety measure claim. We agree with application of this requirement for point-of-care tests that were validated against culture but do not think it is necessary either for secondary cultures or for the approach of delayed primary culture at 36 to 48 hours.

Of note with regard to inventory management and platelet availability, since PI platelets, which are currently restricted to 5-day storage, do not need to undergo primary culture, these platelets are available to transfusion services

up to 24 hours sooner than conventional platelets and already have a longer period of functional availability.

As you have heard today, AABB has surveyed its member hospitals regarding plans to implement additional bacterial interventions. Of those responding, most (59%) report that they anticipate challenges in meeting the guidance requirements, and many prefer the provider to perform the additional mitigation steps.

The survey indicated that demand for PI platelets is expected to exceed 1.25 million units a year.

In the absence of an intervention by the blood collector, the hospital survey suggests that some hospitals will attempt to avoid secondary testing and transfuse platelets that have been stored for 3 days or less. This will likely decrease the number of collection facilities willing to distribute platelets on consignment and rotate stock between hospitals to avoid outdating. The result is decreased platelet availability and increased waste through outdate.

In summary, deaths due to transfusion-transmitted bacterial infection still occur, and it is necessary to provide enhanced safety to protect patients.

The allowance for multiple approaches to enhance bacterial safety recognizes balancing the need to improve safety with economic and logistic considerations that may influence decision making in different institutions.

Last, our request to FDA to simplify the regulatory framework for wider PI availability is based for concerns of patient safety rather than decreasing the regulatory workload at blood centers.

Thank you for the opportunity to offer these comments.

DR. STOWELL: Thank you.

We've had two additional requests for people to make comments. The first of these is from Dr. Nancy Hornbaker from Verax. Dr. Hornbaker. Oh.

MR. SANDERS: No, Joe Sanders with Verax. We were actually in the program, I think.

DR. STOWELL: Yeah. And for these other two people, please keep your comments to 5 minutes, and don't recap the history for us, if you would.

MR. SANDERS: Certainly. I think we have a slide deck here. That's not it.

(Pause.)

MR. SANDERS: Can you put that back up? Sorry. I'm used to seeing that. Yes, okay. Sorry. Joe Sanders with Verax Biomedical. I'm the founder of the company. We make the Platelet PGD Test.

And there have been a number of comments and issues raised pertaining to the practicality and viability of implementing secondary testing as an approach to deal with bacterial contamination. So I thought it would be useful and possibly

informative to the Committee to see and hear some information from actual users who have implemented the test, because what we've seen over the past 2 to 3 years is a significant increase in the usage of the product, driven primarily by the interest in the topic and the draft guidance as it's gone through its process.

To put it in a broader context, current users of the PGD test count, there's about 217 U.S. institutions that test, at least, part of their platelet inventory. As you heard from some of the folks who have already been to the podium, they may test a fraction of their inventory at Day 4, Day 5's, or Day 6's, and Day 7's. The key point is in the total context of all the platelets at those sites that use the test today, they consume 486,000 platelet units a year, which is about 20% of the U.S. inventory. And among those sites, we're seeing interest in Day 6 and Day 7, and that 72 of those sites are live now with Day 6/Day 7 or purchase the product and are finishing their validation to implement for Day 6/Day 7. And just those 72 sites outdate over 31,000 platelet components a year at a cost of $15 million to the healthcare system.

So we perform a user survey every 2 to 3 years. This is done to assess overall experience of the customers of a product, their satisfaction with it and their actual implementation experience. It's done by performing a random sample of 50 of the current users, so these are people that are

live running the test, and this is a very broad range of sites.

We have a number of very small users. You'll see people here in the range of 100 to 500 tests per year; some of those are at the very low end of that scale, and some others are very large, among some of the largest sites in the country who transfuse over 16- to 30,000 platelets per year. So there's a very good representation across a wide range of sites, mostly hospitals, one blood center here, and a couple of centralized transfusion services.

So some of the basic questions that we worked through are ones we typically do each time we do this. They're asked very basic questions on how they find the ease of use of the test, and they're asked, on a simple five-point scale, is it harder, is it easier than, and what you'll see here is very consistently people find it similar to or easier than the test they run in their test today, in their lab today. Only one actually marked it low/comparable, and that was one who, when asked later a question on whether it was practical for routine use, said that it was. They were referencing it to their prior experience of using a pH test as a bacterial release test.

How many days did it take them to become comfortable running the test and for their staff to become at ease using it? Actually found this happened very quickly. Training of sites is very quick; it only takes a day or two of training and get someone up to speed, and then as they work people through

the workstation, we find everyone is basically comfortable running the test within a month.

How long after being trained did it take them to put the test and use as test of record? What we found is the majority of sites get the test live and test of record within 3 months. This is usually related to just when they schedule their timing for proficiency, validation, and making any edits to their LIS system and production of labels.

I skipped over one slide there.

Did you hire extra staff to implement the test? We get a unanimous no to this, in spite of the fact that some sites are very small, and some of those sites that use the test are actually extremely large and do quite a large number of tests, which you think might stress them and require them to hire extra people, but we have not found that to be the case. Everybody's been able to implement the test with current staffing.

We also asked if it cost them anything to do an upgrade to their LIS system to upgrade the test. Many people raise this as a concern before implementing the test and will it have an impact, will they have to buy a new LIS module, will they have to make some kind of major IT upgrade? Again, across all the respondents, there was a unanimous no to that.

We did ask if they transfuse SDPs and they have outdates, why do they not test Day 6/Day 7 now? There are people who

have outdate platelets and who choose or have chosen so far not to implement testing for Day 6/Day 7, and far and away the most common response to that is they're waiting to see final guidance and what form that takes.

One of the key questions we asked them, that was 14 of the sites in the survey of the 50 sites have implemented 7-day dating with PGD. And so they reported both their pre-implementation outdate rate and their post-implementation outdate rate, and you can see here illustrated in the height of the orange bar is the overall rate they had before implementing the test, and the blue bar is what it dropped to after the implementation of the test.

What we really see here is there's kind of a two-step process in this. When they first implement the test, their outdate rate drops, and then as they adjust and start changing their ordering patterns and adjusting to the reality they don't need quite as many platelets, their rate tends to drop lower than that with increased time and use.

We asked them very specifically what is the economic impact of them implementing the test and going to Day 6/Day 7. Every single site that implemented it reported significant savings, anywhere from 25,000 to $200,000 per year, and no site reported saving less than $20,000 per year implementing the test with Day 6/Day 7 dating.

I can update this, and say we now have a significantly

larger number of live 7-day sites, and the average savings is actually creeping up. It averages slightly over $200,000 per year. Part of that is because we now have five or six blood centers live who are doing this as well, in units that they retrieve and ship back, and their savings actually go as high as a million dollars per year.

And an obvious and simple question, then, in light of the savings, does this fully fund your PGD testing? And the answer, again, was a unanimous yes.

So a little bit of an overview of those 14 sites, just 14 sites in this particular survey of implemented Day 6/Day 7: Those sites alone transfuse almost 30,000 doses annually, and they're saving a total of little over $1.2 million per year through reduced outdating. And those savings are more than fully funding implementation of the test.

We did ask a couple questions because people ask -- and in fact, I can speak to many of these people in the survey. Before they implemented the test, they had doubts, they had questions: Can we do this? Can we really support this? Will our labor be able to deal with it? Will we have to hire people? Will it reduce or release our components or cause more outdates? And their experience has been that's not the case.

So we asked them what would you tell somebody who was considering implementing this but they were worried is this too hard, is it going to take too much labor, is it practical to

do? And these were typical responses, direct quotes from people in the surveys. And I won't read all these, but they'll give you a good sense for the kind of flavor in the context of the comments we received.

And for sites that were asked the same question who are extending dating to 7 days, you see responses that are, if anything, even more enthusiastic.

So that's my last slide. Thank you very much.

DR. STOWELL: Thank you very much.

Our last speaker is Axel Stover, representing Fresenius.

DR. STOVER: Thank you, Mr. Chairman, for the opportunity to speak here today. My name is Axel Stover. I am the Director of Scientific Affairs for Fresenius Kabi USA. Fresenius Kabi is the manufacturer of the Amicus Separator apheresis device, which is used for the collection of apheresis platelets.

We were made aware of the data mentioned here by the American Red Cross before the study was published and transfusion by Eder et al. earlier this year.

As the manufacturer of the device, we have taken the concerns of our customers about patient and donor safety very seriously.

Fresenius Kabi has worked with the American Red Cross and discussed and evaluated the data in great detail, and we have attempted to determine the root cause. Since most contaminants

are bacteria from normal donor skin flora, we focused on donor blood diversion before the actual collection procedure. The literature suggests that initial diversion of blood significantly reduces the rate of bacterial contamination. For example, a publication by McDonald et al. in 2004 in *Vox Sanguinis* demonstrated that pre-procedure diversion reduced the contamination rate by 47%.

Theoretically, more diversion may reduce this rate even further. To that end, Fresenius Kabi has developed new software for the Amicus device that allows extension of the initial diversion without affecting the donor status.

Briefly, in addition to initially diverting approximately 25 to 35 mL of whole blood into a sample diversion pouch, the new procedure will allow additional diversion of up to approximately 100 mL around the collection and separation chambers and return it to the donor unprocessed. The new software version applies to both single-needle and double-needle procedures and covers all platelet collection procedures with the Amicus Separator.

Although there is no data yet to specifically support this, we believe the contamination rate due to skin flora microorganisms should go down. Future hemovigilance data will determine if this procedural modification is successful.

The Food and Drug Administration has cleared the new software, and it is available to all our customers today.

Customers interested in this new procedure should contact a sales representative or clinical consultant to schedule an update.

As a leading manufacturer of medical devices, Fresenius Kabi is committed to the safety of our donors and patients.

Thank you for the opportunity to speak here today.

DR. STOWELL: Thank you very much.

Okay, so we will adjourn for lunch, and I guess my question to the Committee is, since we have gone as late as we have, if we would like to abbreviate the lunch to maybe half an hour so we can get under way afterwards. I think the discussion of this topic is going to be somewhat lengthy. I think that the discussion of the afternoon topic, however, will be not so lengthy, but I seem to be getting some agreement to make it a half an hour lunch, which means that we should all be back here at 1:50, all right?

LCDR EMERY: So everyone, the lunches should have been provided into the back room that we have reserved for you.

(Whereupon, at 1:20 p.m., a lunch recess was taken.)

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

(1:53 p.m.)

DR. STOWELL: Good afternoon. We're ready to begin the afternoon session. Please take your seats.

All right. So we have a few questions which have been put before us by the FDA folks, and this -- which have been distributed for Topic I here. And the FDA is seeking the advice of this Committee on several questions which have to do with additional steps to mitigate bacterial contamination of platelet components, and there are two questions, one with two subparts.

And the first is: Are the available data supporting the 5-day storage of apheresis platelets without any secondary testing if the cultures are adequate, if the cultures are performed no sooner than 36 hours post-collection and with a sampling volume of at least 3.8% of the collection?

The second question relates to the availability and strength of the data supporting measures to extend platelet outdating to day 7. One of these would be by culture of apheresis platelets sampled no sooner than 48 hours after collection and using a test volume of at least 7%, and the other option would be by repeat culture on Day 4. And this would also require the use for release of a test device which has been cleared by the FDA, manufactured by Verax, as a safety measure.

So we'll take these in part, and the first has to do with whether or not the data which exists would support offering as an option for 5-day storage of apheresis platelets to do only the primary testing so long as that primary culture testing was performed no sooner than 36 hours after collection and the sampling volume of 3.8%.

Everybody was stunned by this morning's onslaught of information and data, I gather.

Dr. Escobar.

DR. ESCOBAR: Just to clarify. We're still talking only aerobic culture?

DR. STOWELL: I think that would be part of the discussion about whether we would recommend inclusion of anaerobic cultures or not.

DR. ESCOBAR: Okay.

DR. STOWELL: Dr. Epstein.

DR. EPSTEIN: Yeah. Thank you, Dr. Stowell. We've left that open for discussion because there's been an argument that it's the added volume, not the fact of the anaerobic bottle, although we do understand that there are some added virtues, rapid detection and, you know, the rare, true anaerobe.

DR. STOWELL: Dr. Leitman.

DR. LEITMAN: I'm sorry. I just wanted to say that we would be voicing opinions not based on data, which we commonly do anyway, but what you'd need is a study of two aerobic

bottles of about 8 mL each and an aerobic and anaerobic bottle of the same volumes, and then everything else is the same in a huge number of donations, and then you could answer the question. In the absence of that --

DR. STOWELL: Yeah, I think the data which have been provided are based upon an aerobic and an anaerobic bottle, and so that's what we have the data to make decisions about. We don't really have the data to make decisions about two aerobic bottles versus one aerobic and one non-aerobic.

DR. QUILLEN: I think the Blood Systems data are based on aerobic-only bottles; they have multiple bottles for aerobic only. So it appears that Question 1 is based on what systems that are -- and I think somebody else pointed out earlier that their method is to allow sampling at 24 to 36 hours so that we keep the 5-day shelf life but added 12 hours. That's not what the data actually -- that wasn't their methodology.

DR. KINDZELSKI: Just a question. In the Question 1, we have not met not less than 36 hours since collection, and the Question 2, we will have more than 48 hours. If the sample was being, let's say, a sample being collected between 36 and 48 hours, will it qualify it for extended life of 7 days?

DR. STOWELL: So what the question is, is whether if that time, if the delay until sampling was 48 hours, the argument is whether or not -- the question is whether those data would support extending the outdate to 7 days.

DR. KINDZELSKI: Right, I understand, but my point is if these -- if the platelets were tested after 36 hours but before 48 hours, if we will answer yes for the second question, for example, they will not be qualified and will have to be discarded after 5 days of storage. They will not qualify for 7 days.

DR. STOWELL: Yes, that's how I understand it.

DR. ARDUINO: So I'm going to go back to anaerobes because right now we don't look for them, and we do know that there are rare cases where there is, so I don't know how to balance that. Do you just turn a blind eye and say we're going to accept that there's going to be these rare events that we're just not going to pick up, or do we include an anaerobic bottle to catch those rare events?

DR. BASAVARAJU: So I don't think that the fact that it's a rare event means you shouldn't do it. You know, just this year at CDC we've -- we're working on several transfusion-related deaths that involve transmission of anaerobes. So I think it's just ineffective and doesn't provide the appropriate level of safety to not include anaerobic culture.

DR. STOWELL: Well, again, to reiterate, all the data that we've looked -- or most of the data that we've looked at has included both anaerobes and anaerobic cultures with the caveat that we aren't really handling these -- these aren't true anaerobes.

DR. CARROL: Really, the advantage of the anaerobe bottle, in addition to detecting anaerobes, is that a lot of the facultative anaerobes, like your gut microflora, come up in those bottles much more quickly, so you could shorten your time to detection, and I think one of the studies showed that very well. So it's not just about the additional volume, but it's also about the fact that the nature of some of these organisms is that they grow faster in that bottle and sometimes only in that bottle.

DR. STRAMER: The data that were shown by Carl did split the results by anaerobic and aerobic bottles, so it's not only obligate anaerobes, which will be few and far between because they don't grow in aerobic platelets, but it's the facultative anaerobes. And if you're going to increase the volume, you're complementing it with another medium so you're not just duplicating the same thing.

But my question is about the question, so from a practical or logistical standpoint from a blood center, if we have 5-day storage of platelets and we're holding platelets for 36 hours prior to inoculation, there has to be a time post-inoculation where you hold the culture bottles before you release the platelets for distribution. So by the time you do a 6- or 12-hour hold, there will be a day or a day and a half left of platelet shelf life. So I don't see how sooner than 36 hours, particularly when that's not the way the data were presented,

and a 5-day storage, they're just not compatible.

DR. STOWELL: That is an issue. On the other hand, for example, if you were to do a 36-hour post-collection and a 12-hour incubation or something like that, this really puts you -- so this puts you on to a day, Day 2, end of Day 2, when you could release. And, you know, sitting in the hospital, we don't get platelets that are any less than 3 days anyway.

DR. STRAMER: Right, but that's doing current 24 hours, so then you're not going to get platelets that are less than 4 days old or maybe only using them on Day 5.

DR. LEWIS: So looking at the way the question is worded, it says, "Do the available data support," so this is a question about whether the data actually support a particular conclusion. And I thought that the information that was presented and the background materials regarding the variable duration of the lag phase strongly supported the idea that testing in the time frame of 24 to 36 was never going to give you a really substantial decrease in the actual incidence of the clinically important endpoints.

So even though the volume does allow you to marginally increase the yield from an early culture, I don't think the early culture actually has the potential to give us the kind of increase in safety that we're looking for. So I think, as worded, the answer is no.

DR. STOWELL: So let me make sure I -- or I heard. So

what you're saying is that the issue of how long the platelets have been stored is more important in terms of -- than the volumes?

DR. LEWIS: Right, because the volume gives you a linear effect on the sensitivity of the test. If you sample twice the volume, you can pick up half the concentration on average of the same sensitivity. That's a linear effect. Once the bacteria leave the lag phase and go into log phase, it's a multiplicative thing, so time has a much more effective or much larger effect on the sensitivity of your test.

And so I think just the fact that this is limited to 36 hours, the question as written, and understanding that the data that were presented was for 24 to 36, so there's a little bit of just lack of direct apples-to-apples comparison, I don't think that there is the potential for 36-hour sampling to give us the kind of multiplicative improvement in safety that we'd be looking for.

DR. STOWELL: Dr. Haddad.

DR. HADDAD: Yeah, so this first proposal has two enhancements compared to the traditional practices. There is a delay of the sampling, and then there's an increase in the volume. And so both those factors would play into increasing the yield, increasing the bacterial detection.

DR. LEWIS: I understand exactly, and I'm saying that mathematically it doesn't look like that gives you the kind of

effect you would be looking for.

DR. STAPLETON: I may have misunderstood what you said, then, but this does say no sooner than 36 hours, so you're extending 12 hours minimum on this, right? Which will exponentially increase the bacteria if they're in log phase.

DR. LEWIS: As long as they've already gone into log phase sometime before that, but it seemed to me that there was evidence to suggest that the log phase for some of the organisms, and I'm not the microbiologist here, but I'm gathering in the gram positives, are likely to be beyond that, and those you simply cannot get by an increase in volume until they get to the log phase.

DR. STAPLETON: But it depends on initial inoculum, of course, but yeah.

DR. LEWIS: I'm sorry, say it again.

DR. STAPLETON: It depends on the initial inoculum, of course.

DR. LEWIS: Not --

DR. STAPLETON: Yeah.

DR. LEWIS: Not --

DR. STAPLETON: Because if you have 1 per 500 mL, that's going to be different than if you have 100 per 500 mL.

DR. LEWIS: Exactly, but you immediately -- I don't mean to be argumentative here, and I'm a newcomer, so I'm going to apologize ahead of time. I'm going to apologize proactively.

DR. STAPLETON: Oh, argue all you want.

(Laughter.)

DR. STAPLETON: That's what we're here for.

DR. LEWIS: It's interesting to me that you immediately went, as your example, from 1 to 100; you're already thinking logarithmically.

DR. STAPLETON: No, I do think logarithmically because I'm a virologist but --

DR. LEWIS: And the volume is -- right.

DR. STAPLETON: But your inoculum you don't know, so that's why I asked a question earlier about replication kinetics versus inoculum and --

DR. LEWIS: And I think that's exactly the issue.

DR. STAPLETON: Yeah.

