FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)

119th Meeting of the

Blood Products Advisory Committee

July 18, 2018

FDA White Oak Campus
Great Room B
10903 New Hampshire Ave.
Silver Spring, MD 20993

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PROCEEDINGS (8:00 a.m.)

Agenda Item: Call to Order and Opening Remarks/Introduction of Committee

DR. ALLEN: Good morning. I would like to call the meeting of the July 18, 2018 Blood Products Advisory Committee to order. It is now 6 minutes after 8. I'm Dr. James Allen, the acting chair of this panel for today. I'm a physician trained in public health, spent 20 years with the U.S. Public Health Service, much of it at the Centers for Disease Control, background in hospital infection control, HIV and AIDS, subsequently moved more into administrative stuff, retired from the public health service and had a variety of activities including being the director of health for the state of Arizona for a couple of years, and retired doing public health education. I've been a member of the board of trustees for Blood Systems, Incorporated, for 17 years before being age retired from that in 2016.

I would note for the record that the members of this committee today present -- we do constitute a quorum as required by 21 CFR part 14. I would also like to add that the panel participating in the meeting today has received training in FDA device law and regulations. For today's agenda, the committee will discuss strategies to control the risk of bacterial contamination in platelets

for transfusion. There is not a primary question to answer. It's a discussion of where we are now and where we need to go.

Before we begin, I would like to ask our distinguished panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation and do so as briefly as possible.

Dr. Baker, would you start, please?

DR. BAKER: Thank you. My name is Judith Baker. My expertise is in public health. I serve as the public health director for the Center for Inherited Blood Disorders. I'm also affiliated with UCLA, Division of Pediatric Hematology/Oncology, and I work primarily in hemophilia and sickle cell disease.

DR. DEMARIA: Al DeMaria. I'm a medical and laboratory consultant at the Massachusetts Department of Public Health.

DR. DEVAN: Michael DeVan. I'm the medical director of transfusion service at Walter Reed National Military Medical Center.

DR. ESCOBAR: Miguel Escobar, hematologist, University of Texas, director of the Hemophilia and Thrombosis Center.

DR. LEITMAN: Susan Leitman, expertise in transfusion medicine, for 30 years deputy director of the Department of Transfusion Medicine at the Clinical Center at NIH, currently with the Medical Scholars Research Program in the Clinical Center at NIH.

DR. LEWIS: Roger Lewis. I'm professor and chair in the Department of Emergency Medicine at Harbor-UCLA Medical Center in Los Angeles. My expertise is in clinical trial design and statistics.

MR. REES: Robert Rees. I am the manager of the New Jersey state blood bank regulatory and compliance program. My expertise is pretty much in public health and transfusion medicine.

DR. STRAMER: Good morning. Susan Stramer, American Red Cross, vice president of scientific affairs. My expertise is in infectious disease testing, and I was trained as a public health microbiologist.

DR. HARRELL: Lizzie Harrell, I am formerly the associate director of clinical microbiology at Duke University Medical Center. I am now a research professor emeritus of molecular genetics and microbiology at Duke University, and my expertise is clinical microbiology.

DR. ALVING: I am Barbara Alving. I am formerly the director of the Blood Division at NHLBI and acting director. I am a professor of medicine at Uniformed

Services University, retired colonel, expertise is in bleeding and clotting disorders.

DR. SCHREIBER: My name is Martin Schreiber. I am the chief of trauma at Oregon Health and Science University, and I give people a lot of blood.

DR. KAUFMAN: My name is Richard Kaufman. My expertise is in transfusion medicine, and I'm the medical director for the transfusion service at the Brigham and Women's Hospital in Boston.

DR. CALIENDO: I'm Angie Caliendo. I'm professor and vice chair of medicine at Brown, and my expertise is in infectious diseases and clinical microbiology.

DR. ALLEN: Thank you all. If you have not already done so, please sign the attendance sheets that are on the tables by the doors. Lieutenant Commander Bryan Emery, the designated federal officer for this meeting, will make some introductory remarks.

MR. EMERY: Before I get started, is Dr. Jones on the phone?

DR. JONES: Yes, this is Jefferson Jones. Trained in pediatrics and public health especially in infectious disease, epidemiology, and outbreak investigations. Thank you. With CDC.

MR. EMERY: Thank you, Dr. Jones.

Agenda Item: Conflict of Interest Statement

MR. EMERY: Good morning. I am Bryan Emery. I'm the designated federal official for today's July 18, 2018 meeting of the Blood Products Advisory Committee. Mrs. Joanne Lipkind is the committee management specialist, and she and Angelica can assist you with any of your needs at the tables located in the hall. Also, working with them is my division director Dr. Atreya and they can answer any of your needs at this time.

I would like to welcome all of you today to the 119th meeting of the advisory committee held in the FDA White Oak Great Room. Dr. James Allen is our acting Blood Products Advisory Committee chair for today. The CBER press media contact is Ms. Megan McSeveney, who is in the audience, I believe. Actually, I do not see her at this time, and Chandra Chhay is our transcriber.

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

Coffee, drinks, and snacks are out the door and to the right, located at the kiosk. Members lunches will also be brought to the back of the kiosk right before we

break for lunch, and we will have reserved a back room for the members to eat at. These lunches must be purchased ahead of time at the kiosk. There are restrooms out the doors and to the right at the end of the hall.

All committee topic discussion needs to be done in a public forum and not in groups during breaks. The FDA and public need your advice, thoughts, and expertise. There are also two public written statements that can be viewed at the table outside the meeting room today.

The public and industry must stay behind the stanchions and in the audience area. Please do not enter into the FDA or Blood Products Advisory Committee area. Please wait until the open public hearing designated time to make any remarks, using the center aisle microphone when invited by the chair.

Now I would like to read into record, the public record, the conflict of interest statement for this meeting.

Good morning, everyone, I am Lieutenant Commander Bryan Emery, the designated federal officer for this Blood Products Advisory Committee meeting of the Center for Biologics Evaluation and Research. FDA and I welcome you all to the 119th meeting of the Blood Products Advisory Committee being convened by the Food and Drug Administration both today, July 18, 2018, and tomorrow,

July 19, 2018, 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 today. In the open session, the committee will discuss topic I, the bacterial risk control strategies for blood collection establishments and transfusion services to enhance the safety and availability of platelets for transfusion. Tomorrow on July 19, 2018, the committee will function as a medical device panel and meet in open session to discuss and advise on topic II, the device reclassification from class III to class II of nucleic acid serology-based point of care and laboratory-based in vitro diagnostic devices indicated for the use as aids in the diagnosis of human immunodeficiency virus infection.

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 representatives, 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 and minor children, and, for the purposes of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents, and royalties and primary employment. FDA has determined that all members of the 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 which, 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. James Allen is a temporary voting member and serving as the acting chairperson for topic I. He is an appointed special government employee. His financial interests were screened and cleared prior to his participation in this meeting.

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. Industry representatives are not appointed special government employees and, hence, they are not voting members and they do not participate in closed sessions.

Dr. Judith Baker is a voting member and is serving as the consumer representative for topic I during this meeting. She is employed by Western States Regional Hemophilia Network and Policy. Dr. Baker is appointed as a special government employee and therefore is screened for her financial conflict of interest and cleared prior to her participation.

At this meeting, there may be invited regulated industry guest 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 interest.

FDA encourages all other participants to advise the committee of any financial relationships that you may 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 July 18 and 19 BPAC meeting. Please note that each of the topics, namely topic I and II of this meeting are determined to be a particular matter of general applicability and, as such, does not focus its discussion on any particular product but instead focuses on the classes of products under discussion.

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, and any discussion of individual products will be only to serve as an example of the product class. This meeting of the BPAC does not involve the approval or disapproval, labeling requirements, post-marketing 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 this meeting over to Dr. Allen.

DR. ALLEN: Thank you. We will now begin our discussion with the formal presentations on the strategies to control the risk of bacterial contamination in platelets for transfusion. Dr. Jones, since you are on the telephone, during the discussion periods, if you want to make a comment or ask a question, please sing out, because I can't see you requesting recognition.

Our first speaker today is Dr. Emily Storch who will introduce the topic for us. She is with Office of Blood Research and Review, Food and Drug Administration.

Agenda Item: TOPIC I: Strategies to Control the Risk of Bacterial Contamination in Platelets for Transfusion

Introduction to Topic

DR. STORCH: Good morning. My name is Emily Storch, and I'm a medical officer in the Division of Blood Components and Devices. Today, I will be providing an introduction on this morning's topic, Strategies to Control the Risk of Bacterial Contamination in Platelets.

The issue for discussion is that bacterial contamination of platelets remains a concern. While the Blood Products Advisory Committee has previously discussed some strategies to reduce bacterial contamination in platelets, there has not been an opportunity for the committee to discuss all available strategies in one session. These strategies include culture-based methods, rapid-testing methods, and pathogen reduction technology.

FDA intends to issue a revised draft guidance on strategies to control the risk of bacterial contamination in platelet products. The specific question for the committee is to please comment on the advantages and disadvantages of each of the various strategies to control the risk of bacterial contamination in platelets, including the scientific evidence and the operational considerations involved.

For some background, bacterial contamination of platelets remains a leading cause of septic transfusion reactions and fatalities. Platelet storage conditions are conducive to bacterial growth for multiple reasons, among them that platelets are stored at room temperature with agitation and in oxygen permeable bags. To address this issue, blood establishments have implemented various strategies to reduce the risk.

FDA has also taken steps to address this issue. The regulation on control of bacterial contamination in platelets is found in 21 CFR 606.145(a) which states 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 by FDA. FDA states in the preamble to this regulation that this requirement can be met by testing for bacterial contamination or pathogen reduction.

FDA's efforts to address the risk of bacterial contamination in platelets include a BPAC meeting held in 2012 where it was determined that additional measures were needed for 5-day platelets. The committee advised secondary rapid testing on day 4 or 5.

This was followed by a draft guidance published in 2014 with recommendations including BPAC's 2012 advice.

In March 2016, FDA revised the draft guidance to include pathogen reduction of 5-day platelets and 7-day storage when platelets are retested with a device labeled as a safety measure.

In May 2016, the donor eligibility rule became effective, including 21 CFR 606.145, requiring the control of bacterial contamination of platelets. Most recently, a BPAC was held in November of 2017, where additional culture based strategies were presented based on comments to the 2016 draft guidance and newly available data. The committee supported additional culture-based strategies. At this meeting today, we will ask the committee to discuss all available strategies to control the risk of bacterial contamination in platelets.

Current platelet dating is a maximum of five to seven days, based on the preparation method, storage container, and bacterial testing. For 5-day storage, primary culture is performed no earlier than 24 hours after collection, or the platelets are treated with an FDA approved pathogen reduction device within 24 hours of collection. For 7-day storage, primary culture is performed as well as additional secondary testing, using a test labeled as a safety measure when collected into an appropriately labeled container.

Although several strategies to control the risk of bacterial contamination of platelets are available, common practice in the United States is to perform primary culture alone. This method generally uses only aerobic media. The sample size is 8 to 10 milliliters, taken at least 24 hours after collection. The culture is incubated at least 12 hours and found negative before distributing components.

Looking at bacterial contamination of platelets through fatalities reported to the FDA of septic reactions from apheresis platelets, you can see that existing strategies have reduced the number of fatalities but risk remains. This reduction in risk coincides with AABB's standard 5.1.5.1, which became effective in 2004, calling upon blood establishments and transfusion services to limit and detect bacterial contamination of platelets.

As you can see from the graph, before full implementation of the standard, there were six to eight fatalities per year, whereas after full implementation around 2005, fatalities decreased to zero to four per year. Data show that with current primary culture practice, bacteria are detected in approximately 1 in 5,000 donations at the time of sampling. Reported septic transfusion rates by passive surveillance are 1 out of 100,000 and by active surveillance 1 out of 10,000.

There are, however, some limitations of current primary culture practices in that there is a residual risk of septic transfusion reaction at the time of transfusion. As you can see from the top diagram, when you have low numbers of bacteria early in shelf life, you are less likely to transfer the bacteria to your sample and be able to detect contamination, leading to a high likelihood of false negatives.

There is also a lag time between inoculation and growth as shown in the bottom diagram. Here is the lag phase. This lag time is species dependent, but for all organisms, detection is most likely during the exponential phase of growth as seen here, whereas false negatives are likely during the lag phase. A correlate of this is that clinical sensitivity of day one culture for contamination of platelets on days five to seven has been shown to be less than 40 percent.

FDA cleared and approved devices for bacterial contamination in platelets fall into three categories. Bacterial culture, rapid testing, and pathogen reduction. The following slides will give an overview of strategies to be discussed in today's meeting as shown in the table. The invited speakers will describe studies related to these strategies.

Starting with strategies to control the risk of bacterial contamination in 5-day platelet products. The first strategy we will discuss is primary culture, followed by secondary culture, on day three. In this strategy, primary culture is performed at least 24 hours after collection using an 8 milliliter sampling volume collected into aerobic media. Secondary culture in contrast is performed on day three after collection, using a 5-milliliter sample, also collected into aerobic media.

The next strategy to be discussed is primary culture followed by secondary rapid testing on the day of transfusion. In this strategy, primary culture is performed using the same standard methodology. Secondary rapid testing is performed within 24 hours of transfusion using a .5 milliliter sampling volume.

The next strategy for discussion is culture based on a minimal proportional sampling volume. This strategy comprises a single culture with no secondary testing whereby the sampling volume is increased proportionally to the collection volume. In this strategy, the sample volume is at least 3.8 percent, taken 24 to 36 hours after collection. The sample is inoculated into one to three aerobic culture bottles, depending on the final volume collected, and stored for up to five days.