DR. LEWIS: And it's the heterogeneity in the lag phase that cripples the ability to fix it at an early time point.

DR. STOWELL: So, I think, Dr. Leitman.

DR. LEITMAN: So whenever this Committee discusses risk mitigation in terms of bacterial contamination, it's always a question of making perfect the enemy of the good because you need a transfusable product.

The study we're all quoting from BSI showed a halving, and so a doubling in the detection rate from 1 in 11,000 to 1 in 5,000 or 0.9 to 1.8. So it's done in that study, it was highly significant, and there was a significant effect, so that's

good. That supports "Do the data support 5-day storage," and that was 24 to 36, so longer than 36 would be better than 24. Yes, it does. The data in that article do support this.

The other thing that the Committee -- so period. The other thing the Committee is not asked to consider is the quality of the platelet component; we're purposely not asked that. But every study that looks at the in vivo recovery of autologous-stored, radiolabeled platelets for each additional 24 hours of storage shows that you take the hit in the recovery of those platelets.

So a Day 4 stored platelet is not as good as Day 3 in terms of the recovery and function of the platelets, Day 5 versus Day 4, Day 6 versus Day 3. So you're taking a hit, but it's above a minimal acceptable level, but it's not as good as shorter storage. And so I think we ought to consider the fact that if we're moving the entire blood system to Day 4, Day 5, Day 6, Day 7, we're actually not doing that much of a favor for some of our patients.

DR. STOWELL: And this becomes sort of the counterbalance, is the drive on the one hand to detect every single bacterium that could possibly be in the units, as opposed to having a unit which is, I don't know what, 90% as effective, 80%, and 70%.

Dr. Stramer.

DR. STRAMER: Salim wants to make a comment.

DR. HADDAD: No.

DR. STRAMER: But regarding this question, could we go to Slide 24 of Salim's presentation, because what disturbs me is the lack of statistical significance in answering these questions.

DR. STOWELL: Whose presentation did you say?

DR. STRAMER: Salim's presentation.

DR. HADDAD: FDA.

DR. STRAMER: Because I think Slide 24 gets to the crux of what we're trying to discuss, in my opinion, because the background rate that is being compared, certainly within the BSI study, they showed a significant improvement in bacterial yield, but it's still within the range that we observe for primary culture aerobic conditions using the culture systems we use today and that there was no way to assess clinical significance by a reduction of septic transfusion reactions. So I'm not sure that it's making much of an improvement. I mean, I think that's the point that Dr. Benjamin was making as well.

So I know I'm not formally voting, but it bothers me that we have no statistical evidence to say one is better than another besides comparing a fruit salad, as Dr. Vassallo said, and besides which the question is written is not exactly what the data were. It says a minimum of 36 hours. So in an operating blood center, it doesn't mean that people are going

to stop everything and get those platelets off onto culture at 36 hours.

DR. STOWELL: So with the statistical significance business, are you referring to the frequency of septic transfusion reactions?

DR. STRAMER: I'm referring to bacterial detection if we're using that as a surrogate --

DR. STOWELL: Um-hum, um-hum.

DR. STRAMER: -- for safety, that is if you detect more, it's better. Here, the rate that we're seeing in the last column is within the range of what we're doing today, and you know, if we look at septic transfusion reactions, clearly that's also within the range that has been reported in those data, Red Cross data. So I don't see how we can make a decision that Column 3 is better than Column 2.

DR. STOWELL: Some of the people we haven't heard from, any thoughts on this?

DR. ARDUINO: You know, this is where a statistician comes in handy because I think this might be a sample size issue because we have something that's fairly low frequency, and maybe our denominator is not big enough.

DR. STRAMER: That's right.

DR. STOWELL: Well, I think that is the issue; it's the issue with all these very low-frequency adverse events, you know, HIV infection and so forth that we deal with.

DR. WAGNER: Steve Wagner, American Red Cross.

I think the data in Column 2 in the second row comes from a compilation of data from different blood centers doing different things with different apheresis instruments, and so it seemed higher range. And so it's very difficult to compare something that specifically came from a particular study with the entire range of what's been experienced, and I don't even know if it's U.S. or not. I guess Dr. Haddad can say where that came from.

DR. HADDAD: For U.S. using the traditional practices, 8 mL aerobic only.

DR. STRAMER: Well, the septic rates are clearly Red Cross data since the Red Cross is the only system large enough to produce those, and those were the published data from Eder et al. comparing the Amicus and the Trima collection devices.

DR. WAGNER: But the two give very different rates of positives and BacT/ALERT culture as well as sepsis, and so there's a huge range there because the devices behave differently.

DR. STOWELL: Dr. Ortel.

DR. ORTEL: So just -- I'm trying to clarify the question again. I know we've gone back to this. Is the question specifically trying to ask are we saying that the method in the question is superior to what we're doing now? It just asks does it support 5-day storage. So are we being asked to say

compared to what's being done now this would be better?

DR. STOWELL: So I think what we're being asked is what is being done now or is going to be done now is bacterial culture and then release testing for Day 4 and 5 platelets. This would be culture only up to Day 5 and -- but with a longer delay before sampling and a larger volume sampled.

DR. ORTEL: But are we trying to compare the two? Are we trying to say one is clearly what should be done?

DR. STOWELL: I think what we're trying -- or think what they are asking us is, is this a reasonable alternative. I don't think it's a matter of they will -- you know, the guidance will say do this and not the other.

DR. ORTEL: Right.

DR. STOWELL: It's a matter of is this another option?

DR. EPSTEIN: Yes, I can clarify that. FDA's intent with the question is to ask the Committee whether these two additional alternatives are acceptable alternative options to what was recommended in the March 2016 guidance, right, which looked at pathogen reduction or secondary testing. And what's being asked here is if you will augment the primary culture, can that stand in lieu of the secondary testing? Is it an acceptable alternative?

Also, I would suggest that it might be helpful to come back to Slide 21, as long as you've got Dr. Haddad's slides up, because this is the cleanest comparison to look at the effect

of moving to the combination of larger volume and delayed sampling.

Here, you're looking at the effect of volume alone, right? And the volume-alone effect was a roughly doubling of the detection rate. It came at the cost of a significant increase in the false positive rate, which we know is true; the more bottles you add, it's almost proportional. Every time you have a bottle, you have a false positive rate; two bottles, three bottles, that many more false positives.

And the point was also made in the discussions that because we discard based on initial reactives without knowing whether they're true positive or not and may never evaluate that, in other words, you pitch the unit, you end up discarding roughly the same number of collections even though the true positive detection rate did go up. So those are the cleanest data.

When you compare the whole spectrum of practices, yes, it's true that these outcome data lie within the range of current practice. But when you look within the same system, right, these are the same blood collectors, right, transfusing at the same hospitals, the only change being how many bottles were inoculated.

So, again, I think it's helpful because this is sort of self-controlled data. It doesn't answer all the questions, but it helps suggest your point, Dr. Stramer.

DR. STRAMER: I think that, and Ralph could probably address this better, but Period A and Period B didn't exactly use the same collection devices either. I think Period A had a combination.

DR. HADDAD: Both Trima, both Trima.

DR. STRAMER: Didn't collection A also have Amicus?

DR. HADDAD: No.

DR. STRAMER: No? Okay.

DR. BASAVARAJU: So going back to the issue of anaerobes, so what is FDA's feel on whether these alternatives would include an anaerobic culture bottle?

DR. HADDAD: I mean, you know, regarding the anaerobes, we have not made a final determination as to whether to include an anaerobe versus in addition to the aerobes. And in my presentation, you know, I showed the benefits of adding an anaerobic bottle versus its limitation. And so, you know --

DR. EPSTEIN: I suggest that one way of dealing with this, Dr. Stowell, would be to offer the Committee, if the Committee recommends in favor of the larger volume collection, then either this, you know, minimal proportion volume or the 7% volume for the 7-day, that the Committee then advises, as an independent question, whether the larger volume should include the use of the anaerobic as well as aerobic bottle because their argument is pro and con.

And it's certainly an important issue; FDA may need to

speak to it directly, so we'd appreciate the advice of the Committee on that specific question. But it's contingent on, first, whether the Committee recommends these larger volume strategies as acceptable alternatives.

DR. STOWELL: So why don't we make that the third question from the FDA and to address severally? My feeling about Question 1 is that what we are recommending or what this recommendation would do would be to improve the capture rate of the culture system that we'd be using for platelets, which I could see that as being an improvement. It's not a perfect system and -- but I think it's better than the current culture systems that we're using in terms of the additional capture rate, which is afforded by the longer delay time before sampling and the increased volume.

DR. STAPLETON: I guess the way the question is worded, that stipulation without the secondary testing, which I don't know that the data show us a comparison of the two systems together with the smaller volume with secondary testing versus a larger volume.

DR. HADDAD: So we do have that data separately for the rapid testing. I think that's the last slide of my presentation.

DR. STOWELL: Could we go to the last slide of Dr. Haddad's presentation, the last slide?

DR. HADDAD: Yeah, before the questions.

(Pause.)

DR. LEITMAN: Slide Number 38.

DR. HADDAD: So these data correspond to the use of the secondary testing following the early primary culture.

DR. STAPLETON: I think the big limitation is the lack of a denominator, is that --

DR. HADDAD: You mean small denominators?

DR. STAPLETON: I mean that that's why you have the greater than or equal to.

DR. HADDAD: Well, I have the equal or greater; this is pertaining to the false negative rate because in the study only a subset of the products were concurrently cultured. All the rapid test positive results were cultured; however, the negative results, only a subset of them, 10,000 out of the 27,000 were concurrently cultured with a negative rapid test.

DR. LEITMAN: As has just been stated, it's very hard to compare one study using one technique with another study using a totally different technique, but the rapid point-of-issue testing appears to interdict, when done on Day 5, roughly 1 in 3,000 additional units. And the use of the 3.8% proportional sample volume at 24 to 36, again, it leads to a reduction from 1 in 11,000 to 1 in 5,000. So those are in the same ballpark, so they accomplish about the same risk reduction, understanding that I'm not using risk reduction the way a statistician would, but it's a sort of the best risk reduction in a comparison that

you can get from different studies, different populations.

If I understand the FDA question correctly, the available data do support the use of 5-day storage with a minimal proportional sample volume as approximately equivalent to what was in the draft guidance from March 2016, which is a point-of-care test on the day of issue, that they appear to be -- they appear to accomplish about the same risk reduction.

But having said that, it's not 36 hours; it's 24 to 36 hours, so 36 hours would, perhaps, accomplish even more. But even with the caveat of perhaps missing a lag phase, I would be in favor of 24 to 36 hours. When one has a policy in the transfusion or the blood bank or transfusion center of 24 to 36 hours, it's always greater than 24 hours. It's usually about 30 to 36. If you make it 36, it will be 36 to 48 because of when you batch your testing and try to get as many products from the previous day as possible for cost efficiencies.

DR. STOWELL: Well, as you point out, the data are based on 24 to 36 as opposed to 36.

Is there more discussion of this point, or would people like to vote? I feel ready to vote on Question Number 1.

DR. LEWIS: So I would like the Chair to restate the --

DR. LEITMAN: The question again. Me, too.

DR. LEWIS: -- question because I heard it -- I've heard it two different ways, and I just think we ought to all vote on the same question, whatever it is.

So one way I've heard interpreted was a question regarding whether these changes in the primary testing algorithm, by itself, are associated with a higher detection rate and therefore presume greater safety.

The other way I heard, I believe the Chair stated, it sounded as if the question was whether or not the data support a conclusion that this approach would be non-inferior to what was in the proposed guidance.

DR. STOWELL: Dr. Epstein.

DR. EPSTEIN: Yes, I'm happy to clarify. FDA's intent is to ask the Committee the second version of the question, namely, whether the large volume/delayed sample is an acceptable alternative to secondary rapid testing. And I hope that's clear enough. But the question is whether the Committee would prefer to vote the question if it were to say 24 to 36 hours, because I think that's a separable issue.

We posed it as 36 as a conservative measure because it could only be better than the available data, right? But if the Committee is uncomfortable because those aren't actually the data, and I heard Dr. Stramer's point about delay of issuance and older platelets, we understand that, we could permit the Committee to vote it with 24 to 36.

DR. STOWELL: What's the feeling of the Committee? Would you like to change the wording there to be 24 to 36 hours? Would that make it easier?

Dr. Ortel.

DR. ORTEL: I would stick with the data.

DR. STOWELL: Okay. Is that the general sense? I don't think we need to vote on that, I see all the heads nodding. Okay. So we'll reword that to say 24 to 36 hours post-collection. And the question is, to rephrase a little bit, are the data consistent with the fact that this approach is non-inferior to the current approaches? Approach. Is that clear?

UNIDENTIFIED SPEAKER: Yes.

DR. STOWELL: Okay. So does the Committee feel ready to take a vote on this? Okay. The electronic wizards need to make this happen.

(Pause.)

DR. STOWELL: All right, looks like we're set. So the question before the Committee is: Do the available data support the non-inferiority for 5-day storage of apheresis platelets without secondary testing if they are cultured no sooner than 24 to 36 hours post-collection with a sampling volume of at least 3.8% of the collection? Vote on your microphones here for yes, abstain, or no.

LCDR EMERY: And before we post the results, I would like to ask the Industry Rep if they have any comments to make.

DR. STRAMER: Yes. Based on the fact that we're saying that they're not inferior and we modify the question to 24 to 36 hours, and aerobic and anaerobic will be a separate

question, are you asking if I am in favor or just for comments?

LCDR EMERY: Just what your comments are.

DR. STRAMER: Okay. Well, those are my comments.

(Laughter.)

DR. EPSTEIN: I would just clarify that we didn't actually elect to add the words "non-inferior." Non-inferior is sort of a very strict statistical term. I think that given the limitations of the data, FDA's concept is to ask the Committee whether these are comparable alternatives. Comparable is a less statistical, more, you know, intuitive kind of view of the data. So if you don't mind, I would suggest that that's how the question needed to be understood. So do the available data support comparability of?

(Committee vote.)

LCDR EMERY: The Committee has voted in majority, and I'll read the individual results. For Question 1:

Dr. Stowell, yes.

Dr. Baker, yes.

Dr. DeMaria, yes.

Dr. DeVan, yes.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, no.

Dr. Ortel, yes.

Dr. Rees, yes.

Dr. Sandberg, yes.

Dr. Stapleton, yes.

Dr. Basavaraju, yes.

Dr. Kindzelski, yes.

Dr. Stroncek, yes.

Dr. Arduino, yes.

Dr. Carrol, yes.

Dr. Quillen, yes.

Thank you. So we have 16 yeses, 1 no, and no abstentions for Question 1.

DR. STOWELL: So the second question addresses the issue of extending platelet outdate to Day 7, and they're looking for our opinions about whether the data that we've seen would support, first of all, the approach of culturing apheresis platelets no sooner than 48 hours after collection and using a test volume of at least 7% without secondary testing. So this would be a means of extending the outdate from Day 5 to Day 7 by delayed sampling and increased volume as it applies to apheresis platelets.

So comments? Dr. Stramer.

DR. STRAMER: Should the same adjustment be made as we made for Question 1, no sooner than 36 to 48 hours?

DR. STOWELL: Would that make it easier for the Committee to --

DR. STRAMER: I mean, based on the presented data.

DR. STOWELL: Yeah. I think that would be a reasonable approach. So let's change that to 36 to 48 hours. And again, I think what we're looking for are the -- do the data demonstrate comparability?

DR. LEITMAN: So I object to the 7% because that study wasn't designed to sample a 7% volume using a Poisson formula the way the -- or any formula, the way the BSI study was designed. It was designed to sample enough to get two 8 mL aliquots into each of two bottles, and so if one had two products, splits into doubles, and it was 16 times 2, 32. If one had a very large content donation, you had three products, and it was 16 times 3, which is 48. So if the design was sample sufficient to aliquot 8 mL into each of two bottles, that's what this should state.

DR. STOWELL: Um-hum.

DR. LEITMAN: It's actually easier than 7%.

DR. STOWELL: Um-hum.

DR. LEITMAN: It's a little arbitrary. So I would prefer, again, for it to state what -- how that study was designed.

DR. STOWELL: Okay.

DR. QUILLEN: I would second that, and I would also perhaps suggest that since we are basing this on the Irish and the English data, that it has to be one aerobic, one anaerobic because that's what we're basing it on.

DR. STOWELL: Well, I think --

DR. QUILLEN: For this, for the 7-day dating.

DR. STOWELL: Yeah. So I think we're going to address that as a separate question, Karen, so that's going to be Question 3, which we just added for ourselves, about whether they should be both aerobic, one anaerobic, one aerobic, and so on.

DR. LEWIS: But I think the point is that people may vote differently depending on the answer, so we'd be voting contingent on what we think our answer to Number 3 would be, that's sort of tough.

DR. STOWELL: So maybe we should go ahead and address the anaerobic/aerobic thing at this point, then, even though it's Question Number 3. Okay. And so I think we have a reasonable sense of what the Committee thinks, but any comments about the advisability of doing both an anaerobic and an aerobic culture? We've had several comments favoring it, largely. That seemed to be the general sense of the Committee, that this was -- okay. So then why don't we vote on that formally? So this would be Question 3 is that the recommendation for culture would include using both an aerobic and an anaerobic culture.

(Pause.)

DR. LEITMAN: Dr. Stowell? I'm sorry, just could we reopen the discussion a little bit? We haven't seen a study, a head-to-head comparison of what the yield would be, 16 mL of aerobic versus 16 mL of both; is that correct? That wasn't

presented to us. There is no such study.

DR. STOWELL: Yeah, I don't think we've seen a head-to-head study like that. We've seen some studies which have had aerobic and anaerobic and another one which had, I think, just two aerobics.

DR. LEITMAN: So the negative side of anaerobic testing is that the false positive rate goes from 1 in several thousand down to 1 in 3- to 4- to 500. It's a log-fold increase and discard of likely safe units for transfusion. So that's my major concern without seeing sort of large volume data on the safety of adding an anaerobic bottle as opposed to individual case reports of one in several tens of millions of --

DR. STOWELL: Yeah.

DR. LEITMAN: -- Clostridia infections.

DR. STOWELL: Hold on a second.

(Pause.)

DR. STOWELL: So no, I'm -- yeah. I'm getting confused with two different studies. Never mind. Okay, any other comments on the possibility?

DR. STRAMER: Just to Susan's point, the UK system, Carl did a good job of breaking out the aerobic versus anaerobic yield, so it was 65%, at least in what he presented, and 66.2%, in the publication, it was anaerobic.

Clearly, though, the majority of them were probably clinically insignificant, and there was the statement made as

far as how to limit the number of false positives using the anaerobic bottle. And then, of course, any time you add a bottle, whether it's aerobic or anaerobic, you're going to at least double the number of false positives you have. Clearly, it won't be a lot higher, but certainly with control of how you use the incubator, or perhaps the next-generation incubator should control that. And the rate of anaerobes are not one per tens of millions; they're actually -- the rate is actually higher than that.

DR. STAPLETON: The other issue with the anaerobe culture was that the time to detection was much faster.

DR. STRAMER: It is faster, yeah.

DR. ESCOBAR: I think that the -- you know, the fact that there has been reports of fatalities and morbidity with anaerobes, I think that is enough evidence for us to be able to support the use of one aerobes tube for this population. I mean, no matter if it's very rare, but still, that could be -- you know, you could be saving a life just by detecting, no matter what the number is.

DR. STOWELL: And the impression I got, also, is that we don't know if this is really actually terrific -- a wonderful technique for detecting true anaerobes as opposed to facultative anaerobes and accelerate their growth.

Dr. DeMaria.

DR. DeMARIA: This is what I was going to say, but you

know, I was taught and I trained people if you only have one bottle, use the anaerobic bottle because you have the maximum number of organisms that you can grow in there. But this is in the context of the 7-day platelets and in terms of product availability, the balance in terms of having more product available, because going to 7 days may outweigh the false positive. Even though those platelets may not functionally be as good, it still gives you more product potentially at the end.

DR. STOWELL: I mean, this would also apply for the single culture approach to 5-day storage as well, where you would not have the benefit of reduced outdating.

Other thoughts about the utility of both anaerobic and aerobic cultures?

Dr. Ortel.

DR. ORTEL: So we would be recommending using aerobic and anaerobic? No matter which methodology you're using, any time you're drawing cultures, it should be done whether it's current methods or proposed methods?

DR. STOWELL: That's the proposal.

DR. BASAVARAJU: So, I mean, there would be no current method, right? This would be in place of that, right? That's what the --

DR. STOWELL: Yes. So right now, the only method is a guidance document. It's not been promulgated as an official

recommendation at this point.

Dr. Epstein.

DR. EPSTEIN: I want to propose some language for the Committee to vote on, on this issue. This will be projected, I hope. Should primary testing of platelets with large volumes include the use of both an aerobic and anaerobic culture system?

Why I'm framing it that way is that it's not clear that we want to preclude the current system inclusive of secondary testing, right? And the current system is smaller volumes with an aerobic bottle; that's the current practice.

So, again, should primary testing of platelets with large volumes include the use of both an aerobic and anaerobic culture system?

And then that makes reference to what we've been talking about, which is minimal proportionate sampling or the larger volume sampling as practiced in the UK and Canada.

DR. STOWELL: Is there further discussion, or is the Committee ready to vote on this?

(No response.)

DR. STOWELL: I think we're ready to vote. So the question is: Should primary testing of platelets with large volumes include the use of both anaerobic and aerobic culture systems?

(Committee vote.)

LCDR EMERY: I was going to allow the Industry Representative -- do you have any comments before I read into the record the results?

DR. STRAMER: Just that I would support what the Red Cross/ABC statement stated, and it said it recommended both bottles.

LCDR EMERY: Thank you.

The Committee has voted and has voted in a majority, and I will read the individual votes for the record:

Dr. Stowell, yes.

Dr. Baker, yes.

Dr. DeMaria, yes.

Dr. DeVan, yes.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, yes.

Dr. Ortel, yes.

Dr. Rees, yes.

Dr. Sandberg, yes.

Dr. Stapleton, yes.

Dr. Basavaraju, yes.

Dr. Kindzelski, yes.

Dr. Stroncek, yes.

Dr. Arduino, yes.

Dr. Carrol, yes.

Dr. Quillen, yes.

It is 17 yeses, 0 no votes, and 0 abstentions. Thank you.

DR. STOWELL: Okay, so this brings us back to Question 2a, and we had already mentioned about changing the wording here to reflect the actual data that had been presented, so that this would be sampling no sooner than 36 to 48 hours after collection, and then there was a proposal to change that from a test volume of 7% to -- I forget how you worded it exactly, Susan, but you had enough bottles of blood to inoculate two bottles or something along those lines. Probably a more eloquent way to say that, but that would be the sense to it.

Dr. Haddad.

DR. HADDAD: Okay, so if the objective is to mirror the study and adjust the key for apheresis platelets, they were taking 16 mL from each split and from the -- pool, obviously you have one pool, so that's also 16 mL. But regarding the platelets, it was 16 mL from each split.

DR. STOWELL: So then the proposal would be to modify this to using a test volume of at least 16% for each split. That's 16 mL for each split.

Any further discussion of this, any thoughts?

(No response.)

DR. STOWELL: Does the Committee feel ready to take a vote on this?

Dr. Escobar.

DR. ESCOBAR: When you say without secondary testing, what does that mean at that point? I mean, meaning that for that 7-day is only going to have one culture done between 36 and 48 hours, and that's it?

DR. STOWELL: Yes, that's the sense of it.

DR. ESCOBAR: Nothing done at Day 4, 5, 6? I mean, 7 is one culture?

DR. STOWELL: No, that's not the proposal here.

DR. LEWIS: So I'm struck about the change that we made to the question about changing the no sooner than 48 to no sooner than 36. I understand that data that were presented had a range of 36 to 48, but we have no idea where in that time interval the distribution of actual tests occurred, is my understanding. So if I'm not mistaken, what we're basically doing is assuming that if this recommendation were followed, the distribution of testing time wouldn't be near what was done in a particular setting, and I'm not sure why we would make that assumption.

DR. STOWELL: Well, I think one of the issues, if we say the testing must be done at X hour, is it may be very difficult to operationalize that, for one.

And I think the other is based on the fact that we don't know what the timing was, the median time that was in the course of that study, nor are we necessarily going to know what it is when it's actually operationalized, but just assign the

range to it. I mean, unless we specify it has to be exactly at 48 hours or exactly at 36 or something, we're not going to know if they're comparable practices. Or identical practices, let me say.

DR. LEWIS: Well, furthering the pattern of being in the minority here, I saw some wisdom in the original wording that set the minimum of the range at the upper limit of what was allowable in the data that were presented.

DR. STAPLETON: And the other issue, I think I agree with you, is that this is going to create a problem in operationally a lot of places will decide we're just going to wait until 36 hours to start, and then you get the delay, and that because once you waited until 36 hours, then you can go to 7 days instead of 5, if that's the guidance.

And I guess the other issue is in the first one we did not specify per split, so those are issues that I think we ought to maybe think about.

DR. STOWELL: In the first we did not specify what? I didn't catch that.

DR. STAPLETON: Per split. I think --

DR. STOWELL: Per split.

DR. HADDAD: What, for the lot, the 3.8% volume, they were sampling the mother collection, not the splits.

DR. STOWELL: To address your point, this has to do with extending outdating to 7 days, not 5 days.

DR. STAPLETON: I think, operationally, it will be interesting if what some places may decide to do if you got 24 to 36 versus 36 to 48 to add 2 days of shelf life and then you do run into problems with less functional platelets, etc.

DR. STOWELL: But, again, in this situation, this is going to be for licensing to 7 days, so you're going to pick up time at the back end.

Further discussion? Yes.

DR. BASAVARAJU: It might be naive, but if you're going to extend the life to 7 days, they can't wait another 12 hours just to make it 48 hours. I just don't see why we're cutting it to the lower end of time if you're going to get 2 extra days.

DR. STOWELL: So I think the suggestion was based upon -- the actual data that we saw was based on 36 to 48 hours?

DR. LEITMAN: It said it's also that a substantial proportion of platelets will be able to be transfused 1 day earlier and then more functional. Their quality is better. So I'm in favor of higher quality platelets, balancing the two. And since the study was 36 to 48, we're voting on the data that we read about and saw in that study.

It might be that centers, big centers, want to have all 7-day platelets so they might all move to a minimum of 36; that's their option. But that was the -- again, that's the data in the study, and I think was that the study that had zero

reported septic transfusion reactions? So I mean a confidence interval around zero is large when the denominator is smaller.

DR. BASAVARAJU: No, I think it had one, right?

DR. LEITMAN: Is it one? The same confidence intervals.

DR. STRAMER: One, but some near misses as well.

DR. LEITMAN: Right, near misses.

DR. BASAVARAJU: So it was one and then four near misses, right. So it's not zero, so I don't know. I mean, I don't see how that 12 hours, you know, not making it 48 hours somehow saves anything, to be honest.

DR. EPSTEIN: Just as a clarification, if I might, there were zero septic reactions reported for the apheresis platelets. The one septic reaction was a whole blood-derived platelet.

DR. BASAVARAJU: What about the near misses, because they had clumping and clotting and stuff?

DR. EPSTEIN: Those were apheresis. Yeah, all four were apheresis. But, again, we require 100 percent inspection, but it has been pointed out that you can have heavy contamination and not see clumping, or an effect on swirling. We require both swirling and visual inspection, but that's not 100 percent either.

DR. STRAMER: Can I make --

DR. STOWELL: Sue.

DR. STRAMER: Sorry. Just to respond to Sridhar, it would

be a minimum of 36 hours. It doesn't mean at 36 hour and 1 minute, it just adds the flexibility that you could start the process. There's still going to be an in-house hold while culture is ongoing before the platelets are released, so the platelets are still aging within the blood center prior to release. It just goes back to Susan's points. The platelets, then, could be released earlier when they're more functional, and that supports the data that were presented.

DR. STOWELL: Additional discussion?

(No response.)

DR. STOWELL: Are we ready to bring this to a vote? Okay. So the proposition is do the available data support the following measures to extend dating to Day 7? And in this case, it's the culture of apheresis platelets sampled no sooner than 36 to 48 hours after collection using a test volume of at least 16 mL per split without secondary testing.

(Committee vote.)

LCDR EMERY: While they're voting, is there anything else the Industry Rep would like to say?

DR. STOWELL: Oh, I keep forgetting to do that, sorry.

DR. STRAMER: That's okay. I have no further comments.

LCDR EMERY: Thank you.

The Committee has voted in majority. I will read the individual votes for the record.

Dr. Stowell, yes.

Dr. Baker, yes.

Dr. DeMaria, yes.

Dr. DeVan, yes.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, yes.

Dr. Ortel, yes.

Dr. Rees, yes.

Dr. Sandberg, yes.

Dr. Stapleton, yes.

Dr. Basavaraju, yes.

Dr. Kindzelski, yes.

Dr. Stroncek, yes.

Dr. Arduino, yes.

Dr. Carrol, yes.

Dr. Quillen, yes.

That is for Question 2a. It is 17 yeses, 0 noes, and 0 abstentions. Thank you.

DR. STOWELL: And actually, I'd like to ask a question of the FDA about 2b here. So a clarification. The question here is whether or not the data support extension to Day 7 based upon repeat culture on Day 4, and then there was does it require using a device cleared as a safety measure? So would this be both repeat culture on Day 4 and the use of a safety measure device, or just the safety measure device?

DR. HADDAD: Yeah, I mean, like what's in parentheses is essentially a regulatory matter. So as long as the culture-based devices, they can shorten sensitivity at least as high as those of the rapid test, then they could qualify for the safety measure. So, essentially, the scientific question is whether a repeat culture on Day 4 would extend dating to Day 7. That's our question.

DR. STOWELL: I see.

DR. HADDAD: I think we can drop the parentheses, ignore the parentheses.

DR. STOWELL: I see. All right, as a separate -- entirely different option. So any discussion of this option?

Dr. Stramer.

DR. STRAMER: Yes. Regarding the safety measure, the way I understand, the safety measure was assessed for the point-of-issue test was against culture. So it seems if culture was going to be used for the secondary test, you would have to compare culture to culture. It seems going back from culture to a predicate device that was cleared as a safety measure -- okay, I'm misunderstanding it.

DR. EPSTEIN: Yeah, that's actually not correct.

DR. STRAMER: Okay, good.

DR. EPSTEIN: The safety measure claim was granted to the Verax test based on evidence that it could pick up true positives missed by the primary culture. In other words, it

added a measurable benefit. And why we did that was to try to distinguish the claims that had been granted as a quality control test based on the unspiking studies from evidence of an actual, you know, clinical value, okay? So what you heard from Dr. Haddad is that the mindset of the FDA is that tests at least as analytically sensitive as the rapid test could be granted a safety measure claim because we already know that tests of that sensitivity will have additional yield. But, again, the claim was based on showing added value.

DR. STOWELL: Any commentary from the Committee?

Dr. DeMaria.

DR. DeMARIA: Can I just, for the sake of making sure I know exactly what we're voting on, could you give me an example of the device that we're talking about here?

DR. STOWELL: The device we're talking about is the Verax device.

DR. DeMARIA: Okay, that's what I needed to know. Thank you.

DR. STOWELL: Dr. Haddad.

DR. HADDAD: The answer is not yet, but there are candidate devices that might very well qualify.

DR. STOWELL: Is there further discussion of this question? Comments?

DR. ARDUINO: Oh, I have one.

DR. STOWELL: Yes.

DR. ARDUINO: Is that really a culture, or are we talking about --

DR. DeMARIA: No, it's not.

DR. ARDUINO: -- a PCR or some other sort of test?

DR. STOWELL: No, we're -- the question has to do with this repeat culture on Day 4, not about the use of this safety measure device.

DR. EPSTEIN: Yeah, perhaps it could be a little helpful. Remember that the sensitivity of the rapid test is 10^3 to 10^5 CFU/mL. The sensitivity of cultures that are available is between 1 and 10 CFU/mL. So we believe that if any of the manufacturers of a culture were to come to the FDA and say can I have a claim as a safety measure, we would say yes, okay.

But this is about culture, and the distinction that needs to be understood is that we've approved the rapid test only to qualify the product for 24 hours, right, because it may miss detection of bacteria present below the lens of the sensitivity of the rapid test. That concern is less with a culture, which is why we think it could qualify the product for several days. So this is about qualifying extension of dating for several days based on a point culture on Day 4 versus the current approved technology of Verax, which some hospitals may continue to wish to use, which is to extend the dating only one day at a time.

DR. DeMARIA: So we're actually voting on a culture on

Day 4, not the Verax?

DR. STOWELL: Correct. We're voting on culture on Day 4.

DR. CARROL: And can we define culture? Are we talking about the 8 mL bottle that's the standard, or are we talking here about the 20 mL volume aerobic/anaerobic?

DR. HADDAD: So this is based on the study from the Irish Blood Transfusion Service, and they used two bottles, aerobic and anaerobic, and about 8 mL in each.

DR. CARROL: I just wanted to make sure we all have the same definition of the culture.

DR. ESCOBAR: The question says repeat cultures, so just to clarify, I mean, a culture was already done 24 hours previously or 36, and we repeat another one on Day 4?

DR. STOWELL: Correct.

DR. HADDAD: No.

DR. ESCOBAR: Is that correct?

DR. HADDAD: This is secondary to the primary culture, which would have been done at least 24 hours after collection.

DR. STAPLETON: It seems that the (a) would cover that because that's no sooner than. So if you repeated it on Day 4 and you didn't do it at 36-48 hours, it would fall under (a), it seems to me. No? I'm missing something, sorry.

DR. EPSTEIN: Yeah. So what we're saying is if the blood center follows its current procedure of an 8 mL sample at, at least 24 hours, can dating be extended if an additional culture

is done at Day 4? And it's been clarified, and we should add it to the text of at least 16 mL/8 mL each into an aerobic and an anaerobic culture system.

DR. STOWELL: Yes.

DR. LEWIS: But I think the comment that was made is actually logically correct, that anything that fulfilled our modification for part (b) would also have fulfilled the requirement for part (a).

DR. EPSTEIN: Well, I look at it the other way; 2a obviates the need for (b). We're saying you've already got 7-day dating if you did large volume/delayed sampling up front.

DR. LEWIS: So you could do (a) at 36 hours, 48, or on Day 4, they're all the same. And if you do it at any point before it expired at Day 5, you're good to Day 7.

DR. EPSTEIN: Yes, but the distinction here is that if you only did an 8 mL aerobic culture on Day 1, 24 hours, right, you cannot extend dating unless you do something more. Right now, we permit extension of dating with rapid testing, but you only get 24 hours of additional dating for each negative rapid test.

What we're asking the Committee is whether, as an acceptable alternative based on comparable data or outcome data, you could substitute the culture on Day 4 in lieu of other forms of additional testing, which today is rapid testing. Is that not clear? I'm happy to say it all again.

DR. LEWIS: It's clear. Let me try my --

DR. EPSTEIN: Sure.

DR. LEWIS: -- wording.

DR. EPSTEIN: Sure.

DR. LEWIS: And then we'll see where I'm making a mistake here. We voted in support of 2a; is that correct?

DR. EPSTEIN: Yes.

DR. LEWIS: 2a was modified to specify a minimum volume for that testing. If we modify the culture intended in part (b) to be the same as in part (a), Day 4 does occur after 48 hours. Part (b) is completely subsumed within our support of part --

DR. EPSTEIN: That would be correct.

DR. LEWIS: So if what -- having --

DR. EPSTEIN: That would be correct.

DR. LEWIS: Let me just finish. Having supported part (a), the Committee would seem to have expressed the opinion that if you use that larger volume sampling culture approach at any time from 36 hours on, you're good to Day 7.

DR. EPSTEIN: I think that's true. Again, you're saying we don't need to vote (b), but it's a different practical scenario. There's the scenario in practice.

DR. LEWIS: But we may have inadvertently --

DR. EPSTEIN: Yes.

DR. LEWIS: -- or unintentionally already answered (b) when we answered (a).

DR. EPSTEIN: Yeah.

DR. LEWIS: If we didn't mean to do so, we should rethink it.

DR. EPSTEIN: Yeah.

DR. HADDAD: I think Dr. Basavaraju has a question.

DR. BASAVARAJU: I just had a question about this (b), the scenario, that Day 1 culture in the Irish study. Did they not do aerobic and anaerobic on Day 1? Was it just aerobic, or was it both?

DR. EPSTEIN: Yeah. I think part of the distinction that FDA had in mind is that we've looked at proposals from industry to do the 8 mL aerobic bottle only on Day 4. Now, it's true that the data that you've seen from the Irish Blood Transfusion Service is the 16 mL with aerobic and anaerobic. So that would've been a distinction, but I take Dr. Lewis's point. If we elect, in Question 2b, to limit this to 16 mL, then we've already voted it in 2a. I take that point.

DR. LEITMAN: So coming from an institution where 25% of platelets corrected within the institution were for dedicated recipients who were HLA immunized or otherwise, there are reasons for which you call in a specific dedicated donor for a specific recipient, and you want those platelets as soon as possible. So I still see the need operationally, and for patient care, to have something available within 36 hours. You collect it and you test it in 24, and you release it in 36.

And often, you have to ask the FDA for permission to release it before then because a patient with a platelet count of less than a thousand is HLA immunized and you had a hard time getting a donor.

So you still need the option of getting it out as quickly as -- centers do, some centers do, of getting it out as quickly as possible without making -- requesting a deviation from policy, from standards.

DR. STOWELL: Well, I think we've heard, also, from Dr. Katz, one of the things he was enjoining us to do was to provide multiple routes whereby these interventions to prevent bacterial contamination could be operationalized.

DR. KINDZELSKI: I do believe that we still have to consider (b) because if we go to the Question 1, we have the 5-days approved platelets that potentially could be approved for 7 days, and if we, let's say, approve (b) for the second question, we will be able to do that.

DR. STOWELL: Yeah. So the scenario I could see is where you have done the culturing at, you know, 36 to 48 hours, and now, for some particular reason, you want to have this platelet available out for a longer period of time, Day 6 or 7, and maybe this could be an HLA-matched unit, for example. And then (b) would give you the option, the alterative, of being able to reculture and then make that unit available through Day 7.

DR. EPSTEIN: Just to be clear. If Question 2b is amended

to state with a volume of 16 mL in an aerobic and anaerobic bottle, then I do agree with Dr. Lewis that that has already been answered by 2a. If it was good enough to do at 36 hours, it's certainly good enough to do on Day 4, right?

But that's subject to amending (b) to require the 16 mL including an aerobic and anaerobic bottle, which is actually not what was proposed to FDA. That's why we haven't stated a volume in (b). But, again, if the sense of the Committee is that that ought to be the aerobic and anaerobic bottle at 16 mL, then you've already answered the question.