The last strategy to be discussed for 5-day platelets is pathogen reduction technology. There's currently only one device approved by the FDA. This device is based on amotosalen/UVA technology, which as you can see in the diagram involves treatment with amotosalen, targeting the nucleic acids and causing intercalation. Then following UVA illumination, there's crosslinking the nucleic acids, and subsequent replication is blocked. The intended use of pathogen reduction technology is to reduce the risk of transfusion transmitted infection, including sepsis, and is performed within 24 hours of collection.

Now I will outline the strategies to control the risk of bacterial contamination in 7-day platelet products for discussion today. The first method for 7-day storage is primary culture followed by secondary culture performed on day four. In this strategy, primary culture is performed 12 to 24 hours after collection for apheresis platelets and 36 to 48 hours after collection for platelet pools. The size of the sample is 16 milliliters, which is divided evenly, 8 milliliters into an aerobic medium and 8 milliliters into an anaerobic medium. There's no hold period after testing of bottles, which means that units are immediately released after sampling.

Secondary culture is then performed on day four. Each apheresis product and each pooled product is sampled.

Again, the sample volume is 16 milliliters, divided 8 milliliters into an aerobic medium and 8 milliliters into an anaerobic medium.

The next strategy to be discussed for 7-day platelets is primary culture followed by secondary rapid testing to extend beyond day 5 up to day 7. This is the same strategy as mentioned as rapid testing for 5-day platelets, with the exception that for 7-day platelets secondary rapid testing is performed with a test labeled as a safety measure.

The last strategy to be discussed is large volume delayed sampling. This strategy entails a single culture to allow storage to seven days. The sample is taken 36 to 48 hours after collection using 16 milliliters from each component. The sample is inoculated into aerobic and anaerobic culture media and held for six hours after sampling.

There are, however, some challenges in strategy comparison and the committee is not being asked to make direct comparisons. The studies on the strategies are not directly comparable, because many variables affect bacterial contamination and/or detection rates. For example, the apheresis technology used, the timing of sample collection, sample volume, whether aerobic and/or

anaerobic culture are used, as well as techniques of skin preparation and diversion.

There are changes in standards and practices over time, and definitions and reporting of septic transfusion reactions vary. Different outcomes are evaluated and, importantly, different strategies have not been evaluated in parallel.

In summary, bacterial contamination of platelets remains a leading cause of septic transfusion reactions and related fatalities. Today's speakers will present available strategies that could further reduce the risk of bacterial sepsis due to contaminated platelets.

The following slides show a list of today's speakers, which you can review in your handouts.

Finally, to reiterate the question, today we are asking the committee to please comment on the advantages and disadvantages of each of the various strategies to control the risk of bacterial contamination in platelets, including the scientific evidence and the operational considerations involved. For your review, I will leave the last slide up listing the various strategies to control the risk of bacterial contamination in platelets for discussion during this meeting.

Thank you.

DR. ALLEN: Microphone system seems to be down. Thank you, Dr. Storch, for that presentation.

(Off mic comments.)

Agenda Item: Bacterial Culture Testing Strategy

MS. ANHEUSER: Good morning. Thank you for allowing me to address this committee and tell you about the use of the BACT/ALERT, BPA and BPN culture bottles for secondary safety measure testing of platelets. Specifically, I would like to tell you about the approach to developing this test and then give you an overview of the supporting data.

I should back up. I did forget to introduce myself, Mary Beth Anheuser, with bioMerieux. I am currently working in regulatory affairs as a regulatory affairs specialist. My background is in microbiology, and I had the opportunity to spend about 10 years in research and development working with the BACT/ALERT.

The BACT/ALERT 3D systems have been widely used for in-process QC testing of platelets since 2004, when the AABB standard requiring 100 percent screening of platelets became effective. In 2005, the BPA and BPN bottles were cleared for use as an in-process method for testing leukocyte-reduced apheresis platelets and leukocyte-reduced single units and pools of up to six units of leukocyte-reduced whole blood platelet concentrates.

As we're all aware, in March of 2016 version two of the draft guidance came out, and although the draft guidance had many important points, there were three that we focused on. The first point was, that told us -- that was the why of a safety measure test. This was why we needed to do this. The second point was the how of the test. What was going to be our objective? What did we need to do? And the third statement told us that we had some work to do. So, we got busy.

Our objective was clear. We needed to provide evidence that the BACT/ALERT 3D systems are an effective safety measure for secondary testing of platelet products, to extend the platelet dating beyond day 3 and up to day 7. Then we had to decide what was going to be our method. With almost 14 years of the 3D being in the market for blood blank applications and hundreds of publications associated with it, we decided to go to the literature for the data. We felt that that would be the most comprehensive and efficient way to develop this test.

We did a literature review and we also queried customers for data associated with unpublished studies that could be used to accomplish this. We identified nine publications and two unpublished studies that met this criteria.

Our success criteria for developing the test was going to be that we could show the benefit of the 3D for detecting contamination that was not revealed in previous testing, but we also needed to show clinical specificity. The next challenge was, once we had identified the studies and the data, how were we going to summarize that data so it was meaningful for the performance of the system?

Every publication was a little bit different in the way they presented the data. In general, most of the researchers presented the platelet test results based on the AABB definitions. What we did then, was we needed to make some assumptions, because maybe the details weren't the same, so we said, okay, we're going to present the data as the number of tests, the number of positive tests by the number of tests that were performed.

Since the data of interest are secondary and QC surveillance test results, it was assumed that one test was performed per platelet unit and that all units eligible logically were negative by the primary test. Since the objective was to look at the instrument performance -- in the studies, the researchers tended to use different protocols. Some researchers used 4 mls in aerobic bottles, but then others used as much as 10 mls in an aerobic bottle and an anaerobic bottle, with different volumes in between. What we decided was that wasn't our focus. The protocol

used to identify the contamination wasn't the focus; it was the performance of the instrument.

The next step in the process was to take the data from the studies and put them into meaningful instrument definitions. We evaluate the performance of the instrument as instrument true positive, instrument false positive, instrument true negative, and instrument false negative.

For the true positives, essentially we took any bottle that was positive in the study, no matter what the source of the contamination was, that that was a true instrument positive. For the false positive, this is where the bottle is signaled as positive by the instrument, and no organism is recovered from the subculture. This included platelet results designated false positive due to instrumentation error, where that was called out in the studies. The instrument true negative and the instrument false negative, these were measures of performance that we couldn't get from the study data, because typically, our customers are not going to subculture a negative bottle. So, we looked to internal performance validation studies for that data.

With the 11 studies, and like I said, this is just the overview. This is a summary. We looked at the data many different ways in the actual report, but we were able to look at results from 217,932 tests, and of that we

had 174 true instrument positives. Testing in the studies was performed on day 3, day 4, or on day 6 or later. That was associated with the QC surveillance testing. We were pleased with the volume of data that we were able to pull from the publications.

You can also see from this slide at the bottom, we broke out how many tests of each type of platelet. Now, on the third type, right here, the apheresis plus the buffy coat, they were not pulled out in this situation, because in the publications the researchers didn't pull them out, so we couldn't either.

The next thing that we looked at, we said, okay, is there anything that could affect the ability of the system to detect contaminants later in the shelf life of the platelets? So we wanted to look at if age of platelet affected recovery. So, we did a seeded study. In this study, we had platelet units, and we tested those on days 3, 4, and 5. They were placed on rockers between each day of testing. And we had 100 percent recovery. The biomath folks applied a chi-squared statistic to the data to see if age of platelets had an effect on time to detection. And if we had p values that were greater than .05, there was no statistically significant effect. This data further supports that age of platelets is not going to impact the

instrument's or the system's ability to detect contamination.

The next thing that we looked at, that we pulled from the studies -- so there were 11 studies. Eight of the 11 studies, the researchers listed out the contaminants that they identified. Five of those eight further gave us the times to detection. This table is a summary of that information. What you'll see is that 44 of the 77 contaminants were staph species, and in general, those clinically significant contaminants were detected in less than or equal to 27 hours on the system.

Then we went on to instrument specificity. Five of the 11 studies included data on false positive results. What we found was, you can see that we had 19,404 units tested on day 3, with no false positives, over the course of the study. Where they were tested at 6 days or later, the over 48,000, there was 180 false positives. If you look up at this line up here, this will tell you, by day, what the false positive rate was. You'll notice, too, that these two values, that was actually one site.

What we arrived at is that our overall false positive rate is .27 percent. However, we do have, broken out by platelet type, you can see that for the LRAP platelets we had from 0 to 1.1 percent for the range. Actually that's a good way of looking at the overall data.

Again, at the bottom here, we did a breakdown of the types of platelets and how many tests per type.

The next was instrument sensitivity, and as I stated before, you know, typically our customers are not going to subculture negative bottles. So we looked at our internally sponsored data, and what we found is that there were no false negatives observed in seeded studies or in negative controlled bottles. Because when we typically do performance studies, we subculture the negative bottles. But if it's a seeded bottle and it's negative, it's subcultured. If it's subculture-negative, then it's a true negative.

In summary, the contaminants missed during primary quality control testing were detected by the BACT/ALERT 3D system when secondary testing was initiated on days 3 through 8 post-collection. Staph species were the most prevalent contaminants reported during secondary testing, and these species were detected from 3.1 to 26.6 hours. Propionibacterium species were the second-most prevalent contaminants identified. These slower-growing organisms were detected in 3 to 7 days. And although this would not allow for the unit to be interdicted, performing the safety measure test could provide valuable information to initiate patient follow-up that could otherwise be delayed.

For the overall false positive rate, the current BPA/BPN bottle IFUs report an overall false positive rate of 0.1988 percent with a range of 0 to 0.49 percent. This was based on testing platelets on day 2 after collection. The overall false positive rate in the studies, as related to secondary safety measure tests, indicate an overall rate of 0.27, with a range of 0 to 1.1 percent. There were no false negative results reported in the performance validation studies.

Our conclusion is that the BACT/ALERT system is an effective safety measure for secondary testing of platelet products, and we received clearance for the BPA and BPN culture bottles for this use on February 1, 2018.

DR. ALLEN: Thank you for your presentation. We're open for discussion. Questions from the committee members? There are no questions or comments from the committee at this point. Yes, Dr. Caliendo.

DR. CALIENDO: Angie Caliendo. When you do your seed studies, for sensitivity, what's the lowest concentration that you seed with?

MS. ANHEUSER: In the most current studies we use the BioBall product where it was available, and we had a target level of 3 CFU per ml.

DR. HARRELL: Lizzie Harrell. I'm curious to know; did you purposely decide not to do any anaerobic culturing?

MS. ANHEUSER: Actually, we do anaerobic culturing. All of our seeded studies include a bottle pair, and in this particular study, when we did the safety measure claim, when we looked at the study data, this speaks back to what I mentioned about, we did not consider the study protocols because everybody was doing their own thing. Some people used 4 mls in just an aerobic bottle, some people used as much 10 mls per bottle pair. So we decided that -- and that's what we've always recommended, is that a bottle pair be used. If we refer back to the slide on the contaminants that were isolated, there are some anaerobes in there. So, it further supports the bottle pair. And in fact our clearance is based on using a bottle pair.

DR. STRAMER: Just one point of clarification regarding the AABB standard 5.1.5.1. From AABB in 2004, it initially was defined as, and it still is, limit and detect. So, it wasn't initially required to do testing, testing as in bacterial culture. You can do pH measurements, or glucose, or swirling. So, it recommended some measure that AABB institutions use to limit and detect, later it was expanded and further clarified,

expanded to include pathogen reduction, as used outside of the United States. But I just wanted that clarification for the record.

DR. ALLEN: Thank you.

Let me just remind committee members, as well as any other speakers, please identify yourself with name and affiliation, because this is being transcribed and we need to get that accurately.

Dr. Jefferson, from the Centers for Disease Control.

DR. JONES: Yes, Jefferson Jones, CDC. For the BACT/ALERT package insert and instructions, this is kind of related to the question a couple questions back, about anaerobic cultures. I was wondering, because the discussion today we'll talk about many strategies, including whether or not to include anaerobic cultures. On the package insert, it looks like you strongly recommend doing both aerobic and anaerobic, and then instructions for gathering blood cultures from patients, kind of standard patient blood cultures, also appear to strongly recommend doing both aerobic and anaerobic cultures.

I was wondering if you could comment on where those recommendations come from, the data to support it, and how you think that might fit in to recommending anaerobic cultures in general, when BACT/ALERT is used.

MS. ANHEUSER: When the BPA and BPN bottle were originally cleared, in the studies that supported it a bottle pair was done, and so the recommendation was based on that -- was developed at that time. So, it's years ago.

When our new package inserts come out with the safety measure test, it's no longer -- for the safety measure test -- it's no longer a recommendation. It's required, if it's going to be used as a safety measure, that a bottle pair is used. Does that answer your question sufficiently?

DR. JONES: Jefferson Jones, CDC. Is the data supporting using both because that's how it was tested originally, and nothing more?

MS. ANHEUSER: No, there have been situations where there have been septic transfusion reactions that were based with anaerobes, and as I understand, it's not as common. I'm not really an expert in that area. But it makes sense. Some of the staph and the strep that were isolated as contaminants prefer the reduced oxygen environment of the anaerobe, so I think it was a combination of those things, where it was a recommendation, but not required.

DR. ALLEN: Thank you. We have two speakers who are requesting recognition from the audience. This is supposed to be a committee discussion time. We are okay on

time, so very quickly, please ask your question, identify yourself.