DR. STOWELL: Dr. DeMaria.

DR. DeMARIA: Since I don't do this, I mean, I don't test platelets, is there any reason why you would want to do two 8 mL samplings on 36 to 48 or even 24 to 36 and then again on Day 4 versus what we already voted on, which was -- which is to do 36 to 48 and 16 mL? You know, Jay said it doesn't make sense otherwise. You would have to choose to use the current testing process and then retest again in that same way or better on Day 4 when you could've just did the better on Day 1. I don't see any advantage.

DR. STOWELL: So I think part of this has to do with whether or not you're setting up your inventory to the 5-day platelets or 7-day platelets or a mix thereof. So if your default is 5-day platelets and then you have a special unit that you want to extend the outdate, (b) would give you an

option to do that. If you're going in at the beginning with everything, it's going to be a 7-day platelet, then obviously you would delay your testing and do it as in 2a.

DR. STAPLETON: My assumption would be, then, that it's true that you can still use the point-of-care testing, the rapid test, as an alternative.

DR. STOWELL: Yes.

DR. STAPLETON: Before 24 hours.

DR. STOWELL: Right, because that would give you an additional 24 hours of shelf life.

Further discussion?

(No response.)

DR. STOWELL: Okay, so let's amend -- oh, first of all, should we amend 2b to specify the volume? Okay. So we will amend 2b to repeat culture on Day 4 using a test volume of at least 16 mL per split. Per split, period.

DR. LEWIS: And then can the Committee then, instead, vote on the fact that (b) has already been answered as opposed to having a separate vote that might come out differently?

DR. STOWELL: Can you say that a little more loudly? I couldn't hear.

DR. LEWIS: I'm sorry. With that modification, there is no longer a separate item to vote on, so I don't think we should vote on something that we already voted on.

DR. STAPLETON: I guess one comment to make, too, is that

there's a cost issue, but that would not -- we don't -- I guess the bottom line is do we have data on this question with an 8 mL or a low-volume culture, and I don't think I saw any, but I looked at a lot of stuff the last few days.

DR. STOWELL: No, but we have seen data on 16 mL, and that's what's -- that's what we're proposing here, right?

DR. STAPLETON: But that's duplicating (a).

DR. STOWELL: Yeah.

(Pause.)

DR. STOWELL: Yeah, so okay. So here's the scenario, though. You are set up to do 5-day platelets, right? You do your culture at, you know, 24 to 36 hours, and now you've decided on Day 5 of shelf life that you want to be able to use it Day 6 or 7. So I think that's where 2b would apply.

DR. ORTEL: Because currently you are -- or currently it's okay to do a small volume within that 24- to 36-hour time frame, and this would allow you to extend that --

DR. STOWELL: Right.

DR. ORTEL: -- subsequently. So it is a different point than (a), unless as you said --

DR. STOWELL: Right.

DR. ORTEL: -- you were planning on doing 7 days or 7-day platelets all the time.

DR. STOWELL: Right. And again, the idea here is to have some flexibility that there could be different approaches to

accomplishing this test.

DR. EPSTEIN: I have the sense that the Committee would like to vote Question 2b as if they never heard 2a, and I think --

(Laughter.)

DR. EPSTEIN: I think we should allow that, and if people are inconsistent, well, so be it.

DR. STOWELL: Any further discussion, or are we ready to vote on this? I don't know about you all, but I'm ready to vote on this.

(Laughter.)

DR. STOWELL: So the question is do the available data support the following measure to extend dating to Day 7? And that would be repeat culture on Day 4 using a test volume of at least 16 mL per split.

DR. DeMARIA: While we're waiting, could I just -- it seems to me that by Day 4 you probably don't need 16 mL anymore because you have that logarithmic growth. There's no data, there are no data for this, but it could be an argument that you actually don't have to use 16 on Day 4. I wanted to say that before the vote.

DR. STOWELL: Okay. Oh, and Dr. Stramer, any comments?

DR. STRAMER: No further comments.

(Laughter.)

DR. HADDAD: So it needs to be a total of 16 mL. Yeah,

split. Okay, a split, that's good.

(Off microphone comment.)

DR. HADDAD: No, it's 16 mL split into an aerobic and anaerobic bottle because --

(Off microphone comment.)

DR. HADDAD: Yeah, but Day 4 you only have splits. You don't have a collection anymore.

(Pause.)

DR. LEITMAN: Chris, could I ask the FDA a question? If we vote yes, as we likely will on this, that means that platelets be 80 to 85% of platelets collected in a certain way right now in the United States, which is one 8 mL bottle at 24 to 36 hours, that has an outdate of 4 days. You can't --

(Off microphone comment.)

DR. LEITMAN: That will have an outdate from this time on when these become a guidance of 4 days but not 5? I'm asking it. I don't understand what that -- what the outdate of that product will be. It won't be 5 days because you have to do something in addition to get to 5 days. What does that mean the shelf life of that component will be?

DR. EPSTEIN: Well, our thinking at the time of the March 2016 guidance, consistent with the recommendation of the Advisory Committee in 2012, was that there would only be dating through Day 3 without secondary testing, so that would mean that you had to do a rapid test on Day 4 and Day 5.

So what we're talking about here is alternatives that have been brought forward through comments, you know, with the data you've seen, to either do, if you will, enhanced upfront culture or alternatives at the back end to rapid testing. But, again, this was all based on modifications to the 2016 guidance.

Again, in 2012, the Committee was uncomfortable with use through Day 5 of platelets that did not have secondary testing based on the 8 mL sample at 24 hours. Is that helpful? That could be changed, but that's the current thinking.

DR. STAPLETON: I think Dr. Haddad noted that the grammar is incorrect on (b). It should be per split divided equally into or divided into an aerobic and anaerobic culture; otherwise, you're talking 32 mL.

DR. HADDAD: Yeah. Or maybe we can say per component split between an aerobic and an anaerobic.

(Pause.)

DR. HADDAD: I think we can drop the split, I think.

(Pause.)

DR. STOWELL: We're going to vote on this version of 2b. So the question is, as you can see, I'm not going to read it to you again.

(Committee vote.)

LCDR EMERY: While the Committee is voting, does Industry have anything that they'd like to say?

DR. STRAMER: No comments.

(Laughter.)

LCDR EMERY: Thank you.

And the question that is being voted on is 2b: Repeat culture on Day 4 with a volume of 16 mL per component divided into an aerobic and anaerobic culture tube. And the voting will be up momentarily. Still waiting on one vote? I see. I believe Dr. Quillen has left, so we will take her out of the last of it. So 16, yeah.

The Committee has voted in majority. And I will read the individual votes.

Dr. Stowell, yes.

Dr. Baker, yes.

Dr. DeMaria, yes.

Dr. DeVan, yes.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, yes.

Dr. Ortel, yes.

Mr. Rees, yes.

Dr. Sandberg, yes.

Dr. Stapleton, yes.

Dr. Basavaraju, yes.

Dr. Kindzelski, yes.

Dr. Stroncek, yes.

Dr. Arduino, yes.

Dr. Carrol, yes.

Dr. Quillen has left and she has not voted. So there is a total of 16 yeses, there are 0 abstentions, and 0 noes. Thank you.

DR. STOWELL: Okay, thanks to the Committee. That was yeoman's work.

We are scheduled to take a break at this point. I would wonder what the Committee would like to do, if you'd like to just continue on and have the presentations about the HLA, HPA and HNA testing devices. We are scheduled for break a little bit later on, and we will take that break, certainly, but would you just as soon charge ahead? All right, I think people would just as soon charge ahead. Okay. Well, it looks like we're going to have to take about a 10-minute break, anyway, until they round up the speakers. So we'll be back here at 3:35.

(Off the record at 3:24 p.m.)

(On the record at 3:36 p.m.)

DR. STOWELL: Let's get started with our second topic for the day. What we're being asked to do is to opine upon the classification of a medical device and these particular devices used for HLA, HPA and HNA testing. And to start us off, Dr. Lathrop is going to talk to us about the system for classifying medical devices, and that we'll be using as the rubric to make the determination about these particular

devices.

DR. LATHROP: Thanks. So I'm Julia Lathrop from the Division of Emerging and Transfusion Transmitted Diseases in the Office of Blood Research and Review, and I'm going to be giving an overview of device classification.

So the purpose of this session of the meeting today is to ask the Panel to provide input to the FDA on the classification of human leukocyte antigen, human platelet antigen, and human neutrophil antigen device types, in other words, to consider if FDA should call for PMAs or to classify these as Class II or Class I devices. So in subsequent presentations, you're going to hear about the details of these devices, how they work and how they're used in clinical practice. I'm going to give an overview of how FDA thinks about device classification and risk and about the mechanics of how classification is actually done.

So the FDA considers -- classifies devices based on risk, and for in vitro diagnostic devices, this generally means the risk to a patient of a wrong result based on the intended use of the device.

So, for example, in an in vitro diagnostic, this can be the risk of a false positive result, but depending on how the device is going to be used, this risk can be fairly minor, if it's just one result in a whole panel of tests that are being done and the patient is not going to really be adversely affected by that wrong result, compared with a false positive

in a diagnostic test where it's a single result and the patient may be sent for an invasive biopsy or treatment with a drug that has significant side effects.

Or conversely, a false negative result in which case a patient, you know, again, if it's in a suite of studies, it's not going to have that much of an effect for the result of a single test versus a false negative in a screening device, which is very high risk if you have a patient with a disease who gets a false negative and then doesn't get treatment that they need.

And another example would be for a molecular blood-typing device, which getting a wrong result in a blood test can have catastrophic effects on a patient.

So FDA looks at device classification based on the risk and on the availability of controls that are necessary to provide a reasonable assurance of safety and effectiveness.

And it's worth pointing out here, the controls in this context don't have anything to do with assay controls, so it's not your positive or negative control. Controls in this context are regulatory elements that are put in place that, for example, provide assurance that your manufacturing process is under control, so that's what we mean when we talk about controls here. And the determination, then, is a reasonable assurance of safety and effectiveness.

And it's also worth pointing out that risk is not

necessarily associated with the complexity of the device, since you can have a clear way point-of-care lateral flow device that is a high-risk device or you can have a complex manual ELISA that's a moderate-risk device.

So general overview, and I'm going to go into detail in each of these classes in subsequent slides, but a general overview: The FDA looks at risk, and it divides devices into three risk categories: Class I, which are the low-risk devices, which are governed by general controls; Class II, which are moderate-risk devices, which are governed by general and the additional special control elements; and Class III devices, which are subject to premarket approval.

The goal is to place a device in the lowest-risk category possible that still provides a reasonable assurance of safety and effectiveness. And most new and unclassified devices are reviewed by default as Class III devices because if they're new, we don't know what the risk profile is.

There are several mechanisms by which a new device can come in; it doesn't have to be reviewed as a Class III. One is by a de novo petition, when a sponsor has a new device but can provide sufficient evidence to demonstrate the benefit and risk profile and the special controls to mitigate those risks so it can come in as a Class II. Or a device can be classified or reclassified, which is part of what we're doing here today.

Class I devices are devices for which general controls are

sufficient to provide a reasonable assurance of safety and effectiveness. So these are low-risk devices where we know that the general controls are going to be sufficient.

There's another way a device can fall into the bin for Class I, however, and those are devices where we may not know for sure that general controls are going to be sufficient, but it's clearly a low-risk device, and that determination is made by evaluating the intent of the device.

So the device cannot be purported or represented for use in supporting or sustaining human life, and it can't be for a use which is of substantial importance in preventing impairment of human health, and that's where most IVDs come in the picture here. And also, they cannot -- the device failure cannot present a potential unreasonable risk of illness or injury. So if a device comes in and it's new, but it doesn't meet any of these standards, it can still be a Class I device.

Class I devices are usually exempt from premarket review, which means they can be legally marketed without coming to the Agency for review. It's important to note, though, that these have not been cleared or approved and cannot be marketed as such. Exempt devices, most Class I devices are exempt from premarket review, but there has to be internal documentation that the manufacturer holds that shows that they do adhere to the general controls.

There's a small handful of Class I devices that are not

exempt; those are called Class I reserved devices, and those do have to come in with a 510(k), and you can look on the FDA -- search on FDA's website for Class I reserved devices, and it has a list of those devices. But most of them are exempt.

So general controls are regulatory elements that are put in place that apply to all devices regardless of class, and these are basic provisions that provide this reasonable assurance, and they include such elements as a prohibition against adulterated or misbranded devices, and what this means is you can't make claims that your device can do things that it can't do, so that's prohibited. It has to be produced under quality systems and good manufacturing practices, the establishments have to be registered, the devices have to be listed, and all devices are subject to adverse event reporting requirements.

Examples of some Class I devices are bandages and crutches or, in the in vitro diagnostic world, assay controls. The reason these are Class I low-risk devices and controls our devices is because if your controls fail, you get an invalid result. The patient won't get an answer from their test. So failure here is not going to affect the patient management.

So the goal, then, is to put a device, if you can, into Class I, but some devices can't be classified into Class I because it's clear that the general controls, on their own, are not sufficient to provide this reasonable assurance. But we

have enough experience with these devices that we can write special controls that can provide the reasonable assurance of safety and effectiveness.

Class II devices typically require a premarket notification, which is a 510(k) submission, prior to being marketed, and the proper terminology is that these devices are cleared based on demonstration of substantial equivalence to a legally marketed predicate device. And I'm not going to go into defining substantial equivalence or predicate, except to say that substantial equivalence encompasses a wide variety of evidence, and a legally marketed predicate device is a legally marketed device that has the same intended use as the device that's being evaluated.

Special controls, again, are additional regulatory elements that are put in place to mitigate the risks associated with the device, and these are based on experience with how the device performs and where the failure modes are going to be found. And these can include anything that's necessary here, so performance standards.

For example, the special control may require that the clinical sensitivity have a 95% confidence interval lower bound of 90% if it's been demonstrated that that kind of sensitivity is necessary to provide reasonable assurance. It can require that patients that use the device are enrolled in patient registries. It can be other premarket data, special labeling

requirements. There are number of special controls.

And it's important to note that all devices are subject to special -- all Class II devices of this type, with this intended use, are subject to -- they must adhere to the special controls. And there is a small handful of Class II devices that are exempt from premarket review, so that means the same thing as a Class I exempt device in that they can be legally marketed without coming into the Agency; however, they still must adhere to the special controls, and the manufacturer must retain -- must have documentation that they do adhere to the special controls in their internal documentation that is subject to inspection.

So special controls, this is an example of how special controls have been used in the past. So nucleic acid TB devices were down-classified by the Division of Microbiological Devices in 2014 -- this is a division in CDRH -- because they had a lot of these devices and they knew now -- they were Class III, but they had accumulated evidence that they knew they could write special controls that could mitigate the risks that were known now with these devices and it was appropriate to down-classify them.

So they wrote special controls, and these special controls specify a number of different elements, including demonstration that nucleic acid extraction is appropriate, it spells out which organisms have to be used in the cross-reactivity study,

the device description, including a description of the oligonucleotides, specific assay controls, and labeling specifications. So these special controls, then, in combination with general controls, provide the reasonable assurance of safety and effectiveness. And as I said before, all new devices of this type, even -- although these are not exempt, but even if they were exempt, must follow these special controls.

Some examples of Class II devices in vitro diagnostics would be some IVDs for monitoring viral load. These are devices that are used on patients who have already been diagnosed, they're already under treatment by a physician, so you're not going to lose them to care, so these are Class II devices for monitoring.

Some devices, though, there are no special controls that can be written that can mitigate the risks, so these can't be classified into Class II because we have insufficient information, and it doesn't necessarily really mean that there's just not enough yet; it means the data that is there doesn't support the use of special controls.

And Class III high-risk devices, then, are life-sustaining or life-supporting or of substantial importance in preventing impairment to human health, or the failure of a device presents a potential unreasonable risk of illness or injury. And Class III devices typically require premarket approval prior to being

marketed.

And an example, as I mentioned earlier, of a Class III high-risk in vitro diagnostic are molecular blood-typing tests, which if the test gives you a wrong result and it turns out you think the patient has the wrong blood type, that can have potentially catastrophic effects on the patient.

So this is just a flowchart that goes through the decision tree that we go through when we have a new device and we're deciding how it should it be classified, and it's just reiterating what I just said.

Basically, you look at the device and see, "Are general controls sufficient?" If the answer is yes, it's Class I. If they're not sufficient or there's not enough information they are, then you ask the question, "Are they life-supporting or life-sustaining?" If the answer to that is yes, then they are sufficient -- then you ask the question, "Is there sufficient information for the special controls?" And if there is, then they can be Class II, and if they're not, then they're Class I.

So that's how FDA looks at how a device should be classified, and the mechanics of when or specifically how we go through the process, then, is the topic of the next part of this talk.

So the FDA can classify or reclassify a device, and there are a number of different scenarios. We're required by law to classify all devices. So you can have an initial

classification proceeding, which is what we're doing here today.

The FDA can decide to reclassify a device or classify a device, or somebody can petition the Agency to classify a device based on new information about the device. So this can be a case where the clinical picture has changed significantly from when the first devices were originally approved and so maybe Class III is no longer appropriate.

You can have a situation where there's a sufficient experience with the device that they can now be down-classified, like you saw with the tuberculosis devices. Or conversely, people can understand that, in fact, these devices are riskier than they were originally thought and that, in fact, they should be up-classified, which is what also happened with the Division of Microbiological Devices when they up-classified flu diagnostics from Class I to Class II. So new information can change the classification of a device.

And a third scenario is the Agency can classify or reclassify a specific device when they make a classification decision on an intended use for other devices of a similar type that have previously been reviewed by the Agency.

So the classification process: Devices are classified after the FDA generally holds a panel meeting to obtain feedback. We'll publish a proposed order announcing the proposed classification. For an initial classification, the

administrative process is a rule, and for reclassifying, it is an order, and that's just administrative procedure.

And we'll publish a proposed order with the special controls of a Class II device and seek feedback from the public in response to that; that's published in the *Federal Register*. The public can respond, the FDA evaluates all the comments, takes into account -- takes into consideration the feedback from the panel, and then publishes a final order on the classification of the device.

So the input we're looking for from the Panel today is how these devices that are at issue should be classified. And this input should include:

- Identification of risks to health from the device, if there are any.
- If the device should be considered life-supporting/life-sustaining or of substantial importance in preventing impairment of human health, or if it presents a potential unreasonable risk of illness or injury.
- If the answer to that question is yes, then the question will be asked: Is it theoretically possible to write special controls that can mitigate these risks?
- If the answer to that is yes, then the Panel will consider what the special controls might be that

could be involved in this -- that could mitigate those risks.

After the panel meeting, the FDA will consider all the available evidence, including the input of the panel and public comments. FDA will issue a proposed order proposing the classification, as we mentioned, of the device and seek the public comment from the *Federal Register*, and then we'll issue a final order. And in this case, if it's Class I or Class II, these devices that are already in the market can continue to be marketed. If, however, the FDA decides that these, in fact, should be Class III devices, we will issue a separate call for PMAs telling manufacturers the devices they have on the market, they have to come in and submit a PMA for those devices. They can continue to market under that timeline until such time as the deadline for which they have to submit the PMA, and if in some case for whatever reason the PMA is not approved, the devices will be considered misbranded and they have to be removed from distribution. That's, you know, if it turns out that that is the case.

So thank you very much, and we look forward to the discussion on the classification of these devices. Thank you.