DR. WAGNER: Hi, my name is Steve Wagner, I'm with the American Red Cross, and I understand that the literature study that you did involved many different countries, possibly, and many different conditions. But one of the things that I noticed is that the risk as measured on day 6, which was 0.12 percent, of true positives, was three times the amount that was measured on day 4, which was 0.04. Could you comment on any increased risk of detecting slow-growing bacteria that might have longer lag times, with continued storage beyond day 5?

MS. ANHEUSER: I think the data speaks to that point. It is what it is. I think that we know, and especially the fact that the staph, I think, that this goes along with what's in the literature, is that the gram negatives come up quickly early in the shelf life, and it's the gram positives that have the extended lag period. So, I don't know what to say, other than that I think there is a risk. I think that the data speaks to that.

DR. ALLEN: Thank you very much. We are going to have to cut it at this point. We do have the open public hearing later, early afternoon, and would appreciate your comments then. Thank you, I appreciate that it clarifies the point, I saw when you rose that it was in response to a

particular point. We would like to hear that during the open public hearing, please. Thank you.

Our next speaker is Dr. Evan Bloch, from Johns Hopkins University School of Medicine. He is speaking on primary culture and secondary culture on three-day testing strategy, with dating to day 5.

Agenda Item: Primary Culture, and Secondary Culture on Day 3 Testing Strategy, with Dating to Day 5

DR. BLOCH: First, thank you very much to the committee for the kind invitation to speak. I am Evan Bloch. I'm assistant professor in the Department of Pathology at Johns Hopkins University School of Medicine. I'm also the associate director of Transfusion Medicine.

Today, I'm going to presenting on implementation of a secondary culture system for detection of bacteria. I'm going to try to present this in the context of alternative strategies to contend with residual risk of bacterial contamination, presenting some of the data from studies which support this approach, actually support any laboratory-based approach, acknowledging the limitations or advantages of each.

Just some disclosures. I'm a coinvestigator on the MiPlate trial, which is a randomized control trial to evaluate the Mirasol pathogen reduction system, comparing pathogen-reduced platelets with standard apheresis

platelets. I'm also a coinvestigator on a DoD-funded study to evaluate pathogen-reduced whole blood in Uganda, which is due to start later this year. And I have no financial disclosures.

The first study which I'm going to present, from Hopkins, which is soon to be in press, which is on transfusion reactions at Johns Hopkins Hospital over an eight-year period. It was a retrospective analysis. We're fortunate at Hopkins that all suspected transfusion reactions are routinely investigated, both through review of clinical presentation and clerical checks, but we have gram stain and bacterial culture of all suspected transfusion reactions, of residual blood from the transfused product, or the associated blood bag.

Then we classify those reactions based on criteria from the CDC, the hemovigilance criteria, and then for the purpose of this study we defined reactions as BCPTR, which is bacterial culture positive transfusion reactions, which is, when we had a positive culture in the product or bag, the recipient, or both, and then a septic transfusion reaction, which represents a subset of those, when there was concordant culture positivity between the product and recipient, meeting definite criteria for a septic transfusion reaction, which had since been renamed

transfusion-transmitted infection by the CDC criteria. Both by the definition criteria, as well as imputability.

Over that eight-year period there were almost 700,000 blood products transfused. There were 3,170 transfusion reactions reported, 18 of which were blood culture positive, and 7 of those 18 conformed to a definition of septic transfusion reaction. As to be expected, the overwhelming majority were from apheresis platelets. There was a two red cells and one unit of plasma, which were also culture positive.

Just to mention, symptoms and signs, to illustrate how nonspecific this is. About two-thirds presents with chills and fever, which overlap with other reactions. Also nausea, vomiting, pain and dyspnea. Blood pressure, which is often considered in the context of septic transfusion reactions, decreased in some and increased in some. But for the vast majority it remains unchanged over those culture-positive reactions.

When we look at septic transfusion reaction specifically, overwhelmingly due to platelets, over half were either severe or life-threatening, with respect to outcomes. Given that I'm presenting on a culture system, it's worth looking at the variables which impact risk of bacterial contamination, and why there is so much

variability in reported incidents, when we look at all of the data.

So everyone is aware, primary culture, we have collection, we have sampling at some predefined period after sampling, we have bottle incubation, and then ultimately release to the blood center. So, just with respect to collection, we wanted to know what mitigation measures have been in place from disinfection, how long has that been in place, diversion pouches, are we collecting via whole blood or single donor technologies?

With respect to sampling, looking at the timing relative to collection, what volume, what bottle types, whether it's aerobic, and/or anaerobic, and then whether sampling is undertaken before or after splitting?

Then with respect to bottle incubation, how long prior to release, and that's somewhat variable depending on the different approaches out there. And then, importantly, it's subject to the bacterial kinetics themselves, which in platelets is going to impact the risk. There's various kind of growth forms. One possibility is that you actually have auto-sterilization, very low inoculum, and essentially nothing happens over time. Second possibility is that bacteria persists at very low concentrations throughout the platelet shelf life and again, have no real measurable effects.

Where primary culture comes in is where we go from, as shown in the previous talk, we go from a lag phase to ultimately a log phase of growth, and then that timing relative to collection will impact the ability to detect bacteria in that timeframe. What's concerning is really with slow growth of certain bacteria, where they escape capture with that 24-to-36-hour sampling.

There's also other factors. There was nice study which came out last year by Anne Eder and others, just looking at the collections technology, where over a five-year period they compared Amicus collections to Trima collections, kind of a standard approach, 8 mls sample from apheresis platelets, inoculated into an aerobic culture bottle at least 24 hours after collection and then held for 5 days.

When they looked at the number of confirmed positive reactions, there was a significant increase in culture positivity with the Amicus collections as compared to the Trima collections -- about twofold higher odds of positivity. When they looked at overall rates of septic transfusion reactions, again, it came to about 1 in 100,000 apheresis platelets and was overwhelmingly associated with the Amicus procedures. As a caveat, I believe that a lot of this has been addressed subsequent to this paper.

Another nice paper came out of Blood from Hong and others, looking at active versus passive surveillance, over a period from 2007 to 2013 -- so, again, kind of a standard culture approach. The authors also looked at sets of septic transfusion reaction criteria, including the then recent AABB criteria. What they found was that with active surveillance, there was about a 1 in 2,500 incidence of bacterial contamination. None of those reactions were reported by passive surveillance.

In contrast, if you look at the 284 reactions reported by passive surveillance, none were associated with contaminated platelets, and a high proportion met criteria for septic transfusion reactions, so that the authors commented on the lack of specificity of the criteria. Collectively, the reason why everyone's here today, is that really bacterial contamination of platelets remains a leading cause of morbidity and mortality. There's clearly a failure of passive surveillance to detect septic transfusion reactions, a lack of specificity of associated criteria, and actually, as an aside, that impacts the national surveillance data, and collectively support an additional measure to contend with residual risk of bacterial contamination, either through testing or pathogen reduction.

Just looking quickly, what are the alternative strategies? Some of those have already been mentioned. The first is pathogen inactivation or pathogen reduction, just as a -- it's important for me to say that I'm a firm proponent of pathogen inactivation. There's a variety of approaches in use, including photochemical inactivation, which has gained the most traction, but there are other strategies. There is the FDA-licensed INTERCEPT system. Mirasol has been CE marked in Europe.

The pros behind this approach, well, it really offers a comprehensive approach to infectious risk. There's broad activity across all classes of pathogen, which is going to address both the major infections which are currently being tested, as well as emerging agents. Zika, I guess, is now being tested. As well as protozoa -- babesia remains an important risk to the blood supply. And then there are secondary benefits, such as mitigation of transfusion-associated graft-versus-host disease, and importantly, has shown comparable safety and efficacy to untreated platelets.

The downside, acknowledging that cost is a sensitive issue and shouldn't really detract from the scientific merits of an approach, but cost is high. It's about 20 to 30 percent gain on current cost of platelets. There's also lower platelet recovery and survival and,

importantly, there's a lack of a licensed red cell or whole blood technology, so many of the collateral benefits, such as transfusion-associated graft-versus-host disease, may be overstated in the absence of a comprehensive strategy.

Second is really point of release testing. We have the platelet PGD test, which detects conserved antigens and gram positive and gram negative bacteria. We have the BacTx assay, which, again, detects bacterial peptidoglycan.

The pros -- undertaken near time of issue, so within 24 hours of transfusion. The PGD test is able to extend shelf life to seven days, which is really favorable to transfusion inventories; it reduces risk of platelet outdating.

The cons, at least for myself, is perhaps flawed perception. When I think of point of release, I think of rapid testing, so there's an expectation of low technical complexity and ease of use, and I'm not sure that is completely true. It's logistically challenging. The turnaround time is a minimum of 30 to 60 minutes for a negative result.

Then when we talk about less expensive, it's certainly less expensive than pathogen reduction, but it's not cheap. Estimates of $25 to $35 for the purchase of the test kits and the technologist's time to run the tests, and

then, testing needs to be undertaken less than 24 hours of release, so in some way needs to be able to predict one's transfusion needs over the 24 hours. Alternatively, one needs to repeat testing if not transfused within that timeframe.

I'm presenting -- it's kind of a long-winded approach -- an alternative approach, which was really spearheaded by Paul Ness at Hopkins, which is phased implementation of secondary bacterial culture. This was really spurred by a mini-epidemic, I'll show you the data in a subsequent slide, of culture-positive transfusion reactions in 2016. It prompted us to evaluate existing mitigation strategies. The presumptive root cause of residual risk is the initial inoculum was potentially too small for detection, or alternatively, it was a slow-growing bacterium, leading to false negative test results.

What was proposed was implementation of a secondary bacterial culture system at the transfusing facilities at Hopkins at time of receipt, which is approximately three days post-collection. The hospital administration was very strongly supportive. There was some debate as to who should perform the culture. Should this be the blood bank, should this be micro? Ultimately, we've actually adopted, in the blood bank.

Testing was initiated in October 2016, of all platelets on the morning of day 3 post-collection. Platelets are stored up to five days. It's a 5 ml sample, and testing in the blood bank by a dedicated lab technologist. It's in aerobic bottles, a single-bottle system, and then held for three days incubation at 35 degrees, and then the micro lab performs confirmatory testing for any positive. As I mentioned, this led to the addition of one full-time equivalent, one technologist, at the blood bank.

Just in terms of logistics, of initiating this, we achieved almost 100 percent culture at six months, and we've managed to sustain that. This has been published in Transfusion, so, looking at the data from 6th of October 2016, to 30th of November 2017, for about 23,000 platelet transfusions were cultured, we had 8 positives, which represents an incidence of about 1 in 2,800.

Seven of those positives occurred within 24 hours of secondary culture, so within 24 hours of receipt at Hopkins. Five of the eight were designated as probable true positive, and they were interdicted, so, they were not transfused. Three cases we've labeled as indeterminates, as in, they were transfused, albeit without adverse event. But that culture positivity came up after they had been released.

Unsurprising, coagulase negative staph accounted about four of the eight positives. Importantly, there were no false negatives. There were no septic transfusion reactions reported during that observation period. Contrast that with the preceding 13-month period -- we had four possible and three definite septic transfusion reactions, including one life-threatening event and one fatality. Going back to revisiting that earlier study which I mentioned, the majority of platelets at Hopkins were collected on an Amicus system, that has, I believe, has been addressed, which could have contributed to this surge in cases.

Subsequent to that, just collecting the data from the end of that study to the 30th of June, I just wanted to update this, we had one case which I would label as a possible case of laboratory contamination, or false positive, in which, on repeat testing, it was negative. The product was discarded. We also had, embedded within that, there were two additional probable true positives and an additional case which was transfused, so was not interdicted, but it was transfused without adverse event.

Collectively, we've had 12 positives out of about 32,000 products transfused, so, an incidence of about 1 in 2,600. Seven probable true positives, so, 1 in 4,600.

Four indeterminates, and one case of laboratory contamination.

The pros of this approach, secondary bacterial culture, represents an additional safeguard against contamination. It's complementary and it's overlapping with primary culture. It optimizes detection, given the interval growth. It's procedurally simpler than at least point-of-release testing in the transfusion service setting. So it could be implemented at both hospitals or blood centers. Pertinent to Hopkins, it was able to be implemented at a large institution where transfusion volume is high, and is oftentimes sensitive, and we were able to bypass many of the logistical challenges, so it was really not disruptive to routine workflow.

It is comparable or lower cost than alternative strategies. We estimated, at least on the initial study, to be about $16, just below $17 per product, including the supplies, equipment, and labor. So, the cost for those initial positives was about $77,000 per averted case. And this could facilitate 7-day storage. Internally, there's been a decision not to pursue that beyond 5 days.

The cons. It's a redundant system, it's going to add cost and labor. We acknowledge that Hopkins is a highly resourced tertiary academic institution. This is debatable -- smaller institutions could adopt this.

There's obviously a risk of false positive results, as we've seen, both from the culture system itself, as well as introduction at time of sampling. That always places a burden on the blood center and results in platelet wastage and market withdrawals.

False negative results and missed septic transfusion reactions has not really been shown to be an issue, but that's -- two additional considerations surrounding that are addition of an anaerobic culture bottle and/or increasing the sample size. There's also immediate transition to active inventory, there's no quarantine period, as there is potential that a positive unit still gets transfused, but one has to really titrate the risk versus having a viable product for patients.

On the subject of aerobic versus anaerobic bottles, is there benefit to adding an anaerobic bottle? Most of the organisms reported in cases of bacterial contamination, about three-quarters, are staph or strep species. Interestingly enough, about 1 in 5 is due to gram negative organisms. The addition of an anaerobic bottle will capture strict anaerobes, but some anaerobes are also air tolerant and will still grow, although not optimally, in an aerobic bottle. Leon Su, who was then at Blood Systems, actually did a study about 10 years ago, comparing 7-day and 5-day platelets, looking at true positive rates

with the two-bottle versus the one-bottle system, and actually found that the rates of true positivity were comparable with the two- and the one-bottle system.

There were three culture-positive cases, in which only the anaerobic bottle was positive. While the rate of true positivity were comparable, however, the rate of false positivity and indeterminate results actually went up significantly when using that two-bottle system. One in 1,700 versus 1 in 6,000.

In terms of sampling volume, data from the primary culture, higher sampling volume will increase the probability of capture, again, when that impacts the split rate. A limitation behind our study is that 5 mls was somewhat arbitrarily selected for this. There is data collection underway to evaluate the impact of actually a 10 ml sampling volume. It's still too early to comment. Anecdotally, in the first month which we started doing this, we had three false positives, where really there was no repeat positivity and nothing cultured. There hasn't been any additional cases since then, but we'll report that in some time.

In conclusion, bacterial contamination is a leading cause of morbidity and mortality related to transfusions. Still certainly underreporting. Surveillance is really challenging, and underscoring a need

for a laboratory-based approach. There are available strategies to guard against residual risk. I don't actually think they're one-size-fits-all. I think there are pros and cons to each and really needs to be tailored to institutional needs.

Secondary culture has certainly proved to be successful in our setting. It's been able to be integrated into workflow. Favorable cost as compared to alternative strategies and could pave the way for 7-day platelets, although, again, that has not been the direction that we've been going. With respect to future directions, I would love to see at least a study looking at the addition of the anaerobic bottle. We are looking at the sampling volume, and we are refining quantification.

Just to acknowledge, I'd love to take credit for all of this, but it's Paul Ness, and particularly Christi Marshall, one of the supervisors in the blood bank, have been instrumental in getting this off the ground.

Thank you very much.

DR. ALLEN: Thank you, Dr. Bloch. And thank you especially for your comments about the academic hospital ability to handle such a thing, versus the community hospital, because that's obviously an important issue.

Any of the committee members have questions or comments for Dr. Bloch?

Let me just ask quickly, obviously, if I were a patient, I'd like to get the freshest platelets possible. What does all of this have to do, in your experience, in slowing down or delaying the transfusion of fresh platelets?

DR. BLOCH: Very, very little. I could probably, in one of those slides, I could probably look at the timing relative to release, but very, very little. It's essentially a seamless transition. It arrives, it gets cultured, and those products go out.

DR. ALLEN: From a bacterial perspective, if we could safely use 7-day platelets, that is helpful in terms of inventory management.

DR. BLOCH: Yes.

DR. DE MARIA: Al DeMaria, Massachusetts Department of Public Health. The $16.38 estimate for the cost, that included the dedicated technologist?

DR. BLOCH: Yes, it included labor.

DR. HARRELL: Lizzie Harrell, Duke University. In your conclusion, I totally agree that I think you hit the nail on the head, your sampling volume, and including the anaerobic bottle, are two things that need to be considered if you're trying to standardize this.

DR. KAUFMAN: Richard Kaufman, Brigham and Women's Hospital. Can you just clarify, what proportion of the

contaminated units were interdicted, and have you considered putting in a quarantine period?

DR. BLOCH: As I mentioned, it's titrating -- this is already three days post-collection, so if one holds it for a day, one's going to be left with a two-day shelf life for those platelets. I think a quarantine, in an ideal world, I think a quarantine period would be nice, but I don't think it's viable. Your first question -- what proportion? Seven out of 12.

DR. SCHREIBER: Marty Schreiber, OHSU. I looked at your data, and in terms of this three-day incubation period, done on day three means that there's one day overlap where the platelets would already have expired, but when I looked at your data I noticed that all the growth had occurred within 48 hours. I didn't see any growth occurring after 48 hours. Is that not correct?

DR. BLOCH: Yes, that's correct.

DR. BAKER: Judith Baker, Center for Inherited Blood Disorders. Again, on the labor costs, were those based on actual labor costs of Johns Hopkins staff?

DR. BLOCH: Yes.

DR. ALLEN: Dr. Jones?

DR. JONES: Thank you, Jefferson Jones, CDC. Would you be able to talk a little bit about -- you mentioned the last slide, about looking at the sampling

volume and anaerobic bottles? Specifically, is Johns Hopkins looking, or your institution looking, at 7-day platelets? And how that would affect volume and anaerobic?

DR. BLOCH: Sorry, to clarify, again, the 7-day, internally we've made a decision not to pursue 7-day platelets, so we don't want to extend beyond five days. It's not to say that a different institution might want to do that. For the sampling volume, we are actively looking at 10 mls. We actually, we are sampling 10 mls at the moment. We are also saving segments in response to our other reviewer comments from the paper, to be able to refine ascertainments of what these reactions mean. With respect to the anaerobic bottle, we're not actively looking at that. I would love to look at that.

DR. LEITMAN: Could I go back to Dr. Kaufman's question and your response? Seven out of 12 interdicted, but I'm looking at that slide now. One was a lab contaminant and likely a false positive, so it's really 7 out of 11. The four indeterminate were because the units were transfused and there was no sample available for re-culture and the recipient did well, and had regular cultures. So they are truly indeterminate.

DR. BLOCH: I'm being more conservative, but yes. You could argue that --

DR. LEITMAN: Were those four all slow-growing -- do you remember the organisms and species?

DR. BLOCH: I probably have them. Two of those are coag negative staph, they're transfused, so there's a viridans strep -- there's two staphs and a micrococcus in the first batch.

DR. LEITMAN: Thank you.

DR. ALVING: This is probably a much more general question, but you're really locked into -- this is sort of a two-step process. You're locked into the American Red Cross and their procedures. I understand you get all of your platelets from the ARC. So, they do their 24-hour and then they hold and release 12 hours after that, so the earliest you could get them is at 36 hours. Are you actually talking to the American Red Cross or working in any way -- I know this is a huge overall question -- but would you change your process, or have you thought about it, if they could change theirs? In other words, you're in sort of lockstep. It's a two-phase.

DR. BLOCH: In actual fact, the blood center could adopt the strategy and actually bypass the hospital. They could do the additional culture themselves. But sorry, I may not understand your question, but --

DR. ALVING: Everything you get from the American Red Cross is by protocol where they have done 24 hours; at

24 hours they do their culture, and they release 12 hours later, after quarantine, right? Have you talked to them, or are you looking at if, for example, if the American Red Cross held it for 24 to 36 hours, did that culture, then released 12 hours later, would that obviate the need for you to do the secondary cultures? But that's just an overall question for the committee.

DR. BLOCH: Those primary cultures, for the most part, have been negative. So we're inoculates and they're positive when we receive them, but by virtue of just perhaps there's been too low inoculum on that initial sampling, I think that's the advantage I think of this system.

DR. ALVING: If they did their culture at 36 hours it might obviate the need --

DR. BLOCH: Absolutely. I think that the blood center could take over this approach themselves, and cut the small hospital or the large academic center out of the equation.

DR. ALLEN: I certainly think those are issues that we need to explore this afternoon during our more general discussion.

I'm sorry, we're not going to take speakers from the floor at this point. There will be an open public discussion session. I would appreciate anybody bringing

forth issues at that time. Do you need to register to do that? Okay, they should register. If you could register out with the FDA representative at the desk outside, that would be very helpful. Thank you.

We will move on with our next speaker, Dr. Stephen Field, from the Irish Blood Service, discussing primary culture and secondary culture on day 4 testing strategy with dating to day 7.

Agenda Item: Primary Culture, and Secondary Culture on Day 4 Testing strategy, with Dating to Day 7

DR. FIELD: Thank you very much for inviting me once again to address this committee.

I have no conflicts of interest.

I'm going to give a very similar presentation to the one I gave in November last year, but I'm going to also move quite quickly through the first few slides, which really just introduce the Irish Blood Transfusion Service.

The Irish Blood Transfusion Service is a statutory body established by statutory instrument in 1995, responsible for the national blood supply of Ireland, and that does not include Northern Ireland, which is still part of the United Kingdom. Regulated by the HPRA, under the European directive in transfusion, reports directly to the government department of health.

Ireland has a population of just under 5 million, it's been increasing since 2011, and there we have all the major demographic data. The three major cities, which really have university hospitals, Dublin has a number of university hospitals, Galway, Limerick and Cork in the south.

Just to give you a flavor of the number of collections, they have come down over recent years, as the trend internationally, and just the whole donation statistics, between 2015 and 2016. I'm not going to dwell too long on this slide. And the donors per thousand of population. So, it varies in different parts of the country.

Platelet production in 2016 -- we collect platelets by two different methods. The great majority by apheresis, and there was a rule to make apheresis platelets which uses the Trima technology 80 percent of our load. Mainly it is a variant CJD measure where we didn't want to expose too many donors to the patient population. This is changing, and we are reviewing our variant CJD strategy, as well.

The MRTC is a center in Cork, and the NBC is the center in Dublin.

The success with the apheresis triples, doubles, and singles, the great majority being doubles. And the

platelets issued are 22,666 every year, and you can see the great majority go to Dublin.

Our components laboratory responsible for processing, labeling, and sampling of platelets for bacterial screening and then the issue. And that's the pictures of the laboratory, we won't dwell too long on that in the interest of time. You might have noticed, we use the buffy coat method, which is not the method in common use in the United States, for our pooled platelets.

Just the timings, for 5-day platelets, donation collected on day nought, pools are produced on day 1, and the apheresis sampled on day 1, mostly after 24 hours but we do concede that some of them, because of the timing, could be collected between 12 and 24 hours. And that is something we're looking at, which we're just a little unsure, we might not be missing a few, because of the organisms which may be present, may be in the lag phase.

Pooled platelets are sampled on day 2, so that's 36 to 48 hours, incubated until midnight on day 5, for a period of the shelf life. That's for the 5-day. Pre-culture preparations, donations are stored overnight at 22. Apheresis, each split/dose is recombine prior to sampling, and we do one sample per donation, whether it be a single, double, or triple. Pools are sampled the day after the pool is made.

It's a 16 ml sample volume, 8 mls into each of the aerobic/anaerobic bottles, representing approximately 3 percent of a double dose apheresis donation, approximately 484 ml or 5 percent of a pool platelet volume of approximately 293 ml.

The moment we have no hold period here after testing loading the bottles, but just remember, we're a blood transfusion service. We're not providing directly to patients. We provide the product to hospital and there is a certain lag time between our issue and the time it gets put into a hospital inventory and issued. We are reviewing that. We are considering a six-hour lag time before we issue.

Just to give you an idea of the process, I'm not going to dwell too long on the picture.

Supplementary sampling to enable us to extend the date, expiry date, to 7-day platelets. For apheresis, the second sample is taken on day 4, pools on day 4 as well, incubated for shelf life of the product, and 1 percent of all tested expiry as well. So we also got data on expired units after 7 days.

The products are sampled, apheresis platelets. Now at this time, we do not obviously recombine the product for the apheresis. Each unit is tested and pools of

course, each pool will be tested. Again, it's a sample volume, 6 mls, 8 mls, into each of the two bottles.

Processing of bacterial -- if there's a positive gram-stained subculture bottle, organism identification, conducted at a co-located hospital, we're right on the campus of St. James Hospital in Dublin, and we collaborate with their laboratories for any of this testing. We have a recall of implicated units and quarantine of associate products, hospital blood bank contacted, physician contacted, for product infused, and this is a 24-hour service.

Recipient samples advised, follow-up recorded, onward reporting if necessary. Testing 10 ml of platelet/red cells if available after a positive is incubated for a further 7 days. We resample the second, 1 ml after 7 days if initial culture negative. So we do a full follow-up of any suspected septic transfusion reaction.

A confirmed positive flag on the BacT organism isolated from BacT is also cultured from platelet associated product or recipient, and unconfirmed positive, is positive on the flag on the BacT organism assay but other components are not available for further testing or negative control cultures are obtained on testing of platelets and other components.

False positive is positive signal from bottle but subculture bottle and associated product is negative. Much the same as you have heard in earlier talks.

Septic transfusion reaction is suspected if transfusion -- if temperature is greater than 1.5 from the baseline, hypotension, rigors. They are immediately advised, blood cultures and specialist infection advice and antibiotic therapy. There's donor review and follow-up. We notify to the National Hemovigilance Office, which is an agency of the regulator.

Okay, so what we have done over the years, I've updated this from the last presentation to include last year's data. So we have for apheresis the day 1, with just over 11,600 donations, unconfirmed 47 positives, unconfirmed rate 0.041 percent. We have confirmed 33, which is a confirmed positive rate of 0.028.

The day 4 for the extension is 55,700, 15 unconfirmed positives, 5 confirmed positives. So we have a contamination rate of 1 in 11,140. That's overall.

Just doing 5-day expired platelets, I just have 6,600, 14 unconfirmed positives, 0.211 percent, 2 confirmed positives which is 0.030, and the 7-day expired, a similar picture as you can see there, but no confirmed positives. So just based on our 2016 data, estimated quantity of

donations retested at day 4, based on the 2016 rate of 48 percent retested.

A similar table for the pooled platelets. I appreciate you don't use pooled platelets here. You use the other methodology. But nevertheless. So 72,443 day 2, 41 unconfirmed, of which 61 confirmed. So that gives a confirmed rate of 0.084. Day 4, 18,700-odd, 9 unconfirmed, 8 confirmed. So a rate of 1 in 2,341. Again, expired data is there. Very little in the way of confirmations, and I will go through some of the organisms we have picked up over the years.