DR. STOWELL: Thank you.

While the next speaker is coming up, I would like to review the introductions, and we will start with Dr. Kathleen Sullivan, who is joining us by teleconference.

Dr. Sullivan? Well, Dr. Sullivan?

DR. K. SULLIVAN: Hello. Sorry, I was on mute.

DR. STOWELL: Okay. If you would just introduce yourself and tell us where you're from.

DR. K. SULLIVAN: Yeah, my name is Kate Sullivan. I'm a pediatric immunologist at Children's Hospital of Philadelphia, and I am phoning in.

DR. STOWELL: Thank you.

And we'll go around the table and start with you, Dr. Stapleton.

DR. STAPLETON: Jack Stapleton. I'm an infectious disease physician and professor at the Department of Microbiology and Internal Medicine.

DR. SANDBERG: Sonja Sandberg. I'm an applied mathematician, and I teach at Framingham State University in Massachusetts.

MR. REES: Robert Rees. I'm the Manager of the New Jersey State Department of Health Blood Bank Regulatory and Compliance Program.

DR. ORTEL: Tom Ortel, Chief of Hematology at Duke University Medical Center.

DR. LEWIS: Roger Lewis. I'm the Chair of Emergency Medicine at Harvard UCLA Medical Center in Los Angeles.

DR. LEITMAN: Susan Leitman. I'm the Director of the Medical Research Scholars Program at NIH, and before that, for

31 years I was Director of Blood Services in the Transfusion Medicine Department at NIH.

DR. ESCOBAR: Miguel Escobar, hematologist at the University of Texas in Houston.

DR. DeVAN: Hi, I'm Mike DeVan. I'm a staff pathologist at Walter Reed and Medical Director for their transfusion services.

DR. DeMARIA: Al DeMaria with the Massachusetts Department of Public Health.

DR. BAKER: Judith Baker, Public Health Director for the Center for Inherited Blood Disorders and the federal hemophilia and sickle cell centers and also at UCLA.

LCDR EMERY: Lieutenant Commander Bryan Emery. I'm the DFO for this BPAC committee.

DR. STOWELL: Chris Stowell, I'm the Director of the Blood Transfusion Service at Mass General Hospital and Associate Professor of Pathology at Harvard Medical School.

DR. BASAVARAJU: Sridhar Basavaraju, Director of the CDC Office of Blood, Organ, and Other Tissue Safety.

DR. KINDZELSKI: Andrei Kindzelski, Program Director in Blood Division, Heart, Lung, and Blood Institute, NIH.

DR. STRONCEK: Dave Stroncek, Chief of the Cell Therapy Section, Department of Transfusion Medicine, NIH Clinical Center.

DR. KOPKO: Patricia Kopko. I am Director of Transfusion

Medicine, Associate Director of our Immunogenics and Transplant Lab, and Associate Director of our Residency Training Program at the University of California, San Diego.

DR. C. SULLIVAN: Cliff Sullivan. I'm at Emory University where I do transfusion medicine, and I am the Associate Director of the H-I -- sorry, HLA Laboratory.

DR. STRAMER: Susan Stramer, Vice President, Scientific Affairs, American Red Cross, and Chair of the AABB Transfusion Transmitted Diseases Committee.

DR. STOWELL: Thank you.

Our next speakers are Jason Liu and Sharmila Shrestha from FDA.

DR. LIU: Good afternoon. My name is Jason Liu. I'm a scientific reviewer from the Devices and Review Branch in the Division of Blood Components and Devices in the Office of Blood Research and Review at CBER. My colleague, Sharmila Shrestha, and I will present to the Panel FDA's proposed classification of human leukocyte, neutrophil, and platelet antigen and antibody devices. We call them HLA, HNA, and HPA devices.

Here is the overview of our presentation. In order for the classification Panel to discuss and recommend classification, we will first provide a general introduction, including the purpose of the meeting and the devices included for discussion, followed by our current 510(k) review elements for these devices. For HLA device-related topics, I will

provide HLA device description, regulatory history, clinical use of HLA test, and our evaluation of their safety and effectiveness as reported in the literature, medical device reports, and product recalls.

Sharmila will then present the same topics for HNA and HPA devices.

After that, I will present the summary of the risks, how these risks can be mitigated, and FDA's proposed classification.

Introduction: The meeting today is for the classification Panel to discuss and recommend appropriate classification for HLA, HNA, and HPA devices that are intended for introduction into interstate commerce in the United States and are used to aid donor and recipient matching in transfusion or transplantation or to aid in disease diagnosis.

There are three groups of devices for today's discussion: HLA devices, HPA devices, and HNA devices. Each group includes devices performing antigen phenotyping or DNA genotyping and the devices detecting antibodies to the related antigens.

We propose to classify these devices under a single regulation because they share similar biological properties. HLA, HNA, and HPA are all blood cell markers. Blood cells are characterized by the surface expression of a variety of molecules, including HLA, HPA and HNA.

In addition, these devices use similar techniques to

determine antigen expression to perform DNA genotyping or to detect antibodies to their related antigens. Some of the test results share similar clinical use. For example, HLA and HPA are both used to select compatible platelet for transfusion.

Lastly, the special controls used to mitigate the risks are common to these devices. We will discuss the special controls later in this presentation.

The devices used as companion diagnostic device, which is labeled to provide information that is essential for the safe and effective use of a corresponding therapeutic product or assays that are designed, manufactured, and used within a single laboratory, are excluded for consideration.

So HLA, HNA, and HPA devices have never been formally classified and are currently regulated as unclassified devices. They are currently reviewed and cleared by FDA through the premarket notification 510(k) process. This process primarily consists of determinants of substantial equivalence of the new device to a legally marketed device of the same generic path. We are required by law to classify these devices.

Now I would like to talk about our current 510(k) review elements for HLA, HPA and HNA devices. For 510(k) clearance of these devices, we compare the intended use and the technology of the new device to the predicate device, as well as evaluate the performance status of the new device.

The performance status include clinical measure comparison

study performed at three clinical sites by intended operators at the intended settings; precision studies that include repeatability and reproducibility; accuracy study using well-characterized samples; interference studies; limit of detection study; stability studies. We also review software and instrument validation, if applicable, and the device labeling.

Description of HLA devices: As we just discussed, there are two categories of HLA devices, HLA typing devices and HLA antibody detection devices. In this presentation, for each HLA-related topics, in general, I will discuss HLA typing devices first, followed by a discussion of HLA antibody detection devices.

Common HLA typing techniques used in FDA-cleared devices generally fall into two categories: early version of HLA typing devices or serological assays using the complement-dependent cytotoxicity (CDC) technique. These methods use characterized HLA antibodies to specific HLA antigens.

Currently, most laboratory use nucleic acid-based method, molecular method, for HLA typing. So HLA molecular assay often use the following techniques: polymerase chain reaction sequence-specific primer (PCR-SSP); sequence-specific oligonucleotide probe (SSOP); and sequencing-based techniques. Sequencing-based techniques include the traditional Sanger sequencing assays and the recently developed next-generation sequencing assay. HLA next-generation sequencing assays have

not been cleared by FDA for clinical use.

So HLA system is the most polymorphic region in human genome; it includes a huge number of alleles, and more alleles are being identified. This figure show the numbers -- the number of named HLA class I and class II alleles by calendar years. Currently, there are more than 17,000 HLA alleles. The international database publishes an updated new list every 3 months.

The extensive HLA polymorphism and the frequent addition of new alleles complicate HLA testing. For example, the manufacturers of HLA typing devices may need to update primer/probes, or the HLA allele assignment for some existing primer/probes.

Early version of HLA antibody detection assays were cell-based assay and used the CDC technique. The same technique is also used to perform cross-matching of transparent recipient serum against a potential donor's cells.

In recent years, solid phase assay had to be introduced for HLA antibody detection in which HLA proteins are coated to solid surface to detect antibodies. Commonly used solid phase assays include ELISA-based assays, flow cytometry assays, and Luminex assays. Both flow cytometry assays and Luminex assays use fluorescently encoded beads that are coated with an HLA antigen or HLA antigens.

An HLA device may consist of a single reagent or a test

kit with all necessary reagents or is designed as a system consisting of reagents, instrument, and software. An HLA device can be complicated, and there is often a multiplex assay detecting many alleles or antibodies. Software is increasingly used to support data calculation or to generate final results. Software may be submitted to FDA as part of a system or in a separate premarket submission.

Now that you have a description of HLA devices, let's move on to how they have been regulated before.

The Agency issued the first product license for leukocyte typing serum in 1974. An FDA guideline for leukocyte typing serum was issued in 1977 and subsequently codified as additional standards in biologic regulation.

In 1982 FDA published a final rule removing the additional standards for leukocyte typing serum. It instructed all related manufacturers to register under 21 C.F.R. 807, which is a medical device regulation. If not currently licensed, submit 510(k) submission. This rule was supported by the argument that this product could be appropriately regulated as medical devices. Since 1982 FDA has cleared approximately 100 HLA device 510(k) submissions.

At the September 15, 2000 BPAC meeting, the Committee, serving as a device classification panel, unanimously agreed that HLA devices should be classified as Class II medical devices.

In 2015 FDA issued a guidance document regarding 510(k) submissions for HLA molecular typing devices used to aid donor-recipient matching in transfusion or transplantation.

So you may be wondering why we are seeking the Panel's classification recommendation again today. Since the last meeting, there have been widespread clinical uses of new technologies, and along with recently identified device limitations, this new benefit and the risk information warrant a new discussion. In addition, the previous meeting discussed only the HLA devices. Today's discussion also include HPA and HNA devices.

Let's go back to the history and take a look at the cleared intended use. So intended use of FDA-cleared HLA typing devices include the use of serological assays for HLA phenotyping to the use of DNA-based method for genotyping. Clinical utilities include donor-recipient matching in transfusion and transplantation and in disease diagnosis. An example of the cleared intended use for HLA antibody detection devices is qualitative bead-based immunoassay used to detect IgG antibodies to HLA class I and class II molecules. Software has been cleared before to support the evaluation of HLA typing results or HLA antibody detection results.

We have just discussed the regulatory history of HLA devices. Now I will discuss their clinical use.

HLA testing has been used to support blood transfusion.

Transfusion-related acute lung injury (TRALI) is typically associated with the presence of HLA antibodies in blood donors or recipients. HLA testing is essential for the investigation and the mitigation of TRALI.

HLA antibody in patients can cause immune-mediated platelet refractoriness. HLA testing is commonly performed on both donor and the recipient to obtain compatible platelet for transfusion.

HLA reacting cells in a cellular product can induce transfusion-associated graft versus host disease (GVHD). Investigation of transfusion-associated GVHD includes HLA typing of both donor and the recipient.

Another clinical use of HLA test for today's discussion is donor-recipient matching in transplantation. HLA typing is widely utilized in transplantation. A key strategy to reduce rejection is to minimize HLA differences between the donor and the recipient in both solid organ transplantation and hematopoietic stem cell transplantation (HSCT). High resolution HLA molecular typing is recommended for HSCT.

Pre-transplant HLA antibodies, especially donor-specific antibodies (DSAs), are often associated with an increased risk of rejection and graft loss. Therefore, identification of HLA antibodies has been used to make an informed decision regarding whether to accept any transplant organ tissue of cells from a specific donor.

HLA testing has also been used to aid in disease diagnosis. Across the entire genome, HLA is recognized as the most important region in relation to disease susceptibility. Many diseases have been reported to occur more frequently in the individuals with certain HLA types. These diseases include a broad spectrum of immune-mediated diseases and malignancies. HLA testing can be useful in narrowing diagnostic possibilities.

The next topic is FDA's evaluation of the safety and the effectiveness related to HLA devices. To identify valid scientific evidence regarding the benefits and the risks of using these devices, FDA conducted a systemic literature review plus a review of the medical device reports and the product recalls.

I will first discuss our literature review. The scope of the literature review addressed the following questions:

- What is the reported analytical performance of the FDA-cleared HLA devices?
- How are the HLA testing results used to aid donor-recipient matching in transfusion or transplantation, or to aid in disease diagnosis?
- What are the risks associated with HLA devices?

The first part of our literature review used search terms related to analytical performance of HLA devices and their clinical use for donor and recipient matching in transfusion or

transplantation. So initial search yielded more than 5,000 records. Currently, the most commonly used HLA devices are for DNA-based HLA typing, molecular typing devices, and the solid phase antibody detection case. FDA started to clear this case in 1994. Accordingly, we limited our literature search to full-text articles published from 1994 to May 1st, 2017, to focus on these commonly used devices. May 1st, 2017, was selected as cutoff date so that we had sufficient time to review and summarize the literature.

After applying this text, we obtained more than 1,500 articles. We first reviewed all titles and abstracts to exclude irrelevant articles. Next, the full text of the remaining articles were assessed for eligibility. A total of 137 relevant articles were included in the literature review summary.

To summarize the analytical performance reported in the literature, I will first discuss HLA typing devices and then discuss HLA antibody detection devices.

The literature showed that molecular HLA typing assays have superior performance compared to the serological method. HLA molecular typing devices provided results with higher resolution, and it revealed serological typing errors. Due to the extreme polymorphism of the HLA loci and the fact that the frequencies of most HLA alleles are low, a complete sample panel may not be available to validate all primers and probes

before product release. False negative and false positive signals were reported in the literature when the reaction patterns of alleles are different from the expected reaction patterns.

The extreme polymorphism of the HLA loci present another challenge to most genotyping devices, typing ambiguity. An HLA assay may not be able to resolve similar DNA sequences, and they report more than one allele pairs as possible HLA type. One review article suggested that typing ambiguities may occur in 41% of HLA-A and 21% of HLA-B typing results.

Loss of heterozygosity have been reported to cause false HLA homozygous result in pre-transplant patients suffering from hematological malignancies while, in fact, HLA had the results.

For Luminex-based HLA antibody detection devices, it is well recognized in the literature that they are, in general, more sensitive than other assays, such as CDC assays and the ELISA assays. Due to their high sensitivity on the resolution, some articles described Luminex as a major breakthrough in this field. Several studies reported that clinically irrelevant antibodies were detected by Luminex assay due to the presence of denatured HLA antigen on the beads. One study reported that 11% of class I DSA, donor-specific antibodies, detected by Luminex assay were caused by reactivities with denatured HLA.

HLA antibodies, especially DSAs, are often considered as a contraindication for transplantation, considering the

clinically irrelevant antibodies may result in an inappropriate denial of transplantation.

Several studies reported Luminex assay reproducibility issues, including differences between case, between loss, and the inter-assay and the inter-machine differences.

Some assays are subject to prozone effect and affected by interference substance, including such as IgM.

As a large number of HLA antigens exist, it is not currently possible to represent all HLA antigens in one single antigen beads assay, so this is a limitation identified in the literature.

Another type of solid phase assay is the ELISA assay. Literature reported that they are more sensitive than CDC assays, and they may be less sensitive than flow cytometry-based assays. So reported concordance between several FDA-cleared ELISA devices ranged from 88.2% to 91.3%. False positive and false negative results from ELISA-based assays have been occasionally reported.

Taking together all of this reported device limitations, such as false positive results, inconsistent results, and the lack of antibody results for some antigens, may post potential risks when using the data to make clinical decisions.

We have just summarized the analytical performance reported in the literature. Let's move on to the reported clinical use. Again, I will discuss the reported clinical use

of HLA typing devices first, followed by HLA antibody detection device.

In transfusion settings, HLA typing assays have often been used to investigate the clinical relevance of HLA system in blood transfusion. It has been reported that transfusion of HLA-matched platelets yielded significantly higher platelet recovery value in patients with immune-mediated platelet refractoriness.

The practice of HLA antigen and molecular typing is widely accepted for kidney transplantation and has been utilized for many decades to aid donor-recipient matching, which remains significant. Study reported that renal allograft survival was significantly improved in recipients with better HLA matches. In general, the value of HLA antigen matching in other solid organ transplantation is not as well documented as kidney transplantation.

There were conflicting reports as whether HLA matching has significant impact for liver transplantation.

For lung transplantation, the study using FDA-cleared devices reported that mismatches at HLA-L locus was a significant risk factor for obliterative bronchiolitis. Obliterative bronchiolitis is a primary cause of chronic graft loss in lung transplantation.

In HSCT, many studies have shown that matches at HLA-A, B, C, DRB1, DQB1 loci 10/10 matches improve survival and the

overall outcomes. These are suggestive that cord blood transplantation can tolerate some degree of HLA antigen mismatches.

In addition to HLA antigen matching, a large number of articles have concluded that the presence of HLA antibodies, especially DSAs, is closely associated with transplantation outcome. DSA data has been used to aid organ allocation. Donor HLA typing results, together with recipient HLA antibody result, is required to determine the assay. We will discuss more about DSA in the next few slides, which summarize the clinical use of HLA antibody detection devices reported in the literature.

Using HLA antibody detection devices in several studies confirmed that some transfusion reactions are triggered by HLA antibodies present in the patients, where others are initiated by HLA antibodies or HLA-reacting cells presented in the transfused products.

It is recognized in the literature that HLA antibody detection devices can be used in blood centers to develop TRALI risk reduction strategies.

Patients who are refractory to platelet transfusion as a result of HLA alloimmunization are generally giving an HLA-matched or cross-matched platelet. One study reported that platelet selection based on HLA antibody specificity prediction, which is similar to virtual cross-match, was as

effective as providing HLA-matched or cross-matched platelets.

Preformed HLA antibodies, especially DSAs, were reported in a large number of articles being associated with worse outcomes after solid organ transplantation. We also noted a few studies have shown that not all antibodies determined by a Luminex assay could be considered clinically relevant in solid organ transplantation. As we have discussed before, Luminex assay may detect antibodies through denatured HLA antigens.

The presence of preformed HLA antibodies in HSCT recipients were reported as a risk factor for GVHD and graft failure and affected overall outcome.

Cord blood transplantation recipients with HLA antibodies against cord blood HLA molecules had significantly lower neutrophil and platelet recovery. Anti-HLA class II antibodies in unrelated HSCT donors was associated with a higher cumulative incidence of GVHD.

Virtual cross-match has emerged as a usable tool for pre-transplant risk assessment and allocation. This method is based on HLA antibody detection results from the recipients and the HLA types of the proposed donors without performing a bench cross-match. Donors having the corresponding HLA antigens can be filtered out.

So prediction rate of virtual cross-match for a bench cross-match reported in the literature branched from 47.9% to 93%.

In a study of pancreas transplantation, the outcomes were comparable among recipient groups of virtual cross-match and flow cytometry cross-match. The authors conclude that virtual cross-match have lower cold ischemia time.

We have addressed and discussed the analytical performance of FDA-cleared HLA devices and of their use for donor-recipient matching, which is the first part of our literature review. The second part of the literature review focused on the use of HLA typing to aid disease diagnosis.

The association of HLA-B27 with ankylosing spondylitis is one of the strongest genetic association with a common human disease. In our literature review, we selected this association as an example for the use of HLA typing to aid disease diagnosis. The literature review method is similar to the first part, and more details are provided in Index A of the issue summary document.

Our literature search identified a large number of articles that have confirmed the strong association of HLA-B27 with AS in most populations. In many populations only a small percentage of HLA-B27 positive subjects develop the disease. Although HLA-B27 is neither sufficient nor absolutely necessary for the occurrence of AS in appropriate clinical situation, HLA-B27 is of value in supporting the diagnosis of AS.