No septic reactions reported for 72,443 whole blood derived platelet collections.

Since 2005, up to 2017, that is the array of organisms that we have picked up. Propionibacterium is the great majority of them, slow-growing bacteria. You see there are some nasty ones there, too. Gram positive pathogenic species of staph aureus and all those other staphs and streps and some listeria. Some gram negative pathogens as well, and some anaerobes.

Okay, this is sort of confirmed positive table over the years and just shows that only two of those over the years were cultured. In 2005, there were three splits positive on apheresis platelet proteus mirabilis which is a nasty gram negative, and I'll talk a little bit later about

that, and then there was a strep dysgalactiae in 2014. In most cases, the contamination, contaminated platelets were not infused.

Okay, time to detection. This just gives the time to detection on the y-axis and the organisms on the x. Just to say that the black one -- this one, yes -- is the proteus, and that did take quite a while to grow. Which might well be an indication it might have been sampled too early. But generally, that's the other one that was infused.

Organisms not detected on initial screen. Lots of coag negative staphs, so these ones would be picked up on day 4. A couple of staph aureuses, but none of them were infused. You can see the other organisms there.

Confirmed day 4 cultures, and those are the organisms.

The culture results by apheresis splits, isolate from initial culture, listeria on a single split, staph aureus a single dose, and proteus three out of three. Isolates from day 4, and those again, the organisms, and most cases where it's contaminated contaminate both splits with the exception of the s. capitis at the bottom there.

Here's a couple of the case histories. I'll just keep an eye on time. We're okay. We currently do our pools now into platelet additive solution, and this was one

in 2014 where red cells also grew the organism. It was not issued and discarded. There's nil of note from the donor questionnaire and the donation of regular donor, and nothing came out of the medical reviews of the donor. Twelve previous donations, satisfactory arm cultures have been done on that particular individual.

Recipient was in his 30s. There was a new diagnosis of AML subsequent, received units. So the recipient had AML, received the units in October 2014 whilst on that particular antibiotic combination. The team contacted by us and advised microbiology opinion due to the discovery of this organism in the cultures. More than five sets of blood cultures between the 2nd and the 20th, none were positive. Obviously in this instance, the antibiotic cover given to the patient was adequate to deal with it.

The other one, which was in 2005, was a triple dose tested and issued and infused on the 31st of August, one bottle only incubated, prior to the introduction of the two bottle testing strategy later in that year. As I said earlier, the three splits were positive. Classical swarming on the plates of proteus. The donor had given 156 donations, normal white cell count and blood pressure day of donation. No follow-up information available.

The recipient was a cardiac artery bypass graft, tolerated the infusion well, no apparent septic reactions, but notes are minimal. So that I think was a lucky escape.

I think time is moving on, so I'm going to skip through this and just say there's a donation in 2015, donation in October, initial test 10th of October, 12th of October, prior to issue, cloudiness, unusual orange discoloration was observed, pack sent back to us for investigation, retested, positive flag after 3.84 hours, gram positive cocci. This is to say that vigilance at the point of issue is also a very important thing.

Just another donor history, again, a chap who had staph aureus, regular platelet donor, systematically well, but on examination he had beard rash and folliculitis, said to be exacerbated by shaving, over the last 12 months. Nasal swab showed Staphylococcus lugdunensis, which is very similar. Chin and venipuncture sites swabs, nil of note, although staph aureus preplus on reference laboratory report, referred to GP, and donor deferred pending resolution of symptoms and condition of skin.

So those are the sort of donor things we would have to deal with.

I think in the interest of time, I am going to just move on. This case of E. coli after five hours, both bottles, pooled platelet E. coli isolated, confirmed on

retest, sensitive to those antibiotics. Red cells all in stock, recultured, no growth, no donor, particular donor, was identified as the cause, because they were pooled so we couldn't isolate which one of the donors was implicated. Nil of note from the questionnaire, but all four donors were contacted. Apart from a mild sore throat in one donor, nil of note.

So the kind of things we would ask, about chills, fever, chills, flulike illnesses, headache, skin rash, infection, acne, venipuncture site assessment. Any dental manipulation, any urinary tract infection, contacts, travel, pets, animals, occupation, or any recent antibiotics?

Okay, remaining significant pathogens. S. pneumoniae, no apparent clinical symptoms. Klebsiella not identified from pool. Listeria, other staph aureus, no apparent signs or symptoms in donor, and same with S. dysgalactiae.

Propionibacterium acnes is something we commonly see. Again, here's a case history, a 7-day pooled platelet and red cells times four donations in 2013. Platelet pool infused. Anaerobic bottles flagged after 3.8 days. Again, the donor questionnaire, shoulder pain 10 days ago, attended doctor, history of RTA. Recipient uneventful transfusion, attendee in the hematology day ward, normal

vital signs at one hour after, patient contacted at home, well, no issues. And again, one of the red cells recipient CLL, already on broad spectrum antimicrobials for pneumonia, nil of note. Three other red cells recovered in house, one of the three cultures positive for P. acnes. So there we are.

Lots of Propionibacterium infused over the times. False positives, false positive alerts between those years, and you can see the graph has gone down. We have improved the false positive rate using designated incubators for each day of the week, avoid loading the incubator three days thereafter, try to load in batches, allocate drawers for later loading of bottles, and minimize interruption of monitoring. We find if you open and shut the doors of these things, it does trigger false positives.

So that's the summary, 77,443 pooled platelets screened between 2005 and 2017, and 116,045 apheresis platelets screened in those same years, and detection rate based on day 4 culture 1 in 2,341 as opposed to detection rate on day 4 of 55,702, 1 in 11,140. Majority of significant pathogens isolated and detected in pooled platelets, even though sampled one day later, than apheresis platelets. All but one proteus of the contaminated product infused, detected in pools. As the rest of it is self-explanatory.

Value in a two-day strategy. Majority of significant pathogens are picked up on the initial test. However, there's a value in the second day 4 test, facilitates extension of shelf life to seven days with extra margin of safety. Opportunity for organisms to grow, interdiction of staph aureus contaminated platelets and two other staph aureus contaminated products.

Pathogens with potentially adverse outcomes were detected and not infused, staph infantarius. Even if a platelet already issued, opportunity to recall red cells if there is a positive flag.

Day 4 also monitors the sensitivity of the initial test. However, IBTS will consider a 7-day strategy, and we have. One test 7-day strategy. Evidence suggests it's also safe and time and cost-saving advantages.

And just to acknowledge Dr. Willie Murphy, my predecessor at IBTS, Dr. Niamh O'Flaherty, who is the consultant microbiology, and Michael Maher and Danny Curran, the senior medical scientists. Thank you very much.

DR. ALLEN: Thank you, Dr. Field. It's always useful to get the experience from around the world different types of protocols and activities. So thank you very much for sharing with us.

Any of the committee members have questions or comments for Dr. Field?

DR. LEWIS: Roger Lewis, from the department of emergency medicine, Harbor-UCLA. Can we look at your table 1, please?

So, I have a question about the overlap and the units that occur in different rows. So should I assume that all of the units that are tested, for example, day 5, day 7, were from the same group and then obviously anything that was positive or transfused was included?

DR. FIELD: Once we have got to the day 4, anything which is transfused or --

DR. LEWIS: There's nothing left over to test. I think this is a very naïve question, but what I'm trying to understand -- sort of like a survival study where you have a smaller and smaller population of units that are available at later times. So there's no way to know, for example, if a unit that was positive on day 7 would have been positive earlier or we know that it was negative. Which, we know that it was negative?

DR. FIELD: We know that it was negative. If we still had the unit at day 7 in the blood service, we would have done 7-day expired -- that's at the bottom of the table -- we have recultured some of those, that number, 2,285, over the years, and they have been, well, nine

unconfirmed positive and no confirmed positives. So that confirms the previous result.

But obviously that's only a subset of the total number that we originally cultured. The rest having been issued out to hospitals. One thing I would say is that once they're issued out of the IBTS, we do not get them back to extend the life to day 7. Once they are issued, in the first 5 days, it's a 5-day life; we only culture and extend those that are still in the IBTS inventory to further send out later.

DR. LEWIS: The thing that strikes me about this is the amazing consistency of the confirmed positive rate given the sparseness of the data over every time period.

DR. ALLEN: Interesting question. Other questions or comments for Dr. Field? Thank you very much.

DR. FIELD: Thank you very much.

DR. ALLEN: We will now have a 10-minute break. I would like to have everyone back here and ready to go at 8 minutes after 10, please. Thank you all. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience. We will see you back here in a few minutes.

(Break.)

Agenda Item: Minimal Proportional Sampling Volume Testing Strategy, with Dating to Day 5

DR. ALLEN: We are back in session. Our next speaker will be Dr. Ralph Vassallo from Blood Systems Incorporated, chief medical officer.

DR. VASSALLO: Very good, thank you. I appreciate the invitation today to reprise our discussion of minimal proportional sample volume. I am Ralph Vassallo. I'm chief medical and scientific officer for Blood Systems for the last three and a half years, and before that, 13 years as a division chief medical officer in Red Cross. You'll also probably remember me as the only male speaker today who does not have a mellifluous commonwealth accent. At least I'll have that.

At this point, I would like to thank several people. Firstly, Hany Kamel, who is in the audience, Dr. Marge Bravo, who crunches all the data for us, and Dr. Peter Tomasulo, who is not here, who started this process at BSI.

My disclosures are on file.

I think it's instructive to start with a discussion of what is the problem that we're trying to fix, because you can get sidetracked to think what we would like to do is to eliminate all bacterial contamination. What we really want to do is eliminate septic transfusion reactions.

So the data from Case Medical Center in Cleveland suggests that about 1 in 10,000 transfusions result in a septic transfusion reaction, but we know that only 30 percent of infected products that make their way into patients actually manifest as a septic transfusion reaction. Unfortunately, 1 in 8 patients will die when they get an infected product that results in sepsis. So that's what we are trying to fix.

But when you look at NBCUS data that show that about 2 million platelet doses were transfused in 2015, and know that in most of the collectors, we have seen a pretty flat curve in terms of platelet utilization. In fact, it's perhaps even a little on the way up over the last year.

We can assume that 1 in 10,000 septic transfusion reactions, we are dealing with 200 people who have an adverse event and approximately 25 of them will die from this. So it's something we need to fix.

The question is NBCUS data also show over time that the cushion between what we collect and what we transfuse is getting smaller over time, because hospitals and payers aren't able to fund that healthy cushion. So any small perturbation in availability can result in patients not getting transfusions, say even a 1 percent decline in availability, has a much greater impact when the cushion is small, and if only 1 in 100 patients who doesn't

get a platelet on time actually needed it, we're still hurting 200 patients. So the cure can't be worse than the disease here. So there's platelet safety, but there's also platelet availability and they're inextricably tied.

So let me talk about our algorithm for minimal proportional sample volume. For many years we had an 8 to 10 ml sample that was inoculated in a single BacT aerobic bottle on day 1 at 24 hours-plus. The new algorithm was between 10 and 28 mls, depending upon the volume of mother bag, was not tied to singles, doubles, and triples; it was tied to volume.

But you will see here that only about 1 percent of the units that we collect have such a low volume that they end up with one bottle. So we generally have two or three aerobic bottles that are inoculated at 24 hours plus, and you'll see what that did is it increased the number of bottles we use 2.4-fold.

What we do when we have a BacT alarm is to send both the bottle and available products, recall them from the hospitals, the ones still on our shelves, but we do this unlike when I was at the Red Cross, the alarm would ring, around 16.5 hours on average, and you would reach onto the shelf, and within an hour or so, you would inoculate. What you see here is that all of our centers that use eperges(?), that we have these data that we are

going to show, are sending to a central place in Phoenix. So it takes time to get units from the hospitals, to the regional center, and then you see, say, a center like Fargo then has to fly it down to Phoenix for cultures. So I think that gives us a robust ability to pick up some of these bugs in the product itself so that we don't have some what are called discordant negatives.

We also culture 20 mls, not 10 mls, as many other folks do.

So what we do is from the bottle itself we take 10 mls, we concentrate that down in plate, aerobic and anaerobic media, we do the same for the platelet product, each one of the splits that we have, but also take another 10 mls and put that in a single aerobic Bactec bottle. So we are culturing both aerobically and anaerobically in 20 mls of the platelet unit.

Our definitions you see here. A true positive is when you have the same organism from both the bottle and the unit or the bottle and if it's been transfused, patient blood. False positives are when the BacT alarm rings but there is nothing in the BacT bottle. So-called machine false positives.

Third option is that you have organisms in the bottle, but there's no growth in every one of the units, or all available, and this of course could be that this is

what are classically called contamination false positives, someone touches the septum and you contaminate the bottle without a contaminated product.

The second option there is that within the BacT bottle, you pulled the only infectious organism from the product. Very unlikely, but possible. Thirdly, you could pull a bacterium from the product, grows in the bottle, but the unit self-sterilizes, as Dr. Bloch has shown, and the last and the one we're really concerned about, is if indeed you have a product where the bottle is positive because there were bugs in the unit, but you sampled too early, you don't sample enough, and you miss a true positive that over five or seven days will then leave lag phase, enter log phase, and be potentially harmful.

Lastly is our indeterminates, when we have a positive bottle culture but you can't get all the units and you can't culture all of the patients. You can't culture patient into negativity, but you can culture a patient into a true positive, when his or her blood contains the organism that's in the bottle.