There are at least 160 HLA-B27 subtypes. Some subtypes exhibit differential association with AS. Many studies also

assessed the association of HLA-B27 with AS disease features. HLA-B27 positive AS patients are younger at the onset of the disease and the diagnosis as compared with HLA-B27 negative patients. They also often have a greater familial occurrence.

HLA-B27 is recognized in the literature as important for patient classification and referral. New classification criteria have been developed to identify patients with axial spondyloarthritis, including patients with early AS. The reported sensitivity and specificity of HLA-B27 of the new criteria are both around 80%.

The literature reported that delayed disease diagnosis was significantly longer in HLA-B27 negative patients than that in the HLA-B27 positive patients. So delayed diagnosis was associated with worse outcomes and unfavorable treatment responses.

In summary, the literature showed acceptable analytical performance of HLA devices in general and widespread clinical use. HLA assays are important in matching of donor and the recipients, mitigating transfusion reaction such as TRALI, and for disease diagnosis such as ankylosing spondylitis.

Given the extreme polymorphism of the HLA system, HLA testing can be complicated, and HLA typing ambiguities remain a major challenge for many devices. Some factors, such as denatured HLA molecules, may affect HLA antibody detection. These device limitations can lead to incorrect HLA test results

that may negatively affect patient care leading to poor graft survival, transfusion reaction, or incorrect or delayed disease diagnosis.

So in addition to what has been reported in the literature regarding the safety and the effectiveness of HLA devices, we also investigated the available data within the Agency, that is the medical device reports and the product recalls. I will discuss our review of the medical device reports first.

Medical device reports (MDRs) are submitted to FDA database to record suspected device-associated deaths, serious injuries, and malfunctions. FDA use MDRs to monitor device performance and to detect potential device-related safety issues.

Although MDRs are a valuable source of information, this surveillance system has limitations. It is difficult to estimate the frequency of an issue because there's no information about the total number of tests performed. The reporting to the FDA database is mandatory for manufacturers, importers, user facilities. However, the reporting is voluntary for healthcare professionals, patients, and consumers. These voluntary reports are often delayed and difficult to verify.

In our database containing records since 1991, we uncovered 464 events as of May 1st, 2017, for HLA genotyping devices. All MDRs with reportable category information are

malfunctions. For 30 MDRs submitted did not identify a reportable event path. There are no MDRs for device-related deaths or serious injuries. There were no MDRs for serological HLA typing devices.

So most commonly reported issue for HLA genotyping devices is incorrect reactivity assignment for primers or probes. Most of the related MDRs were not able to identify the root cause. Sixty-seven MDRs identified the root cause as errors when updating software or data sheets when new HLA allelic -- with new HLA allelic information. Fifty-seven MDRs identified the root cause as errors related to the internal manufacturing software that contains reactivity assignment information. Lacking of samples to verify reactivity assignment before product release was reported as the root cause in eight MDRs.

Thirty-six MDRs were reported for malfunction of the data interpretive software. Sixteen MDRs were submitted for mistype or no type results, but the root cause was not identified. Twenty-four MDR were submitted for sequencing case due to high sequencing background or poor sequencing quality.

In our database, we also uncovered 13 events for HLA antibody detection devices. False positive results or unusually high positive rates were reported in five MDRs. Low assay cutoff was reported as a potential factor. The reports also indicated that samples with reactivity near the sample -- near the assay cutoff make inconsistent results between lots.

Four MDRs were submitted for false negative results. The root cause was the failure to detect antibodies with low affinity and/or low titer, which are specific for low-frequency HLA epitopes. Assay reproducibility issues, specifically different results from two runs, were reported in two MDRs. There were two reports for QC failure of the negative control serum.

In conclusion, most of the reported MDRs are for HLA genotyping devices and are associated with device malfunctions. There have been no reported deaths or serious injuries related to these malfunctions. The malfunctions can lead to incorrect HLA testing results and have the potential to cause adverse health consequence.

As we just discussed, in addition to MDRs, the risk of the device can be identified by the product recalls reported to FDA database. A recall is an action taken to address a problem with a marketed medical device that violates FDA law. Recall occurs when a medical device is defective and/or it could be a risk to health.

Recalls are classified to Class I, Class II, or Class III recalls. Class I represents the highest degree of health hazard of the recalled product, and there is a reasonable probability of serious adverse health risk or death. Class II recalls is for situation in which the relative product can cause temporary or medically reversible of the worst health

consequences; aware of the probability of serious consequences is remote. Class III represents the lowest degree and is not likely to cause adverse health consequences.

In our database, we identified a total of 37 recalls for HLA devices in recent years. Of the 37 recalls, none were classified as Class I recall, 19 were classified as Class II, and 18 were classified as Class III.

Most of the recalls, 32 out of the total 37, were for products that failed to provide correct results. Twenty-eight of the recalls are for HLA typing devices due to failure to provide correct results. The recalls include incidents such as incorrect reactivity assignments, lacking of samples of specific allele before product release, and the manufacturing errors.

So identify the root cause for the three recalls for HLA antibody detection devices included manufacturing issues during the production of recombinant HLA proteins, such as unstable transfectant. One recall was initiated due to software defect which may generate incorrect result.

In summary, all of the recalls related to HLA devices were classified either as Class II or Class III. Most of them were initiated for products failed to provide correct results. There were no Class I recalls in which violative product could cause serious health consequences or death.

Here is an overview, overall conclusion from our safety

and effective evaluation of HLA devices.

HLA devices are effective tools to aid donor-recipient matching and to aid in disease diagnosis.

The analytical performance is generally acceptable.

These complex devices may malfunction and generate incorrect HLA testing results.

There have been no reported deaths or serious injuries related to these malfunctions.

Review of the literature, MDRs, and the root cause also support the overall effectiveness of our current 510(k) review process for HLA devices, which is inconsistent with the proposed special controls. Again, we will discuss the proposed special controls later in this submission, in this presentation.

So this concludes the overview of the HLA devices. Now Sharmila will discuss HPA and HNA devices.

MS. SHRESTHA: Hi, I'm Sharmila Shrestha, and I'm going to continue the discussion for the classification of human platelet antigen and antibody devices and human neutrophil antigen and antibody devices by providing the overview of HPA and HNA devices.

The overview includes: device description; regulatory history; clinical uses; and safety and effectiveness evaluation from systematic literature review, medical device reports, and product recalls.

Description on HPA and HNA devices: The HPA and HNA devices fall into two categories, devices used for typing and devices used for antibody detection. Typing devices are used in determining the phenotype and genotype of HPA or HNA antigens. The antibody detection devices are used for screening or identifying antibodies to HPA and HNA antigens.

These devices usually come in a kit containing reagents, for example, antibodies, antigens, primers, probes, enzymes, and buffers. Also, these devices may require instruments that may include operating and data-analyzing software.

Test methods employed for HPA devices: For antigen typing, serological typing has largely been replaced by nucleic acid-based typing. For antibody detection, test methods used are flow cytometry, mixed passive hemagglutination assay, monoclonal antibody immobilization of platelet antigens assay, antigen capture ELISA, and bead-based assay.

Test methods for HNA devices include, for antigen typing, as with HPA antigen typing, serological typing has largely been replaced by nucleic acid-based typing. For HNA antibody detection, methods include granulocyte agglutination test, granulocyte immunofluorescence test, monoclonal antibody specific immobilization of granulocyte antigens, and bead-based assay.

Regulatory history of HPA and HNA devices: Both devices have been cleared through the 510(k) premarket notification

pathway. Since 1993, seven devices have been cleared for HPA, two for typing and five for antibody determination. Since 2006, four devices have been cleared for HNA, two for typing and two for antibody identification.

This slide and the next slide provide an example of the intended use of the cleared devices. Here in this slide, examples of intended use is shown for HPA and HNA typing devices that use molecular method.

This slide here provides an example of intended use for cleared HPA and HNA antibody detection devices. For HPA antibody detection devices, the intended use statement is for solid phase ELISA-based assay, and for the HNA antibody detection devices, the intended use statement is for the Luminex bead-based assay.

Clinical uses of HPA devices: HPA devices are used to diagnose disease, screen donors, obtain compatible or matched platelet units, or to investigate transfusion reactions. For example, HPA devices are used to diagnose patients with fetal and neonatal alloimmune thrombocytopenia, immune-mediated platelet refractoriness, and post-transfusion purpura.

Clinical uses of HNA devices: HNA devices are used for investigation of TRALI in blood donors and recipients and to diagnose neonatal alloimmune neutropenia and autoimmune neutropenia.

To assess the safety and effectiveness of HPA and HNA

devices, a literature review was conducted. In the literature review, we sought to address the following three questions:

1. What is the proposed analytical performance of the HPA and HNA devices?

2. What are the reported clinical uses of the HPA and HNA testing results?

3. What are the risks associated with HPA and HNA devices?

We performed a literature search for FDA-cleared HPA-related devices using PubMed and EMBASE to find reported analytical performance and their clinical use. The search terms included tests used to detect human platelet antigens and human platelet antibodies and diseases clinically impacted by HPA testing.

We limited our research -- I'm sorry. We limited our literature search to full articles published in English from January 1994 to May 2017. From the review of 343 titles and abstracts, 31 were considered to be eligible for full-text article review, and from the 31 articles reviewed, 15 were included in the summary. Details of the literature search for HPA-related devices were provided in Appendix B of the Executive Summary.

As with the HPA devices, literature searches for HNA-related devices were conducted through PubMed and EMBASE, focusing on the reported analytical performance of FDA-cleared

HNA devices and their clinical uses. The search terms included the type of tests used to detect human neutrophil antigens, human neutrophil antibodies, and diseases clinically impacted by HNA testing results.

The search generated 355 publications. Using the same approach for HPA literature review, titles and abstracts were reviewed to exclude studies not related to the safety, effectiveness, or performance of FDA-cleared HNA devices. For HNA devices we included six articles in the summary from 355. Again, details of the literature search are provided in Appendix B.

From the literature review for analytical performance, no studies were identified for FDA-cleared HPA and HNA antigen typing devices or for HPA antibody identification devices.

However, from the literature review, analytical performance of FDA-cleared HNA antibody detection devices showed that these devices performed comparably to tests such as flow cytometry white blood cell immunofluorescence test, granulocyte agglutination paired with monoclonal antibody specific immobilization to granulocyte antigens, and granulocyte immunofluorescence test.

From the literature review, it showed that HPA devices are used clinically to diagnose disease of fetal or neonatal thrombocytopenia, investigate post-transfusion purpura, select appropriate antigen-negative platelet products for transfusion,

and to evaluate the etiology of platelet refractoriness.

From the literature review, it showed that HNA devices are used to investigate transfusion reactions, investigate or mitigate TRALI, diagnose neonatal alloimmune neutropenia, autoimmune neutropenia, and drug-induced neutropenia.

From the literature review, it showed that there are risks associated with HPA and HNA devices. HPA and HNA devices can malfunction causing false positive or false negative results, where incorrect results may affect patient outcomes through a delayed or missed diagnosis, delayed treatment, and selection of inappropriate or ineffective product for transfusion.

We concluded from the literature review that FDA-cleared HNA antibody devices demonstrate acceptable analytical performance. HPA and HNA devices play a critical role for transfusion and diagnosing disease. However, there are device limitations which can lead to incorrect HPA and HNA testing results that may negatively affect patient outcome.

To further assess safety and effectiveness of the HPA and HNA devices, we also reviewed postmarket reports, medical device reports, and product recall reports.

For HPA devices, there were two MDRs reported as device malfunction attributed to false positive results. However, root cause analysis showed that the malfunctions were caused by testing not being performed according to product labeling or product package insert. There were no MDRs reported for HNA

devices. There were no product recalls for HPA or HNA devices.

The overall conclusion for the safety and effectiveness evaluation for FDA-cleared HPA and HNA devices is that the literature review showed acceptable analytical performance.

HPA and HNA devices play a critical role in investigating or preventing transfusion reactions and disease diagnosis.

However, there are risks associated with these devices. These devices have a potential for malfunction that may lead to adverse health consequences.

This concludes the overview for the HPA and HNA devices. Now I will turn over the presentation to Jason, where he will discuss summary of risks to health and classification proposal.

Thank you.

DR. LIU: So we have discussed the safety and effectiveness of these devices and the potential risks assessed in the literature, MDRs, and the recalls. Now I would like to summarize what FDA has identified as the primary risks associated with these devices:

- Patient injury or death due to poor graft survival or function. This can occur from transplantation of incompatible cells, tissue or organ.
- Graft rejection because of transplantation of incompatible cells, tissue or organ.
- Graft versus host disease may develop because of the transplantation of incompatible lymphocytes.

- Incorrect or delayed disease diagnosis due to incorrect test results.
- Transfusion reaction due to incorrect test results.
- Lastly, platelet refractoriness because of incorrect test results.

All of the risks have the potential to threaten the safety of the patients. These identified risks warrant continued regulatory oversight of these devices.

We believe our current premarket review process is important to ensure the generation of correct testing results. So proposed special controls are similar to the current 510(k) review process.

In summary, available scientific evidence indicates that HLA, HPA and HNA devices are important in the setting of transplantation and transfusion and for disease diagnosis. Adequate information indicates that the probable benefits to health from use of these devices outweigh any probable risks.

Available scientific evidence also indicates that these complex devices may generate false positive, false negative, or inconsistent results.

Due to the risks associated with these devices and their complexities, FDA believes that the general controls alone are not sufficient to ensure the safety and effectiveness of these devices. So FDA proposes that special controls are required and that we have sufficient information to establish the

special controls.

So based on the safety and the effective information and identified benefits and the risks, FDA proposes a classification of HLA, HPA and HNA devices as Class II devices subject to special controls together with general controls to mitigate the identified risks.

Here are the proposed special controls. Premarket notification submission for HLA, HPA and HNA devices must include the following information:

- Device accuracy study using well-characterized samples representing as many targets as possible.
- Precision studies to evaluate possible sources of variation that may affect test results.
- Comparison studies to evaluate the device's performance as compared to a predicate.
- Special controls requires specific information that address or mitigate risks associated with false positive antibody reactivity.

The next one requires a description of how the assay cutoff was established and validated.

For the device description incorporating software, software performance and the functional requirements should be provided in the premarket submission, including detailed design specifications.

For multiplex assays in which a large number of probes

and/or primers are handled during manufacturing process, premarket submission should provide the design specifications that are in place to prevent incorrect reactivity assignment.

The eighth special control require a description of a plan on how to ensure the performance characteristics of the device remain unchanged over time when new HLA alleles are identified and/or reactivity assignments are changed.

The labeling should include the device limitations that results should not be used as sole basis for making a clinical decision. The labeling should also clarify that the use of the device as a companion diagnostic has not been established.

The proposed regulation is as follow: Human leukocyte, neutrophil, and platelet antigen and antibody devices.

(a) Identification - Human leukocyte, neutrophil, and platelet antigen and antibody devices consist of HLA, HPA and HNA typing devices and antibody detection devices. These devices are used to aid donor-recipient matching in transfusion or transplantation or to aid in disease diagnosis.

(b) Classification: Class II - These devices must comply with the proposed special controls.

This ends our presentation. Thank you very much. We will answer the questions you may have.

DR. STOWELL: Thank you.

Any questions from members of the Committee of these speakers?

(No response.)

DR. STOWELL: I'm going to take my chairman's prerogative. I have a question. Would you please define again what a companion diagnostic is?

DR. LIU: The companion, that's an HLA device listed as companion diagnostic that's covered by FDA guidance document, in vitro companion diagnostic devices. For example, HLA devices has been used to select patients to -- specific patients to receive immune-mediated cancer treatment. We don't think this discussion should include HLA use as companion diagnostic because in that situation the risk associated with the use of HLA devices is closely related to the corresponding therapeutic products. It will be reviewed and analyzed most likely as a case-by-case situation because it depends on the therapeutic product also.

DR. KOPKO: Okay, Dr. Sullivan and I have a couple of questions. The first is, although we agree with all of the indications that you have indicated these tests are used for, we've come up with a couple more that we think are really important.

First of all, the HLA antigen testing is used for testing in drug hypersensitivity reactions. So, for example, before you give a patient abacavir, you should be testing for HLA-B*5701, because if you do not, they can get a Stevens-Johnson syndrome. And there are a number of drugs like that that you

are supposed to test for a specific allele; in some of them, it's in a specific population. And so we thought that that was another indication.

And then concerning donor-specific antibodies, they're actually now used to test more for monitoring and diagnosing rejection than pre-transplant. We do a whole lot more testing for donor-specific antibodies post-transplant to see if the patient is making an antibody to the organ and to decide if we're going to change immunosuppression or treat for rejection, antibody-mediated rejection based on that, than we do pre-transplant.

DR. LIU: Yes. For using the HLA test to identify patients may suffer a drug hypersensitivity, that would fall under, most likely, under companion diagnostics.

DR. KOPKO: How would --

DR. LIU: Because that would be used to provide critical information regarding the safety and the effectiveness of the corresponding therapeutic product. That's the drug associated.

DR. KOPKO: So is it a companion diagnostic if every clinical lab in the country is doing it?

DR. LIU: I don't think that's really related because it could be a laboratory test or it could be --

DR. KOPKO: No, no. We are using the test that we use for everything else in HLA. All of our other HLA typing, we use for -- just like B27, we do 5701 with our regular testing

reagents.

DR. LIU: Um-hum.

DR. STOWELL: I think this is going to be one of the specific items for discussion, but it probably falls under this incorrect and delayed diagnosis medically related conditions because, you know, if you have this association, you are at risk for this kind of reaction.

DR. LIU: For the second question. Yeah, for disease monitoring and her second question. Because in that situation, it is likely closely related as companion diagnostic regarding -- it depends on what kind of clinical decision we make after transplantation. If you lower the immunosuppression drug or predict outcomes, that's different from decide which donor or which recipient should be -- could be matched.

So that's we consider -- we don't have -- we currently don't have that much information as for the using of HLA device for donor-recipient matching because that's related to what kind of other clinical decision you will make depends on the result.

DR. STRONCEK: On one of the slides it said that these kits have to be labeled with a limitation statement that reads, "The results should not be used as the sole basis for making clinical decisions." But that, in fact, is what's happening. I mean, people don't -- there's no such thing as serologic, you know, in lymphocytotoxicity type testing anymore; it's all

molecular. And if it's in kits, sometimes you confirm it with sequencing; maybe that's in-house developed, that's not a kit, but --

DR. C. SULLIVAN: And now it's very commonplace, institutions to do a virtual cross-match, so they go straight to transplant solely based on the results of the single antigen Luminex assay. So I don't see how people are not using this.

DR. LIU: Maybe I can clarify that statement. We use that statement for the intention to clarify that, to make a decision. For example, donor-recipient matching is not solely dependent on HLA. For example, age, gender. There are other factors they have to consider. HLA is not often the sole basis for making a final decision.

DR. STOWELL: Other questions for the speakers? Dr. Kopko.

DR. KOPKO: I have another question about the slide about proposed special controls. Number 1, device accuracy study using well-characterized samples representing as many targets as possible, how do you do that when you have more than 27,000 HLA alleles? Do you test all 27,000, which, of course, is not possible? So what does that mean, in reality and practice, as a special control?

DR. STOWELL: I'll have to ask people from the FDA to define that.

DR. LIU: Yes, that's actually why we have that kind of

statement there because we understand it's not possible to test all 17,000 or even lower number. However, during the current review process, we often ask the manufacturer to test representatives and as many as possible to cover a broader branch of the specificities.

DR. ILLOH: So my name is Orieji Illoh, just for the records.