So let me get to the data. You have seen some of these data before. These were published in a paper authored, first author, was Hany Kamel, and we described two periods, periods A and B, the first period being 8 to 10 ml samples. It was a 45-month period. This is one BacT

aerobic bottle, inoculated regardless of the volume of the product, and you see some of the numbers here in terms of the results from the BacT, the initial positives and their resolution, and expressed as a rate per million.

We also gave 31 months of data in period B, and today we are able to extend our minimal proportional sample volume data by another 20 months, and for convenience, we'll lump together periods B and C so that you see here our true positive rate more than doubled. So going -- these are all Trima platelets. So going from 8 ml samples on day 1 to 10 to 20 ml samples, we have more than doubled the true positives.

Unfortunately with more bottles and more bottles requiring the drawer to be opened and closed more often, we also see a lot more false positives. They have increased 3.5-fold, and this is using aerobic bottles. Were one to use anaerobic bottles, you could assume it's the false positives, as Dr. Bloch showed as well, were going to rise even more dramatically because of the use of anaerobic bottles.

What was discussed at the last meeting is our discordant negatives. This rate has fallen by about 45 percent over time, and it was purported that indeed what we have done is because all of these units are essentially interdicted once the BacT alarm rings, all of the

platelets, by the time you culture them, are outdated. So you essentially don't give these platelets to patients.

The discussion centered around removing our discordant negatives, some of which are true positives but are not being sampled appropriately, the product itself, into our true positives, and there hasn't been a change. Well, in fact, I'll present three pieces of evidence that suggests that's not true at all.

The first being that our sampling protocol is more robust than many centers currently use. It's delayed at least 24 hours, and double volume, both aerobic and anaerobic, not aerobic alone. Secondly, this piece of evidence is you go from -- as you look at our periods B and C, as we have gone over time with the minimal proportional sample volume, our false positive rate has fallen by about 35 percent. That's because we are getting better at not opening and closing drawers. We are getting better at the entire process.

Interestingly, the discordant negatives have fallen by exactly the same approximately 35 percent rate, suggesting that much of this improvement, if you will, in discordant negatives is our improvement in general management of our BacT; if we were to use anaerobic bottles I'm sure this would spike again, but as Dr. Field presented last time, the Irish had a very robust program and actually

Dr. McDonald also showed that when you first start a program of enhanced primary culture, your false positive rate rises dramatically, and then you get much better at it and you're able to bring those down.

I'll present a third piece of evidence, but after this. I'd like to draw your attention to these numbers here that show what the residual rate of septic transfusion reactions are, the numbers above the line or above this line here, are all per collection, but of course, we have about a 1.8 split rate. So when you put that into units, this was one collection, but it was two products that resulted in septic transfusion reactions, our rate of septic transfusion reactions was about 1 in 170,000. It's interesting that you contrast that with the American Red Cross data, suggesting that Amicus has a 3.8-fold risk of a septic transfusion reaction as Trima. That's the Eder paper here. Their rate in passive reporting is 1 in 100,000.

It's been stated very, very clearly that you can't exactly compare things. They are different donor bases, different staff, different arm preps, different instruments that you're using, different definitions of septic transfusion reactions, the whole BacT process can be slightly different, but it is interesting that indeed this

follows what one would expect if indeed Trima has a lower rate of septic transfusion reaction than Amicus.

We then, in period B and C combined, have still only a numerator of one septic transfusion reaction. So from the last time we reported, it was 3.5 per million. We're now down with an increase in the denominator to 2 per million. We're at 492 -- 1 per 492,000. This is what you see in the data from Europe and, again, people would say these data cannot be compared. You're absolutely right. Sometimes you are comparing active and passive. We know passive is 10 times lower rate of recognition.

But these data are data, nonetheless. While they're not able to show small differences between them, they are able to show that there is a relatively low septic transfusion reaction rate when you use Trima with a 3.8 percent day 1 enhanced sampling mechanism.

We'll show the bacteriology here. I don't know how many people have 20/10 vision, but take my word for it that these are the gram negatives. These are the gram positive isolates. What we are going is showing periods A and combined B and C in the true positive and discordant negatives. So what we have done in red are to highlight organisms that are either enteric gram negatives or oral and invasive streptococci. Do you want to count staph aureus? That is both on the skin and also an invasive

pathogen. We chose to lump it with the skin and environmental contaminants. You can cut it either way.

But I'll draw your attention here, and that is that when we went from 8 to 10 mls, our true positive rate was -- true positives about 41 percent of our true positives were these invasive and alimentary organisms, nonskin, nonenvironmental contaminants. When we then increased our primary culture volume to 10 to 28 mls based upon the volume of the product, it increased to about 76 percent.

Even more telling are the actual numbers. Period A had about 69 percent of the collections that were evident in periods B and C. So when you adjust the seven nonskin nonenvironmental contaminants up for the volume of collections, that turns into 10 true positive alimentary invasive pathogens in period A and 4 discordant negatives. So indeed, if every single one of those were now just moved from discordant negatives into true positives, we would expect 14. Instead we found 41 organisms in a comparable denominator of collections.

So this clearly shows we are much, much better with 3.8 percent day 1 collection, day 1 -- sorry -- inoculation volume; we're much better at picking up these bad actors that are presumable bacteremic organisms.

How about if we look at the ones that are environmental or skin pathogens? So true positive pathogens 15, 13 in periods in B and C. We have maintained those evenly. But what we have also done is decreased discordant negatives by 50 percent, and I believe that's where we're showing that we are getting better at not contaminating the septum, just as we are getting better at our false positives with much more activity.

Our Trima folks have also produced a 30-ml sampler for us. We are not entering the bottles multiple times with different instruments. So hopefully as I've stated we are decreasing the number of discordant contamination false positives as opposed to discordant, gosh, you may have missed something in the product, because you sampled it too soon. You didn't sample enough, and that product is still hot.

We'll move on, we did a second surveillance study, and again, this was the brainchild of Drs. Kamel and Tomasulo, and what we did is akin to the PASSPORT data that looked at day 8, about 6,000 units predominantly Amicus, some Trima, some Acrodose. We had 100 percent Trima, and when our products expired on day 5, we either got them back from the hospital or took them off our shelves, quarantined them, and two days later did a bacterial sample. It was 10 mls and a BacT on day 7.

Of approximately 8,000 Trima collections -- products -- we had four collections that were involved in positives, and this is a little confusing. The first one was two products, but the second was a red cell. So on day 7 we cultured the platelet. It grew a Leclercia, but the red cell grew nothing.

Second was a double platelet. The first product on day 7 grew coag negative staph, but the second product was outdated. It was one of the 40 percent that we could not get back after outdate for us to culture. Third was another double, and yet another twist, the true positive was a coag negative staph, but when we called the hospital, they cultured the patient and the patient had had absolutely no reaction, but she had coag negative staph in her blood cultures. Is it true, true and unrelated? There are two contaminants? Is it true?

Unfortunately, we did not do molecular testing at that time. So one could presume that indeed you had an infected patient from the second product. But that's not entirely clear. Much more clear in the patient realm is the fourth one, which has its own twist, and that is it was a triple platelet. We had two of the platelets. One of the two BacT bottles alarmed, and instead of culturing both platelets, they said one is as good as two, and they chose the wrong one. So they cultured the one that had a

negative BacT bottle. So we have a clear true negative, or clear negative false positive, if you will, the initial alarm.

The second one, though, since they didn't culture, it was an indeterminate, but let's assume it's positive, because the third one had been transfused to a patient, and that patient, the transfusion service did not have record of a transfusion reaction, but when they went back to the chart, indeed the patient had a florid septic transfusion reaction, and had coag negative staph in his blood, yet again not molecularly characterized, but it was very suspicious, because this person had a florid transfusion reaction.

So what we have are four products that likely cultured positive. Three that definitely cultured positive, and the fourth presumably, had an indeterminate, presumably was infected as well. So that's a rate of 498 per million. When you look at the PASSPORT data, again very difficult to compare these. So these are of interest, but they are not definitive. The day 8 culture of an 8 ml day 1 BacT of mostly Amicus, some Trima, some Acrodose, whole blood derived pools, 662 per million.

We are in the ballpark. That's all I can say, because these are not statistically significantly different numbers. When you compare that to Verax, the Verax study

published in 2011, had 27,620 products that were tested, 10,424 of which were cultured at the same time. You're not only comparing apples and oranges, you're not even comparing fruit. You're comparing fruit to something else totally different, because with Verax, you tested right before transfusion, days 2, 3, 4, 5. We have day 7 data. PASSPORT has day 8 data. So the latest they tested was day 5.

Their only very clear septic transfusion reaction was amongst the 10,424 that were cultured. So active surveillance. And all we know that is that 31 percent of the units of all 27,000 were day 5. So applying that and assuming that the sub-study was very much like the entire study, you can come up with a number around 620 per million. Again, not statistically significantly different, and, unlike PASSPORT, they included patients in their study. So if we include our patients at 746 per million, again 746 and 620 are not statistically significantly different.

These studies are way underpowered because they have -- these are rare events with an N of 1 or 2. So very difficult to compare these, but I would say very strongly, we think we are in the same ballpark at least.

To close with some thoughts here. One, what we are trying to do is increase the safety increment, right?

But we're not trying to sterilize every unit. We are trying to prevent all septic transfusion reactions, particularly the one out of every eight that results in a patient fatality. But inextricably linked with that is platelet availability, because if you have the best system in the world to reduce even all contamination, if you markedly reduce availability, as we saw from the first slide, you can harm as many people as you help, and you have, to coin a phrase, not changed blood safety one iota.

Also, operational impact and cost are important. But they are more important to the blood centers and the hospitals than they are to patients. So that's a secondary consideration. What we need to look at is availability and safety.

Seven day dating actually helps with both. Things that we don't care about as much, the cost, but also with availability, which translates to safety. So of the options that are available to us, that we either have heard of or will hear about later today, INTERCEPT is a 5-day product, and we'll talk more about the guard bands and some of the issues related to that, why it can never reach 100 percent of the way we collect apheresis platelets in the United States, and even if we had whole blood derived platelets to fall back on, there's a reason they're 8 percent of our national blood supply. It's because you

have to be collecting within 6 hours of your manufacturing site in order to do that, to make it under the 8-hour wire to have the product separated and on a rotator in 8 hours.

So that's not necessarily a panacea either, increasing whole blood derived, because not every center is able to do that and is very close and can meet those stringent timeframes.

When we talk about secondary testing, whether BacTx, we'll hear about, whether it's BacT that we have heard about, whether it's on day 3 to get you 5 days or day 4 to get you 7 days. There are few data that allow us to even compare. So if you look at that 2011 Verax study, clearly there was one septic transfusion reaction amongst the 10,424 that were cultured, but the whole study you could use as well. That's 1 per 27,500 with a day 5 product.

There was another day 5 product in that study that the patient had a mild allergic reaction, did not have anything related to sepsis, but when they looked at the bottle, it actually grew an organism. Unfortunately, the paper doesn't say whether or not the patient's blood had the same organism, but I would suspect that it did and maybe Dr. Jacobs can comment on that when he speaks.

So that might be 2 in 27,500. That would be the residual risk of a Verax-tested platelet on day 5 or on day

2 or 3 or 4. So I think that that as a licensed product tells you what our tolerance is for residual septic transfusion reaction rates.

Dr. Bloch reported their Hopkins data. There are now more than 23,000, but they have not found anything. These are rare events, and Dr. Field just presented about 72,000 I think was your number now; you're up from 65 from the last BPAC meeting. Again, no products that have escaped and gotten into patients and caused a reaction.

So these are rare events. It's really hard to characterize, but when you look at enhanced primary culture, our data suggests that we're not at 1 in 492,000. One other event in the numerator could halve that to 1 in approximately 250,000, and that's passively reported, as are the data on BacT and the Verax data are both actively about 39 percent of their data are active surveillance, and the rest are passive surveillance.

So again, very hard to pull these together. But they give you a sense of what you're dealing with. You'll hear from our friends in the UK, Dr. McDonald will talk about the large volume delayed sampling. Their rate when he last spoke was 1 in 1.8 million. People say, well, there were four near misses. True, but one of them could not even be transfused. It was egg drop soup, but even assuming those other four, if you add them back in, that

leaves a residual rate of septic transfusion reactions of 1 in 360,000.

If you presume that these passive rates are about 10 times lower than what you get, then the rate would probably be 1 in 36,000, or our rate would be 1 in 49,000, which is markedly different from what you would expect when you look at the Hong data, 1 in 10,000, again Amicus predominant platelets, some Trima, some Acrodose, all tested with either 8 mls of BacT on day 1 or 4 mls, in an eBDS system, which has now been phased out.

So I would leave you with the thought that, yes, you can't compare these strictly to each other, but the numbers do speak for themselves to some degree. If I had my druthers, I would love to have pathogen inactivation tomorrow, right? Give it to me. Good, fast, cheap, pick two.

Unfortunately, to get -- and Dr. Bloch showed $100. I think that's very generous. That's a loss leader kind of pricing, because to get to 20 or 30 percent, there's not much that needs to be done. Eligibility for those units to be pathogen reduced, don't have to change collections markedly. To get up to 50 to 55 percent, you have some significant costs and significant changes, but in our system, where we have gotten up to 80 to 85 percent eligibility, our availability has dropped dramatically, and

we still can't get beyond 85 percent, because of the guard bands, and in fact, our costs -- it's not one unit, one kit. We don't have triple that are approved. So we use two and sometimes three kits to fit into the guard band. It's much more than $100 each to do all those kits and all the effort related and changing the volumes of the platelets to meet these guard bands.