So in addition to what Dr. Liu has mentioned, we do ask manufacturers to cover as many as -- we can use the word feasible. What we want to capture are the more common HLA alleles that are commonly seen.

DR. LIU: Yeah. Also, alternatively, if possible, we ask them to validate all the primer/probes. Maybe that's not going to cover all the possible alleles, but that's another possibility because we also realize it's not possible to ask them to cover all the possibility of these alternatives. We consider the burdensome and how much information we need.

DR. LEWIS: So I actually like the language in 1. Would it be correct just to say the motivation is to ensure that the submission addresses the rationale for how many alleles and which alleles are tested? I think it just prevents them from being moot on that. Mute, I should say.

And then that question about the kits as a sole diagnostic, would I be correct in assuming that if you did not have that language, that that triggers other regulatory

requirements, because a diagnostic that is intended to be the sole diagnostic or diagnosis of disease has other requirements that you are hoping not to include?

DR. ILLOH: So I think you're coming back to the issue of companion diagnostics.

DR. LEWIS: I was trying to give you an opportunity to clarify the rationale for requiring the additional language that it must include a statement that the -- it's not used -- to be used as the sole criteria for diagnosis.

DR. ILLOH: Right, so I think what we're trying to clarify here is that the kits are used as an aid, so there are other factors that go into the diagnosis of a particular condition. This is just one of the things that are used. Now, if somebody wanted to use it solely to diagnose or to manage a disease, we might want additional considerations.

(Off microphone comment.)

DR. ILLOH: Yeah, including Class III. So that comes close to the companion diagnostics actually also.

DR. STOWELL: Other questions? Susan.

DR. STRAMER: Yes, going -- I don't know who to address this to, but going back, the proposed special controls, 9, the device labeling must include a limitation statement. Would that -- of the results should not be used as the sole basis for making a clinical decision. I understand that for clinical decision.

Would transfusion, compatibility of a donor, a donation, a platelet donation, be considered -- so I'm asking a question about a screening application versus a clinical decision, and right now we use a negative HLA test to qualify platelets for TRALI risk mitigation. So would that not, then, apply for screening tests or tests used for an indication of blood donation screening? Or is that yet to be determined?

DR. KOPKO: Well, technically, it's not the sole indication. They have to qualify for donation to start with.

DR. STRAMER: Right, but the indication for -- well, I was extending --

DR. KOPKO: Well, I was likening it to what they said about doing a transplant, that, you know, the heart has to fit, the lungs have to fit, so it's not the sole decision. And so if you're qualifying a blood donor, there's a whole lot of other things you do to qualify a blood donor. It's just part of qualifying them, can you use the product.

DR. STRAMER: Okay. So that's intuitive; I mean, one wouldn't have to say that.

DR. STOWELL: Well, I think what they're -- this is probably general language applied to many assays with *Listeria*.

DR. STRAMER: Okay, I was overrating.

DR. STOWELL: And, for example, just because you're HLA-B*2701, or whichever "0" it is, it doesn't mean you have an ankylosing --

DR. STRAMER: The sole criteria.

DR. STOWELL: -- spondylitis and that you shouldn't decide to treat somebody. Similarly, if you have a donor-specific antibody and you're a transplant recipient, you don't get treated for acute humoral rejection; you just have a donor-specific antibody. There are other elements to go into the decision about whether or not the patient needs to be treated.

DR. ILLOH: Point is taken. We'll make sure we address that.

DR. STRAMER: Just really a clarification. May I ask another clarification? It's a regulatory question. When you talked about HLA device recalls and divided them into Class I, II, and III, these devices are not classified as -- unless the Class I, II, and III recalls is different than the way products are licensed.

DR. LIU: You are right, I should have clarified that that -- this recall classification has nothing to do with device classification. The recall in the Class I, Class II, that's very different from the device Class I and Class II.

DR. C. SULLIVAN: I have a question for the first speaker. Under your examples of Class III devices, you list molecular blood typing tests. Well, all the tests that were presented in the typing, the ones that are done for HLA, HPA and HNA, most of them are now classified as molecular typing. So I just want to know the rationale for classifying these differently.

DR. LATHROP: So it's just sort of a general -- for example, if you were just doing a blood typing test and you had one result that this is a Type A unit of blood or something and there's no other information that can tell you what the answer is or how this should be used for the patient, that's a very high-risk indication.

So it wasn't necessarily intended to say this specific one that we're talking about today is used all by itself with no other information except the one result from the one test and you're making a clinical decision based on just that one piece of information. So it's how these are used.

I mean, right now some of these tests are Class III, but it's more of a general way of thinking about how devices are used. There are not very many IVDs that are used as just the only decider for all clinical decision making, but if they are, then they could be considered, if it's a Class III.

DR. STOWELL: Dr. Baker.

DR. BAKER: Yes, thank you.

DR. ILLOH: Can I just add an additional comment about the molecular-based assays for red cell types? So we only have one assay approved so far by FDA that was just approved a couple of years ago. So compared to the HLA technology, which is very familiar to us, for over a couple of years that has been relatively new, it was a new device, and so we handled it as a Class III.

DR. STOWELL: Dr. Baker.

DR. BAKER: Thank you.

So under your listing of special controls that would be required under Item Number 2, it reads, "Precision studies to evaluate possible sources of variation that may affect the test results." So my question is what types of sources do you consider?

DR. LIU: This is closely related to the reproducibility of the test for the variations. For example, we typically consider the entire lot, probably also include day to day, run to run, between instrument, and also between different clinical laboratories. There may be other factors, but these are the major ones we usually consider. To make sure, they consistently generate the same result regardless who runs the assay, which lot, or in which laboratory.

DR. BAKER: Thank you. Perhaps it's my lack of understanding of this topic, but I'm wondering would there be a place to include variation in the population sampled, or these are not populations of people that are sampled?

DR. LIU: So far, for HLA typing, molecular typing, we don't have that much information to request us to asking for population-based because DNA is DNA in most situations. We don't have that information to support us to ask population-based, but that could be a separate topic if the HLA testing is going to be used for, for example, cancer patient selection,

but that's not within the scope of today's discussion.

There may be a request because the DNA from the blood, from cancer, certain cancer cells may -- you may have to consider what kind of mutations you may have may affect, but in this -- for this -- to this discussion, we don't have data to support that request.

DR. STOWELL: I think they're using precision --

DR. BAKER: Thank you.

DR. STOWELL: -- in this instance in sort of the analytic sense, that if you repeat the test 20 times, what's the coefficient of variation for the assay.

DR. LEWIS: So in looking at the list of proposed special controls, it says, "Premarket submissions must include detailed documentation of the following." I'm interpreting that -- the intent to be that detailed documentation, it would be an "all" list. And so I was reading through trying to see if I could come up with an example of a situation where you might want to omit one of these, and the one I'm focusing on is Number 3.

I can picture a situation where there's a breakthrough change in technology or approach, and the device accuracy, using well-characterized samples, is so much better than the predicate that forcing someone to go back and do a population study on the predicate doesn't make sense.

And so I guess my question is, does the Agency retain any flexibility in deciding that there's other information that

makes one of the proposed special controls no longer required, or once this is written as your special controls for this class, are you -- are your hands tied?

DR. LIU: But there could be one situation in which the -- if the -- because for determining whether this new device would be a Class II fit into this proposed regulation, we usually have to compare the intended use and the technology of the new device to the predicate. There's a possibility, if the new device uses a novel technology, we don't know the risks, is we'll not consider we have a predicate for the new device but --

DR. LEWIS: But I'm considering --

DR. LIU: -- it could be automatically Class III.

DR. LEWIS: Right, but I'm considering the opposite situation where it's clearly a much better approach, say, that builds on the technologies for the predicate. I'm asking whether -- I'm looking at the burdensome of -- the burdensome nature of the special controls. And in general, I like them, don't get me wrong here.

My question is whether or not the Agency, when they have a list like this of proposed special controls for a class or for a category, I should say, of device, do you retain the option of being able to decide, in a particular case or cause, that you are willing to omit one of the special controls?

DR. LIU: I think so, but probably they will explain why,

you know, the new technology or the better way to do so.

But maybe, Orieji, you can add in.

DR. ILLOH: I think you're going in the right direction. The answer is yes --

DR. LEWIS: Okay.

DR. ILLOH: -- we can exercise some flexibility.

DR. LEWIS: Okay. So if you propose special controls that you decide later you don't need in a particular case, it's okay?

DR. ILLOH: We can look at it on a case-by-case basis depending on the device.

DR. LEWIS: Thank you.

DR. STOWELL: There will be situations where there are -- you know, perform this Category 6 of licensed tests, and if a new assay comes along and has higher precision, higher sensitivity, higher specificity, and so and so forth, I mean, I think you don't need to do a head-to-head test with them.

Other questions for our speakers?

(No response.)

DR. STOWELL: I don't believe that anyone has signed up for the Open Public Hearing. So if there are --

(Off microphone comment.)

DR. STOWELL: Yeah. So if there is anyone in the audience who would like to speak to this discussion?

(No response.)

DR. STOWELL: Apparently not. Okay, so I would say in light of the hour, why don't we just proceed to our committee discussion, if that's acceptable to everybody? Okay, that's excellent.

I believe that Ms. Mercado is going to present the questions to us; is that correct?

MS. MERCADO: Good afternoon. My name is Teresita Mercado. I'm the Chief of the Devices Review Branch, Division of Blood Components and Devices, Office of Blood Research and Review. Now that we've heard all the presentations, I'm going to walk you through the questions.

1. Following the review of relevant literature, medical device reports, and recalls related to HLA, HPA and HNA devices, FDA has identified the following risks to health when these devices are used for transfusion, transplantation or disease diagnosis:

Patient injury or death due to:

- Poor graft survival or function due to transplantation of incompatible hematopoietic cells, tissue or organ.
- Graft rejection because of the transplantation of incompatible hematopoietic cells, tissue or organ.
- Graft-versus-host disease because of the transplantation of incompatible lymphocytes.

- Incorrect or delayed diagnosis of medically related conditions because of incorrect test results.

- Transfusion reaction, for example, TRALI, due to incorrect HLA, HPA or HNA test results.

- Platelet refractoriness because of incorrect HLA or HPA typing or antibody detection results.

Question 1a: Do you agree that this is a complete and accurate list of the risks to health presented by HLA, HPA and HNA devices?

DR. LEWIS: To address the point that was made, if we can go back one slide? For the third bullet, if we said transfusion reaction or adverse drug reaction --

MS. MERCADO: Um-hum.

DR. STOWELL: Actually, I was thinking the place to put it will be this "Incorrect or delayed diagnosis of medically related conditions."

DR. LEWIS: But that's after the fact, whereas the use that was brought up was as -- well, to assess the risk of a patient of suffering future adverse reaction if a drug is used. So I think it actually goes better, if I may, in the third one where it's to prevent something.

DR. STOWELL: But I think that that category has to do with complications of transfusion, not of drug exposure. So --

DR. LEWIS: Well, if we could perhaps expand the second

bullet that says incorrect or delayed diagnosis? Or incorrect or delayed diagnosis or assessment of future risk.

DR. STOWELL: Okay. Works for me.

DR. LEWIS: Just something to capture that, that --

DR. STOWELL: Sure.

DR. LEWIS: -- pre-risk assessment that was pointed out.

DR. STOWELL: Okay. So is it the sense of the Committee that we would like to amend that second bullet to read incorrect or delayed diagnosis of medically related conditions or assessment of risk? Or risk of adverse outcome, something like that.

DR. KOPKO: Yes, I'd like the risk of adverse outcome because --

DR. STOWELL: Okay.

DR. KOPKO: -- that can cover anything else that could come along.

DR. STOWELL: Yeah. I'm just going to look for assent to that edit. Yes, yes. Okay. So now with that editing, if you could then go to Question 1a there?

MS. MERCADO: 1a?

DR. STOWELL: Yeah. Do we think that this is a complete list of the issues related to these tests? Again, I'm going to go for assent. Any dissenters?

(No audible response.)

DR. STOWELL: Okay, I think the motion is carried by

acclaim in this case.

MS. MERCADO: Okay. We go to Question 1b.

(Off microphone comments.)

DR. STOWELL: Um-hum. I'm sorry?

DR. LEWIS: The murmuring behind me is that we have to vote.

DR. STOWELL: Yeah, we have to vote.

MS. MERCADO: Oh, we have to vote.

DR. STOWELL: Okay. So the item that we have to vote on is 1a, and we are voting on 1a on the amended list, as we just amended it, with the comment about adverse outcomes. And we have to wait for them to set up the electronics so we can vote.

Oh, the Industry Representative.

DR. STRAMER: My only comment, and it's not adverse reactions, but it applies to the specificity of these tests because one of the HLA recalls had to do with poor specificity of the HLA test that we use for donor screening, and that continues. I'm familiar with that particular submission.

So, as far as a complete and accurate list, it's really not risks of health; it may be availability of product if the tests have higher than expected false positive rate. So I don't know where that fits in to any of these questions. And maybe just commenting on it is sufficient.

DR. STOWELL: Then would you propose -- do you have wording you would propose to add?

DR. STRAMER: There is no logical place, the way the question was written. I just, I guess, wanted it to go on record --

DR. STOWELL: Okay.

DR. STRAMER: -- that these tests should be as --

DR. STOWELL: So why don't we note that --

DR. STRAMER: Okay.

DR. STOWELL: -- in the minutes?

DR. STRAMER: Yeah.

DR. STOWELL: Rather than --

DR. STRAMER: You were asking for comments.

(Pause.)

DR. STOWELL: Could you go back one? So I think we want to put "medically related conditions or assessment of future risk of adverse outcomes because of incorrect HLA," so and so. Just take "or assessment," that phrase follows related conditions, "medically related conditions or assessment of future risk of adverse outcomes."

(Pause.)

DR. STOWELL: Right. It has to be HLA, HPA, HNA. It's correct as it is. All you need to do is add, after HLA, comma HPA or HNA. Yeah. Okay?

DR. LEITMAN: Put the word "test" in, "test results."

DR. STOWELL: All right. Now, on to Question 1a. Do you want -- there we go.

MS. MERCADO: Yeah.

DR. STOWELL: All right. So are we ready to take a vote on this? Okay.

(Committee vote.)

LCDR EMERY: Does the Industry Representative have anything, any comments at this time?

DR. STRAMER: None.

LCDR EMERY: All right, thank you.

Dr. Sullivan, before we show the results, if you could come off of mute and tell me what your vote is. Yes, abstain, or no.

DR. K. SULLIVAN: Can you hear me? My vote is yes.

LCDR EMERY: I can hear you. Do we have all the votes in? The Committee has voted, and I will read the individual votes into the official record.

Dr. Stowell is yes.

Dr. Sullivan, Kathleen Sullivan, by phone, is yes.

Dr. DeMaria is yes.

Dr. DeVan is yes.

Dr. Escobar is yes.

Dr. Leitman is yes.

Dr. Lewis is yes.

Dr. Rees is yes.

Dr. Stapleton is yes.

Dr. Basavaraju is yes.

Dr. Kindzelski is yes.

Dr. Stroncek is yes.

Dr. Kopko is yes.

Dr. Cliff Sullivan is yes.

There are 14 yeses, and there are no "no" votes, and no abstentions.

DR. STOWELL: Okay, Ms. Mercado.

MS. MERCADO: Okay. We go to Question 1b: If you --

DR. STOWELL: I think we've already basically done that. We already --

MS. MERCADO: Okay.

DR. STOWELL: We already changed that, fixed that.

MS. MERCADO: Okay. This is the process that we are following for this classification panel meeting. The first question we ask is: Are general controls alone sufficient to provide a reasonable assurance of safety and effectiveness? If the answer is yes, then the device is classified as a Class I device. If the answer is no, then we ask this question: Is the device life-supporting or life-sustaining or of substantial importance in maintaining human health, or does the device present a potential and a reasonable risk of illness or injury? If the answer is yes and there are no information available to establish special controls to mitigate the risk, then the device is classified as Class III. If, on the other hand, the answer is yes but there is sufficient information to establish

special controls to mitigate the risk, then the device is classified as a Class II device.

Okay, this is Panel Question 2a: FDA believes that general controls alone are not sufficient to provide a reasonable assurance of safety and effectiveness for HLA, HPA and HNA devices.

i. Do you agree with this assessment?

ii. If not, please discuss how general controls alone are not sufficient to provide a reasonable assurance of safety and effectiveness for HLA, HPA and HNA devices.

So there are two questions, so --

DR. STOWELL: So the first question to us is what do we think about this assessment? Do we agree with the FDA that general controls are not sufficient, which would mean that special controls would be required? Any further discussion?

(No response.)

DR. STOWELL: I think we're ready to vote.

(Committee vote.)

DR. STRAMER: Dr. Stowell, I have no further comment.

DR. STOWELL: At the next meeting, I would prefer if you just sit next to me.

LCDR EMERY: Dr. Sullivan on the phone, do you -- can you vote? Can you tell me your vote at this time?

DR. K. SULLIVAN: Yes, I vote yes.

LCDR EMERY: Yes, all right. The Committee has voted in majority. I will read the individual votes into the record.

Dr. Stowell is yes.

Dr. Kathleen Sullivan, by phone, is yes.

Dr. DeMaria is yes.

Dr. DeVan is yes.

Dr. Escobar is yes.

Dr. Leitman is yes.

Dr. Lewis is yes.

Dr. Rees is yes.

Dr. Stapleton is yes.

Dr. Basavaraju is yes.

Dr. Kindzelski is yes.

Dr. Stroncek is yes.

Dr. Kopko is yes.

Dr. Sullivan is yes.

There are 14 yeses, there are 0 noes, and 0 abstentions. Thank you.

MS. MERCADO: Okay, this is Question 2b: Under the Federal Food, Drug, and Cosmetic Act, a device is potentially Class III if it is life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health. FDA believes that HLA, HPA and HNA devices are not life-supporting or life-sustaining.

i. Do you agree with this assessment?

ii. If not, please explain why HLA, HPA and HNA devices are life-supporting or life-sustaining.

DR. STAPLETON: I'd like to re-raise the issue that was brought up earlier about HLA-B*5701 for abacavir hypersensitivity. It seems to me that that is definitely a life -- or of substantial importance for preventing impairment of human health. So I don't know what other people feel about that, but at least in that HLA instance, I would say it is.

DR. STOWELL: Dr. Sullivan.

DR. C. SULLIVAN: And I would say, just under the previous presenter and their list of summary of risks, they list antibody-mediated rejection, graft-versus-host disease, incorrect or delayed diagnosis. I mean, I would think that would be -- those were all under an impairment of human health.

DR. LEWIS: But, Chair, if I may? That's not this question; that's the next question. This is carefully worded to only ask us about the first two of the three categories here.

MS. MERCADO: That's correct.

DR. C. SULLIVAN: So I'm interpreting the question is only asking us if we believe that it is correct that these tests are not life-supporting or life-sustaining, nothing about impairment of human health?

DR. STAPLETON: The HLA-B*5701, to me, it seems important in preventing impairment of human health.

DR. LEWIS: But this question is not asking that.

DR. STOWELL: Okay.

DR. LEWIS: We're jumping to the question that's interesting.

DR. STOWELL: All right.

DR. LEWIS: We have to get through the one that's not.

DR. STOWELL: The other aspect is that, looking at examples, I find this a little bit confusing, because looking at some of the examples, some of the devices which are classified like this are intra-aortic balloon pumps and heart valves, and these tests are not in that category. On the other hand, we have the sort of anomaly of the RBC antigen testing, molecular testing for RBC genotyping is falling into that category. Now, the explanation they've given us is that the technology for that is considerably newer than the technology for HLA genotyping and so forth, so I don't know.

Somebody from the FDA may want to clarify this a little bit to help us sort of come to a decision about whether this should be a Class III or a Class II device.

DR. EPSTEIN: I think we have to read ahead to understand what's going on here. What you're really being asked is, would this be Class III if not for the adequacy of special controls? And there's a whole set of criteria that would make a product Class III. And so if you come to Question 2c, you'll see there's another criterion for Class III; if you come to the

next part, (d), there's another criterion for Class III. So we're sort of asking you, well, if it's not Class I but it would be Class III, do you think the special controls are adequate, therefore it's Class II? But in order to get there, you have to first tell us whether it would otherwise be Class III. So it needs to have met, you know, one or another of the Class III criteria.

Now, FDA's view is that when we say is it preventing -- life-threatening, right? Right. We think that what you're really talking about is whether it's of substantial importance, which is in (c), of substantial importance for preventing impairment of human health. That's in the next part, 2c. We think it falls under 2c. But if you feel it falls under 2b, well, we entertain your opinion.

But what we're really trying to figure out is would it be Class III if not for special controls. So it's got to meet one or the other criteria, and there's three of them.

DR. STOWELL: So what you're saying is that we could say yes, these test systems are life-supporting, life-sustaining, or of substantial importance --

DR. EPSTEIN: Yeah.

DR. STOWELL: -- so and so forth, but doesn't mean necessarily that they'll end up classified as a III.

DR. EPSTEIN: That's correct. But, again, FDA's opinion, looking at all the devices, mostly in CDRH, we would say this

isn't in this category of life-supporting or life-sustaining. I mean, after all, when people -- we didn't even have HLA testing, right?

DR. STOWELL: I mean, my feeling, again, this is not in the same league as valves and -- this is not in the same league as heart valves and some of the other devices that were -- yeah, that were listed.

DR. EPSTEIN: Again, I think the Committee will feel comfortable once we get to 2c.

DR. STOWELL: Dr. Kopko.

DR. KOPKO: I think I can probably help you with the distinction between this and molecular testing for red cell antigens. When we test for HLA antigens, if we find a new sequence, we give it a different name. With ABO, we don't know all the different sequences, and we don't know what sequence equals how that transferase is going to function, so we don't know whether you're going to get an A or B or an O given a specific sequence. So to me, that's a big reason, in addition to the fact that the molecular typing for ABO is so new, that it would be a different classification.

DR. STOWELL: That seems like a reasonable thought. Any additional discussion or thought about this?

(No response.)

DR. STOWELL: Okay, so the question under consideration is, do we agree with the FDA assessment that these devices are

not life-supporting or life-sustaining?

(Committee vote.)

LCDR EMERY: Dr. Kathleen Sullivan, how do you vote?

DR. K. SULLIVAN: I do agree. I think it's a -- I think it's -- yeah, I'll stop there. I agree.

LCDR EMERY: I think we might have lost you.

(Off microphone comment.)

LCDR EMERY: Oh, she said yes. Sorry.

Question 2b, the Committee has voted in majority. I will read the individual votes for the record.

Dr. Stowell, no.

Dr. Kathleen Sullivan, by phone, is yes.

Dr. DeMaria is yes.

Dr. DeVan is yes.

Dr. Escobar is yes.

Dr. Leitman is yes.

Dr. Lewis is yes.

Dr. Rees is yes.

Dr. Stapleton is yes.

Dr. Basavaraju is yes.

Dr. Kindzelski is yes.

Dr. Stroncek is yes.

Dr. Kopko is yes.

Dr. Sullivan is yes.

There are 14 votes total. There are 13 yeses, there is 1

no, and there is 0 abstentions.

DR. STOWELL: Okay. Ms. Mercado.

MS. MERCADO: Okay, sure. Okay, now we move to Question 2c: Under the Federal Food, Drug, and Cosmetic Act, a device is potentially Class III if it is of substantial importance in preventing impairment of human health. FDA believes that HLA, HPA and HNA devices are of substantial importance in preventing impairment of human health.

i. Do you agree with this assessment?

ii. If not, please explain why HLA, HPA and HNA devices are not of substantial importance in preventing impairment of human health.

DR. STOWELL: Any discussion?

(No response.)

DR. STOWELL: I think we can probably go ahead and vote on this.

(Committee vote.)

DR. DeMARIA: Can I just clarify? So we're saying it's Class III?

MS. MERCADO: It's potentially Class III.

DR. DeMARIA: Potentially. But not -- okay.

MS. MERCADO: Right.

LCDR EMERY: Dr. Sullivan, how do you vote on 2c?

DR. K. SULLIVAN: I vote yes.

LCDR EMERY: All right, thank you.

The Committee has voted in majority, and I will call out, for the record, the individual votes.

Dr. Stowell, yes.

Dr. Sullivan, yes.

Dr. DeMaria, yes.

Dr. DeVan, yes.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, yes.

Dr. Rees, yes.

Dr. Stapleton, yes.

Dr. Basavaraju, yes.

Dr. Kindzelski, yes.

Dr. Stroncek, yes.

Dr. Kopko, yes.

Dr. Cliff Sullivan, yes.

There are 14 yeses, there are 0 noes, there are 0 abstentions. Thank you.

DR. EPSTEIN: Excuse me, Bryan, but --

LCDR EMERY: Yes.

DR. EPSTEIN: -- we're interested to hear the opinion of negative votes, and I know at the risk of going in reverse gear to lay it out, Dr. Stowell voted against 2b, and I think we would just like to hear the explanation for the record.

DR. STOWELL: I voted no on 2b.

DR. EPSTEIN: Correct, which means you disagreed with the FDA.

DR. STOWELL: Yes, that you said that they -- your statement was that you thought these devices were not life-supporting or life-sustaining, and I think that they are.

DR. EPSTEIN: Okay, well, that's the vote itself. We're interested in the rationale. But, you know --

DR. STOWELL: Well, yes, because important decisions are made --

DR. EPSTEIN: Yeah.

DR. STOWELL: -- based upon this information --

DR. EPSTEIN: Okay.

DR. STOWELL: -- and if the information is incorrect, very adverse outcomes can result from that.

DR. EPSTEIN: Okay, fair enough.

DR. STOWELL: Ms. Mercado.

MS. MERCADO: Okay. We go on to Question 2d: Under the statute, a device is potentially Class III if it presents a potential unreasonable risk of illness or injury. Considering the risks and benefits of these devices, FDA believes that HLA, HPA and HNA presents unreasonable risk of illness or injury. (Note that such a device may still be classified as Class II if application of special controls would provide reasonable assurance of safety and effectiveness.)

i. Do you agree with this assessment?

ii. If not, please explain why HLA, HPA and HNA devices are not for a use which presents a potential unreasonable risk of illness or injury.

DR. STOWELL: Any comments from the Committee?

(No response.)

DR. STOWELL: Are we ready to vote? Okay.

(Committee vote.)

DR. STOWELL: Does the Industry Representative have anything to say on this? All right.

DR. STRAMER: No.

LCDR EMERY: Thank you.

Dr. Sullivan, how would you vote?

DR. K. SULLIVAN: I vote yes.

LCDR EMERY: The Committee has voted in majority. I will read the individual votes for the record.

Dr. Stowell, yes.

Dr. Sullivan, yes.

Dr. DeMaria, yes.

Dr. DeVan, yes.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, yes.

Mr. Rees, yes.

Dr. Stapleton, yes.

Dr. Basavaraju, yes.

Dr. Kindzelski, yes.

Dr. Stroncek, yes.

Dr. Kopko, yes.

Dr. Sullivan, yes.

There are 14 yeses, there are 0 noes, there are 0 abstentions.

MS. MERCADO: Okay, Question 2e.

DR. STOWELL: Yes, ma'am.

MS. MERCADO: FDA believes sufficient information exists to establish special controls for HLA, HPA and HNA devices. FDA is proposing the following special controls that would provide reasonable assurance of safety and effectiveness:

1. Premarket submissions must include detailed documentation of the following information:

i. Device accuracy study using well-characterized samples representing as many targets as possible.

ii. Precision studies to evaluate possible sources of variation that may affect test results.

iii. Comparison studies to evaluate the device's performance compared to a predicate.

iv. Specific information that address or mitigate risks associated with false positive antibody reactivity. For example, reactivity

with denatured/cryptic epitopes, if applicable.

v. Description of how the assay cutoff was established and validated, as well as supporting data.

vi. Documentation for device software, including, but not limited to, software requirement specifications, software design specifications, for example, algorithms, alarms and device limitations; hazard analysis, traceability matrix, verification and validation testing, unresolved anomalies, hardware/software specifications; EMC and wireless testing.

vii. For multiplex assays in which large numbers of probes and/or primers are handled during the manufacturing process, premarket submission should provide the design specifications that are in place to prevent incorrect reactivity assignment.

viii. Description of a plan on how to ensure the performance characteristics of the device remain unchanged over time when new HLA alleles are identified and/or reactivity assignments are changed from the assignments at the time the device was evaluated.

2. Premarket submissions must include detailed

documentation of the following information:

i. A limitation statement that reads, "The results should not be used as the sole basis for making a clinical decision."

ii. A warning that reads "The use of this device as a companion diagnostic has not been established."

Question 2f: Based on the information presented today, do you agree that sufficient information exists to establish special controls that can provide a reasonable assurance of safety and effectiveness of HLA, HPA and HNA devices? If not, please explain why.

DR. STOWELL: So I don't think this is an item actually we were supposed to vote on, I think just to comment, is what they're looking for here.

(Off microphone comment.)

DR. STOWELL: Oh, because (f) is what's here, I'm sorry.

MS. MERCADO: 2f.

DR. STOWELL: All right. So then we can go to (g), that's fine with me, if we could just go to the next one. This is -- 2g is a voting item. There we go.

MS. MERCADO: No, 2f is also a voting item.

DR. STOWELL: I'm sorry?

DR. LEITMAN: FDA says we should vote on 2f.

MS. MERCADO: 2f.

DR. STOWELL: Okay. So the question, then, do we think that there is adequate information to make -- to establish special controls, would provide a reasonable level of assurance of safety and efficacy, effectiveness of these devices? And if we do not think that, then to explain why not. So please vote.

(Committee vote.)

LCDR EMERY: Dr. Sullivan, how would you vote for 2f?

DR. K. SULLIVAN: Yeah, 2f. So I noticed it's covered somewhat, but I'm going to vote no because I just don't see that all of these are feasible, and maybe if there had been a little commentary before the vote, I could've gotten some feedback. But, to me, a lot of what's being requested seems to require people to predict things in the future and to talk about things that they couldn't foresee. So I'm unfortunately going to vote no.

LCDR EMERY: Thank you for your vote.

Does Industry have anything that they want to add?

DR. STRAMER: No.

LCDR EMERY: Thank you.

The Committee has voted. I'll read the individual votes.

Dr. Stowell, yes.

Dr. Kathleen Sullivan, no.

Dr. DeMaria, yes.

Dr. DeVan abstained.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, yes.

Mr. Rees, yes.

Dr. Stapleton, yes.

Dr. Basavaraju, yes.

Dr. Kindzelski, yes.

Dr. Stroncek, yes.

Dr. Kopko, yes.

Dr. Sullivan, yes.

There were 14 votes. There are 12 yeses, 1 abstention, and 1 no vote.

MS. MERCADO: Okay, we move on to Question 2g: Do you agree that the list in 2e.1 is a complete and accurate list of the special controls needed to provide reasonable assurance of safety and effectiveness for HLA, HPA and HNA devices? If you disagree, please comment on what additional special controls are needed or explain which, if any, of the proposed special controls are not needed.

DR. STOWELL: Any commentary?

DR. K. SULLIVAN: I would like to see, in 1, "The device accuracy studies and well-characterized samples representing as many targets as possible" changed to "as feasible," because if we go for as many as possible, we will never get an HLA test approved.

DR. STOWELL: So our recommendation is to change the word

to "feasible."

DR. EPSTEIN: We accept that.

DR. STOWELL: Okay.

DR. ESCOBAR: Is quality control included here at all, you know, for these devices? Do we need to have quality control, you know, to make sure there are --

MS. MERCADO: Yes.

DR. STOWELL: Yes, that's already assumed.

DR. ESCOBAR: I mean, is that implied here?

MS. MERCADO: For -- yes.

DR. ESCOBAR: For the devices in general.

MS. MERCADO: Yes, we do. Our quality control is actually kind of a separate, you know, device, but we do expect the test to have quality controls before, you know, you should report the test results.

DR. STOWELL: Other discussion?

(No response.)

DR. STOWELL: I think we're ready to vote.

DR. LEWIS: I'm sorry. I was reassured by the prior discussion that the list of special controls had some potential for flexibility depending on the specifics of the device that is proposed, and yet, 2g seems to be asking us to weigh in on whether this is exactly the right list. It has a certain concreteness to it, complete and accurate.

So I will make a decision in the next 30 seconds how I'm

going to vote, but if I choose to abstain, it will be because I was more reassured by the Agency retaining the right to have some flexibility than the need for us to certify this as the absolutely correct list.

DR. STOWELL: Okay. Other comments?

DR. DeMARIA: I agree with that comment. Would it be possible to say sufficient and accurate list? Because as more is learned, there may be changes anyway, and this is sufficient for the present. Or does that have regulatory problems?

DR. STOWELL: Does the group think that "sufficient" is a better word than "complete"?

(No audible response.)

DR. STOWELL: Okay, so we'll change the wording on (g) to say that the list in e.1 is a sufficient and accurate list.

DR. BASAVARAJU: If something is not on that list but at some later date it becomes evident that something should be on that list, just because we voted on that list doesn't mean that FDA can't add to it, right?

DR. EPSTEIN: The implication here is that we will promulgate a regulation and the special controls will be listed in the regulation. Now, we can always revisit a regulation, but what's at issue here is your advice to us, whether these are things that belong in the regulation.

DR. BASAVARAJU: But you could -- before you write the regulation and it goes, you know, becomes final --

DR. EPSTEIN: Yeah.

DR. BASAVARAJU: -- you can add something else to it, right?

DR. EPSTEIN: Absolutely. Or afterward, we could amend the regulation. But the point is you're advising us whether this is, if you will, a suitable list for the regulation. It's nothing under the process because they will be, you know, a public process. We post it as a draft, we get further comments, we consider your advice, we consider the comments, and then we promulgate a final regulation. And if we learn new things later, we can change the regulation. But you're advising us whether this is a suitable list to go in the regulation.

DR. STOWELL: Could we go back to 2g, please? All right, this is the revised wording. Further discussion? Yes.

DR. LEWIS: Just to state the obvious for the record, if, in the case of a review of a particular device, the Agency decided that an additional special control was required for that device, the Agency retains the right to ask for that prior to clearance without revising the regulation; is that correct?

DR. ILLOH: If we think there is a significant risk, I mean, we can always call it a Class III. We have that option. If we think there's something so different about the device that our special controls that we have currently will not be able to address the risk, we can make it a Class III until

we --

DR. LEWIS: So I understand that, but I actually want the specific question that I asked answered.

DR. ILLOH: Um-hum.

DR. LEWIS: Do you have the option of retaining it as a Class II, asking for a special control that was not in the original list of regulations to enable you to clear the device?

DR. ILLOH: Yes, it depends. I think it depends. It depends on how much risk.

DR. EPSTEIN: Yeah. What you're getting into is how regulations work. You know, regulations have the force of law. You violate a regulation, you know, it's violated, period. Right? If something goes beyond the regulation, it's a battle of the experts; there's our opinion, there's the industry's opinion. They either comply voluntarily or they don't, or they litigate or they don't. But do we have the ability to ask for additional controls? Yes, we do.

DR. STOWELL: If there's no further discussion, let's vote on this.

(Committee vote.)

MS. MERCADO: Okay, this is the final question, 2h: Do you agree that the --

LCDR EMERY: Wait, wait, wait. We're voting on 2g right now.

MS. MERCADO: Oh, sorry.

LCDR EMERY: And I'm going to ask Dr. Kathleen Sullivan how you will vote on 2g.

DR. K. SULLIVAN: I'm going to abstain on this one. I think the stipulations are actually subject to wide variation and interpretation, and I just can't figure out how this would play out in real life, so I'm abstaining.

LCDR EMERY: Thank you.

(Off microphone comment.)

LCDR EMERY: They need us to revote.

DR. STOWELL: So are we re-voting on (g), or are we now moving on to (h)?

LCDR EMERY: We have to see (g), and I have to read into the record.

DR. STOWELL: Okay.

LCDR EMERY: And then on to --

DR. STOWELL: So we're still waiting to see 2g?

LCDR EMERY: Correct.

(Off microphone comments.)

DR. STOWELL: Say again?

UNIDENTIFIED SPEAKER: You haven't voted yet.

DR. STOWELL: I thought I did.

(Committee vote.)

LCDR EMERY: The Committee has voted in majority. I will read the individual votes for the record.

Dr. Stowell is yes.

Dr. Kathleen Sullivan is abstained.

Dr. DeMaria is yes.

Dr. DeVan is yes.

Dr. Escobar is yes.

Dr. Leitman is yes.

Dr. Lewis is yes.

Mr. Rees is yes.

Dr. Stapleton is yes.

Dr. Basavaraju is yes.

Dr. Kindzelski is yes.

Dr. Stroncek is yes.

Dr. Kopko is yes.

Dr. Sullivan is a yes.

There are 14 votes total. There are 13 yeses, there is 1 abstained vote, and there are 0 noes.

MS. MERCADO: Okay, we move on to the last question, 2h: Do you agree that the Agency's proposed classification for HLA, HPA and HNA devices as Class II with special controls will provide reasonable assurance of safety and effectiveness? If you disagree, please discuss why special controls are not adequate to assure safety and effectiveness of HLA, HPA and HNA devices.

DR. STOWELL: Any discussion of 2h? Comments?

(No response.)

DR. STOWELL: All right. Then let's vote.

(Committee vote.)

LCDR EMERY: Dr. Sullivan, how would you vote?

DR. K. SULLIVAN: I vote yes.

LCDR EMERY: Does Industry have anything to say at the last vote?

DR. STRAMER: No.

LCDR EMERY: Thank you.

DR. STRAMER: Nothing to say.

LCDR EMERY: The Committee has voted in majority. I'll read the individual votes into the official record.

Dr. Stowell, yes.

Dr. Sullivan, yes.

Dr. DeMaria, yes.

Dr. DeVan, yes.

Dr. Escobar, yes.

Dr. Leitman, yes.

Dr. Lewis, yes.

Dr. Rees, yes.

Dr. Stapleton, yes.

Dr. Basavaraju, yes.

Dr. Kindzelski, yes.

Dr. Stroncek, yes.

Dr. Kopko, yes.

Dr. Sullivan, yes.

There are 14 yeses, there are 0 noes, and 0 abstentions.

Thank you.

DR. STOWELL: So thanks to the Committee for a very long and arduous day, and to the members of the FDA and the public who have stuck it out with us all day long. I declare this meeting adjourned.

(Whereupon, at 5:58 p.m., the meeting in the above-entitled matter was continued, to resume the next day, Friday, December 1, 2017, at 8:00 a.m.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

116TH MEETING OF THE BLOOD PRODUCTS ADVISORY COMMITTEE

November 30, 2017

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Biologics Evaluation and Research.

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Shaylah Lynn Burrill

Official Reporter