So it's not ready for primetime to be 100 percent of our blood supply, which would I think be the safest thing, particularly if the government and other payers would fund that. So most of the inpatient transfusions are not funded. They are part of a DRG. Outpatients are well reimbursed, but inpatients are not.

So you have another opportunity, and since you can't get to 100 percent, if tomorrow every hospital wanted pathogen-reduced platelets, you would still have a mixed inventory, and who do you give the safer platelets to? It's a difficult decision as a physician.

So right now point of issue testing, right, the secondary testing, or the enhanced primary culture would be at either minimum proportional sample volume or low volume delayed sampling. I think all of them substantially reduce risk. They do not eliminate it. But frankly, neither does pathogen reduction. There are three cases, one of which is recent in the United States, and I believe truly was an

infected unit that occurred in a pathogen-reduced product. It is possible to infect the products afterward, after the pathogen reduction occurs. So there are three cases. I know Dr. Benjamin will comment on them.

So it's not entirely safe but it is as safe as you get, I think, in the early part of the 21st century, but in the interim, we have other options, and I think hospitals are going to need to deal with this. Hospitals that are faced with mixed inventory, hospitals that are faced with cost constraints, blood centers, also facing cost constraints. We're going to need to think very carefully and not let the perfect be the enemy of the good and produce a number of options for hospitals to make their choices.

So with that, I think I am done.

DR. ALLEN: Thank you very much, Dr. Vassallo. Very nice summary of a lot of data. Any questions or comments for Dr. Vassallo?

DR. STRAMER: Ralph, can you talk more about the 197 true positives that you discussed on slide 6 for periods B and C, with your 24- to 36-hour hold? I'm curious when those came up, if you know, within the 24- to 36-hour timeframe, how many bottles were positive for those 197. You really didn't break those out. And then how you make 36-hour platelet hold work with 5-day platelets.

DR. VASSALLO: So let me answer the last one first. We're at 24 hours-plus, but we cannot do everyone at 24 hours, because platelets are collected throughout the day. Sor right now we do have up to 36-hour delay, and we get platelets out on day 3 or late on day 2. So if we were to go to a 36-hour minimum, that would certainly impact shelf life in a 5-day product, and that's why the UK has a 7-day product for a 36-hour initial incubation.

When you talk about the organisms, unfortunately, I don't have the times here. They are in the paper for period B, and my recollection is they're the usual -- they are less than the usual initial BacT, which is about 16.5 hours. They were a little less, maybe 12 to 14 hours as a median for the ones that came up in the periods B and C.

You also had a third question, and I'm blanking.

DR. STRAMER: It was related to how many bottles were positive for the 197.

DR. VASSALLO: The number of discordant bottles, obviously, suggests that you're having lower numbers of bacteria, and again, in the paper we have -- I think there are 12 discordant bottles, bottle sets, among the -- I don't think I have it here -- sorry, the 159,000 or 12 discordant bottle sets.

DR. STRAMER: The reason I ask is because I didn't think the paper was clear, and it said that you really

didn't record the platelet hold time. So I thought maybe you had additional information.

DR. VASSALLO: It is what everyone does, because no one can get exactly at 24 hours.

DR. STRAMER: So everyone is basically doing a minimum of 24 hours and some can go out to longer periods. Thank you.

DR. ALLEN: Other questions or comments? I am assuming that in the real world, not in the study setting, that you get something that is ultimately believed to be a false positive or a discordant result, you don't transfuse that product if it's still available. It gets pulled. Overall, what has that done to the cost of the whole testing process? Because that's obviously -- a thrown unit is part of the cost.

DR. VASSALLO: Well, you see in periods B and C right on the slide our discordant negatives and our true positives are kind of similar to what they used to be. The real hurt is the rise in false positives that will rise even more dramatically with an anaerobic bottle. Anaerobic bottles will pick up, as I think Dr. Leitman said at the last BPAC, that very rare obligate anaerobe, but we have seen them, but that may or may not drive the need for an anaerobic bottle, but it would certainly drive up the false

positives. So our false positive rate really drives the discard of, if you will, good platelets.

DR. CALIENDO: Angie Caliendo, Brown. So both you and the previous speaker mentioned opening and closing drawers of the Bactec system. How logistically feasible is it to do what the previous speaker mentioned, which is to have instruments designated per day so that you're going in and out less frequently? How practical would that be for you?

DR. VASSALLO: Good question. What it means is you buy more BacT instruments and controllers. So actually that is part of why our rate has fallen over time is we are doing that, but it has additional costs associated with it, as are adding additional bottles for people that are doing that, because you actually have to have more incubators and controllers.

The other option about not opening and closing is the bioMerieux folks are trying to produce a son of BacT, if you will, that they call VIRTUO, which you put the bottle on a conveyor and it goes in without having to open and close the drawers. So that's under consideration, I believe, for FDA approval.

DR. ALLEN: Thank you very much.

Our next speaker is Dr. Carl McDonald from National Health Service Blood and Transplant Section of the

UK; large volume and delayed sampling is the topic presentation.

Agenda Item: Large Volume and Delayed Sampling Testing Strategy, with Dating to Day 7

DR. MCDONALD: Thank you for the invite from the FDA to speak here, to Joanne and Bryan for looking after me so well. Very much appreciated.

My talk is NHSBT bacterial screening, two million and counting, because we have now got to 2 million as I stand here now. I have no disclosures.

A little bit about NHS blood and transplants, we incorporate the National Blood Service of England. We are the sole suppliers of blood in England, collect roughly about 1.8 million whole blood donations, and produce approximately a quarter of a million platelets per year.

So in my short 20-minute talk, I'm going to go through the NHSBT strategy to reduce the transmission of bacteria by transfusion, the impact of diversion and improved donor arm disinfection, the NHSBT protocol for bacterial screening, bacterial screening results, the added value of bacterial screening, and any future developments.

So back in the late 1990s, we carried out a study which showed that the majority of contaminants got into our blood components were skin contaminants. So we came up with a strategy of developing an improved donor arm

disinfection method, which we now use the ChloraPrep methods, 2 percent tincture -- sorry, chlorhexidine gluconate plus 70 percent isopropyl alcohol, diverting the first 20 or 30 ml away -- of blood -- away from the collection bag, these will house the skin contaminants, and we looked into bacterial screening methods, including the BacT/ALERT at the time.

These three interventions together have given the success we've obtained, and I think needs to be remembered, not just one of them individually. So improved donor arm disinfection, implemented nationally in 2007, diversion in 2003, and in combination we predicted that 77 percent reduction in contamination, and that's actually what we got. So excellent interventions, but in the period after the implementation of improved donor arm disinfection and diversion, 2006 to 2010, we had seven contamination incidents in components, 10 patients affected, three deaths, and five near misses, and if you bear that in mind what I'm going to say at the end, where we are now.

So NHSBT moved to bacterial screening. The board decided in 2010 to implement bacterial screening and had to be implemented within 12 months. Rolled out in February 2011 and the whole of NHSBT, all the sites for screening, all components, and all going to hospital being screened.

So the BacT/ALERT system was chosen through a tendering process. This is our screening facility. We currently have now three screening sites, culling down in London, Manchester, and filtered in Bristol. And they cover approximately a quarter million platelets per year. So, we have a nice lean system, where we have the BacT/ALERT system, the platelet shakers, and the laminar flow cabinets for doing the inoculating all in the same area, it's a nice easy throughput system. We have barcode labeling to give a specific sample identification.

Our protocol, we do one test. We extend shelf life to seven days. Platelet components are held for 36 to 40 hours, and the idea of that is to allow the bacteria to grow sufficient numbers to be captured in the sample taken to be inoculated. The BacT/ALERT bottles, the platelet components are sampled, and tested. We put 8 mls into each BacT/ALERT bottle. We do aerobic and anaerobic culture. And we also screen all vat splits individually.

The units are held for six hours, and the six hours comes from, that is inherited in, that's through our computer system when it first gets sent the result from the BacT/ALERT system. They're released with a 7-day platelet shelf life, monitored throughout that period, and any positives are recalled.

What happened after the introduction? And this is our quarterly bacterial screening rates for initial reactives and confirmed positives, February 2011 to March 2018. All the reporting periods, bar one slide, refer to that period. We started off, as has been mentioned today already, we had a very high initial reactive rate of over 3 percent, and in NHSBT, when we get an initial reactive, all the components from that donation will be discarded. The red cells, the pooled platelet, the plasma, would all be discarded, so 3 percent was unsustainable for us, so rapid action was put in place. Staff were retrained, as it's a new process for us.

There were issues with the siting of the BacT/ALERT machines near air conditioning vents and stuff which were upsetting the machines. We also noted there was a problem, as the Irish blood service did, that there was a problem with the anaerobic bottle generating false positives due to temperature differences, opening and closing the incubator drawers.

So we adopted the Irish approach of only loading 30 bottles in each incubator drawer, and closing that drawer, and not going back to revisit that drawer for 48 hours, and that dramatically reduced our initial reactive rate. It now ticks along about, the blue column here, the initial reactive rate, 0.3, 0.2, depending on the month.

And note, the confirmed positive rate is consistent throughout the entire reporting period.

Number of initial reactive confirmed positives, same reporting period. Apheresis, over 1.3 million screened, initial reactive rate, 0.33 percent. Confirmed positive rate, 0.02. Pooled, over half a million screened, 0.25 percent initial reactive rate, confirmed positive rate, 0.07. So, in total, from the data up to March, nearly 2 million screened, now it is 2 million, 0.3 percent initial reactive rate, confirmed positive rate, 0.04.

The apheresis rate is a lot lower than the pooled rate, and statistically different, due to the number of venipunctures. We have four donors who contribute to a platelet pool, and surmise that it's the reason why we have the higher rate in the pools.

This is the initial reactive screen bottle data, and I should say, we, in NHSBT, have a policy when we get an initial reactive, we have to remove all the bottles from that donation off the system. The other bottles may have gone positive, but this is what we're showing throughout our initial reactive screening data. With the anaerobic only, we got 73.8 percent of our initial reactives. Aerobic, 21.3 percent, and in both, 4.8 percent. Now, the anaerobic bottle would seem to have good sensitivity, but

poor specificity, as we have 77.9 percent of our false positives from an anaerobic bottle.

This is a different reporting period. This is just looking at confirmed positives. This is reference laboratory data, not screening data. This is for platelet components, and we only confirmed on the platelet component alone. We have confirmed, some confirmed positives, on red cells, where the pooled platelet has not been present. So, 237 in total, and the anaerobic bottle only, and these bottles are left on the system for the entire seven days, we got 49.8 percent of our reactives from the anaerobic bottle only. Aerobic, 1.7 percent. And both bottles, 48.5 percent. And if we deduct the proprionis from this figure, it becomes about 20, 20.7 percent, approximately.

So, the anaerobic bottle has good sensitivity, poor specificity in total. The reason we use the anaerobic bottle, I should say at this point, is the fact that we have a transmission of Clostridium perfringens, and we'd be negligent in not using an anaerobic bottle, as this cause of death in patient.

Confirmed positives, 730 in total, 703 gram positives, 27 gram negatives. We get a wide range of organisms using the two-bottle system. The majority are skin contaminants, the largest group being the proprionis. I'm a believer that we need to detect all the bacteria

present. We shouldn't transfuse bacteria into a patient. And that is a plus for doing bacterial screening, and also for path inactivation, of killing the bacteria, so they don't go into the patient, live bacteria into the patient.

Largest group is skin contaminants, followed on by oropharyngeal, followed on by enteric organisms, followed on by environmental organisms. This slide shows you the confirmed positives we feel are particularly pathogenic. We have Streptococcus dysgalactiae, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus agalactiae, Listeria monocytogenes, Bacillus cereus. Please note the rapid detection times for these organisms. None of these left NHSBT, none of these went to hospitals. We retained these, and they were not transfused. Total cases, 71; 87 components contaminated.

Looking at the gram negatives we feel are particularly pathogenic. Escherichia coli, Serratia marcescens, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, and Campylobacter lari. Again, very rapid detection times, with the exception of the Campylobacter lari, which I believe is the first or second detected from platelet component in the world, reported in the literature.

This is data, really enforces why we screen all our splits. This is data, when we got all the splits back

into the reference laboratory for confirmatory purposes. In the doubles, we got 47.7 percent, only positive in one of the splits, with 52.3 percent in both of the splits. In the triples, 50 percent only in one of the splits, the other two were negative, 20.6 percent in both two-splits, and 29.4 percent in all three splits. And when it was across the board of all three splits, it's potentially a bacteremic donor.

Near misses and transmissions -- one transmission with Staphylococcus aureus. The patient, an elderly patient, became unwell. Fever, typical symptoms, rigors, but after a couple of days, recovered.

Four near misses, three were Staphylococcus aureus and one with Serratia marcescens. This is near miss 3, and by near miss I mean it was on the way to be transfused, either stopped at hospital or by our own staff, due to its abnormal appearance. As you can see, these lovely clumps in here.

The first three near misses all were Staphylococcus aureus. We did not, regrettably, retain the bottles for further investigation. So, we don't know if these bottles actually inoculated. But, I'm pretty certain, with three cases, they probably were. We have very, very stringent verification stages in the bacterial screening process. The bags are weighed before and after

sampling, and we would know, it would flag up on the computer system if that was not the case.

We are actively now investigating why we've missed these Staphylococcus aureus, and it's been reported by other blood services. We are doing 14 genome sequences of the near misses and the transmission, and we're also doing growth kinetic studies using BacT/ALERT sampling at 36 and 48 hours, and also, hopefully, with the BacT/ALERT VIRTUO system.

This is near miss number 4, Serratia marcescens. Positive in only one of the splits, here. Notice pack 2 is completely negative. We did retain the bottles. These are the set bottles, inoculated and uninoculated control bottle. The bottles worked. We put Serratia marcescens into the bottles, and they went positive, and there was no bacteria present within those bottles, whatsoever.

So, why did we miss this one? Can't really call it a BacT/ALERT failure, because there was no bacteria, so it's not really the system's fault why we didn't detect this. Insufficient bacteria at time of sampling? On the next slide I'm going to show you why I don't think that's the case. Maybe we need to think about this. Maybe the pack integrity is not what we think it is, and maybe the contamination got in afterwards.

This is a growth curve for Serratia marcescens, suspended in plasma, which is what we have in our apheresis platelets, and we inoculated 10 per bag -- not 10 per ml -- and by our first point, we'd first take sampling at 36 hours, we got over 10^7 in the bag, so it's extremely unlikely we're going to miss it, and by 40 hours, which is our last point, the longest period we can actually leave the bags for before sampling, we got over 10^9. So, very unlikely we missed it due to lack of growth of the organism.

Added value of bacterial screening? Over the years, we've detected four Streptococcus bovis, which has a link with bowel cancer, and we found four donors who had colonic polyps. And there's a nice paper from Lee, published in Transfusion, with his work in Hong Kong on detecting with BacT/ALERT donors with Streptococcus bovis, again, who had bowel cancer, and referred to the hospitals.

We've also had donors with Streptococcus constellatus, and Peptostreptococcus micros, who had gum disease. And so it has an added benefit. Also, if you detect Pseudomonas, you pretty got a problem with your production facilities. And if you're getting an increase in Staphylococcus species you've probably got a problem with your donor arm disinfection, or maybe diversion. So, it gives you feedback on what is going on out there.

In the future, this is the BacT/ALERT VIRTUO, the new generation BacT/ALERT system. This, as Ralph alluded to, loads the bottles automatically into the system, so there are no incubator drawers to open and close. So, we're hoping that this will get rid of the false positives.

Also, we've done a study in our laboratory for obtaining a CE mark for bioMerieux for pooled platelets and apheresis platelets, and we found that the machine gives fast detection times. I wouldn't say it's more sensitive, but it's picking up the bacteria quicker, which might have added benefit, and it's 1 to 3 hours faster, per species, we noted.

It has automated loading and unloading, which will be a staff benefit. It has also other benefits. It automatically scans the bottles to see if they've been inoculated, and it reads the expiry date on the bottles and calibrates the machines automatically. For an organization that is putting half a million bottles through the system, it has added value. NHSBT is intending, in 2019, to use the system at one of its sites in an operational trial to see if we get the benefits from the system that we predict it may have.

We've had only one transmission in over 2 million platelet components screened, which was Staphylococcus aureus; four near misses, three with Staphylococcus aureus

and one with Serratia marcescens; a false negative rate of 1 in 360,000. We've tested 6,217 types by platelet components, and we've got one confirmed positive out of that, so we do have a secure system -- and that was Streptococcus pneumoniae. But obviously, not infallible. But if you think back to what we had before, 10 incidents, three deaths and five near misses, we have improved the safety of the blood supply considerably.

Why have we got the good results we've got? Delayed sampling, waiting the 36 to 40 hours to sample the units. We test a high volume, 5 to 7 percent of the platelet component, and we screen all the apheresis splits, and we use a two-bottle system, aerobic and anaerobic, to capture a wide range of species. In conclusion, bacterial screening within NHSBT has proven to be an extremely successful risk reduction intervention, and we published on this in Transfusion in 2017, the methoding and our results to that period.

I'd just like to acknowledge Jennifer Allen, Anjana Roy, and Kate Aplin, Su Brailsford, and Mfon Asuquo, for helping me put the presentation together and providing the data. So thank you for your attention.

DR. ALLEN: Thank you, Dr. McDonald. Very interesting information. Any questions for Dr. McDonald from the panel?

DR. LEITMAN: So, I'm going to perseverate on the same thing that bothered me in December of 2017. The reason for the anaerobic bottle, the major reason, was because of the septic transfusion reaction fatalities due to Clostridium perfringens.

DR. MCDONALD: The major reason. We debated, A, the time we actually sampled the bottles, what was operationally feasible. We also debated, do we do an aerobic bottle, an anaerobic bottle, or both. And the debate ended up, there's two reasons. A, we felt if we didn't do the anaerobic bottle and we had a transmission of Clostridium, we would be on very dodgy ground legally, that we had knowledge of this and we didn't put this in place.

DR. LEITMAN: I understand. From February 2011 to March 2018, the seven-year period, there were no Clostridium perfringens. And you had the major cause of, if you will, of discarding components, which would have been overwhelmingly likely to not cause a transfusion reaction, was the anaerobic bottle positivity.

DR. MCDONALD: Yes, the highest false positive rate, yes.

DR. LEITMAN: That's a very sizable cost, if you will, because you're discarding products which are almost certainly safe. Just pointing that out.

DR. MCDONALD: Pros and cons. We're hoping that with VIRTUO, and adopting our new loading pattern that we did, as the Irish blood service, that was substantially reduced, we're probably operating at the tolerances of the system, now.

DR. ESCOBAR: Miguel Escobar, from the University of Texas. You mentioned the amount of sample you draw is about 16 mls, which is 5 to 7 percent of the donation, correct? Is there any data showing that removing that amount, does it make those platelets less effective or patients are needing more transfusions because they're not getting enough platelets due to the amount that is taken out?

DR. MCDONALD: There is no data on that, but the feedback has been -- we can't take any more out, is -- we couldn't do a retest. That is the maximum we can take out. But there's no data on that, no.

DR. ESCOBAR: There's no data saying you are getting less number of platelets for that transfusion.

DR. MCDONALD: For the patient, yeah. We've had no complaints back from the hospitals.

DR. ESCOBAR: I assume the majority of patients that get platelets are going to be the thrombocytopenic patients, transplant, cancer. Okay.

DR. MCDONALD: Obviously, that is a concern, and that has been discussed in NHSBT. The question of the volume we take out, the safety against the efficacy. That's always going to be the issue.

DR. STRAMER: Susan Stramer. To help dissect further into Dr. Leitman's question, I don't know that you showed, or I don't remember seeing where you showed those organisms that were detected in the anaerobic bottle only, and time to detection of those, but the ones that are not P. acnes, and that potentially would cause septic transfusion reactions in recipient, because I think the anaerobic bottles we talked about in December, or November 30, was not only to detect obligate anaerobes, but also facultative anaerobes. It's a richer medium, hence more false positives, but also decreases the lag time in potentially facultative anaerobes that maybe we wouldn't detect in an aerobic bottle. So, I was just curious if you had further data to dissect out what you're detecting in the anaerobic bottle that's not P. acnes?

DR. MCDONALD: Right. We don't have further data, but the data we have shows that captured the wider range of organisms. So, if you were only doing one bottle, the anaerobic bottle, potentially, is the bottle of choice. Though I'm not recommending that.

DR. ALLEN: Just a quick question going back to the initiation of your system in 2011. You went from a 3 percent rate back down very quickly. Was that, the rate of decline, related to the training that went on and so on, or do you think it was the system itself?

DR. MCDONALD: I think it is multifactorial. Some of the systems were housed in areas of the building inappropriately, and they were getting blown on by air conditioning systems, upsetting the machines. We had another problem with electrical interference with the machines, electrical spikes in the power supply, so line conditioners were put in place. So, multifactorial were why, and the loading pattern for the anaerobic bottle, too. Multifactorial, really. And also the staff training, as well, reminded of aseptic technique, et cetera.

DR. ALLEN: So, certainly, a very important object lesson learned from that experience.

DR. MCDONALD: Which was shown by the Australian blood service, when they , I think, had a 1.7 percent initial reactive rate when they implemented bacterial screening. We're not alone.

DR. CALIENDO: Angie Caliendo, Brown. I am still trying to get my head around this anaerobic bottle. You showed a slide of serious pathogens that you detected, and

there was a variety of organisms. Did any of them grow only in the anaerobic bottle?

DR. MCDONALD: I think, as I said in November, I think we are getting too obsessed with the aerobic-anaerobic. I think because an obligate anaerobe is not really going to grow in the platelet environment, in anaerobic bacteriology. It's more the fact the media that's in the environment of the bottle does seem to have a wider range of detection of organisms than the aerobic bottle.

DR. CALIENDO: I guess another way to think about it is, is it just the volume? Or do you really think the media is making the difference?

DR. MCDONALD: I think it's the atmosphere, the atmosphere within the bottle. The media's the same.

DR. HARRELL: Lizzie Harrell, Duke. One quick comment about the anaerobic bottle. I think when we look at the platelets, we're looking back to the same reason we use both bottles for routine blood cultures, to a certain extent, because some of the organisms that we see routinely causing bacteremia, they also grow in both aerobic and anaerobic bottles, and sometimes they will grow better in the bottle that's anaerobic, and therefore having the two-bottle systems sort of gives you a chance to sometimes assess whether you think you are having possibly true

contaminants versus having a true pathogen, because you are seeding in both of those bottles. And also it increases the volume of blood that you're testing by having those two bottles, and you're trying to cover both bases.

DR. MCDONALD: I would agree with that. We've covered a nice range of organisms, also increasing the volume, so increasing that chance of detection. Yes.

DR. CALIENDO: Angie Caliendo. I would just make the comment, though, this is a little different than a blood culture for a patient, where I can look at them and decide whether or not I think it's important, if it only grows in one versus the other. For now, for this situation, they're gone. Those units are gone, no matter what. Even if only one is positive, no one's going to take the chance to say, we're not going to pool that.

So, I feel like getting back to what one of the speakers said earlier, is it's how do we keep from having a supply problem while we're fixing the contamination problem. And I guess that's how I'm thinking about all of this. What's the false positive rate versus how much safer are we making the supply? That's what I'm trying to get my head around.

DR. ALLEN: I think that will be an important topic for discussion this afternoon.

DR. LEITMAN: Just one more quick comment, the plastics of the platelet container are devised by the manufacturer to be oxygen permeable, so the atmosphere environment inside the platelet container is so different from the atmosphere inside the anaerobic bottle, so what grows well in an anaerobic bottle may be meaningless inside the platelet container. I think was said, maybe, by Dr. Stramer. But it's worth pointing out that the platelet containers are designed to be oxygen permeable, gas permeable.

DR. MCDONALD: But the organisms are growing in the anaerobic bottle. Which doesn't sound logical, but they are.

DR. ALLEN: Dr. Jones, CDC.

DR. JONES: Thank you. If at any point you can tell us which organisms were able to grow just in the anaerobic bottle, that would be quite helpful.

DR. MCDONALD: It is in the publication.

DR. JONES: Okay. We did release a report late last month about Klebsiella facultative anaerobe and C. perfringens reactions that did result in a death in the United States, so it's a very important question for us, as well.

DR. ALLEN: Thank you. Any other questions or comments? Dr. McDonald, thank you very much for your

presentation. The next speaker is Dr. Michael Jacobs, Case Western Reserve University, speaking on behalf of Verax and Immunetics.

Agenda Item: Bacterial Rapid Testing Strategy

DR. JACOBS: Thank you, Mr. Chairman, ladies and gentlemen, committee members. I am giving the presentation on behalf of Verax and Immunetics, but I'm primarily giving this presentation on behalf of patients. Because patient safety is our issue, and Verax and Immunetics have kindly allowed me to extend this to a more general overview of the subject, and to try to put everything you've heard up to now into context. And I'm going to try and do this based on the evidence we have, not on supposition.

Here are my disclosures. I have every conflict imaginable. But I am paying my own expenses for this and I am receiving no financial support for my travel expenses or time associated with this presentation.

My presentation covers assessment of the available evidence regarding the efficacy of primary and secondary testing of platelet products in detecting bacterial contamination of these products. It also includes evaluating two FDA-approved secondary test methods on behalf of their manufacturers, PGD Test, Verax, and BacTx Test, Immunetics.

These are some of the source data that I'm using, and you have this for reference. I'm not going to read these all out. I also wanted to give the committee some background. Many of these are redundant because you've seen some of these publications referred to by previous speakers. I'm a clinical microbiologist, I've been the director of clinical microbiology since 1979, Case Western Reserve University and University Hospitals.

I got involved in bacterial contamination in 1991 when Dr. Roslyn Yomtovian, who was the medical director of our transfusion service at that time, came into the micro lab with a septic transfusion case, and I've worked with her ever since, and I'd also like to dedicate this presentation to Dr. Yomtovian, who passed away in 2014. Had she not, she would be giving this presentation. As many of you knew her, she was passionate about patient safety, both as a transfusion medicine specialist and later on as a patient who received multiple platelet transfusions, and in fact, she addressed this committee in 2012 from the patient's perspective.

I continued working on these issues following Dr. Yomtovian's departure from our department, helped define the criteria for the diagnosis of septic transfusion reactions, and differentiation between transfusion reactions associated with contamination versus other

causes. I'm going to show some of my key publications during my tenure at Case Western Reserve and multicenter studies. I also want to point out that our institution has been extremely successful. Our studies on platelets have not bankrupted us yet.

We started off doing a very simple surveillance method when Dr. Yomtovian first came to me in 1991. We simply take 0.1 ml of a platelet aliquot, 3 to 5 mls is withdrawn from a platelet unit into a small bag or a test tube. We plate 0.1 ml onto a blood agar plate. We incubate this aerobically because we aren't particularly interested in anaerobes at time of transfusion, although there have been some cases, so we may have missed some anaerobes. But in transfusion reactions, we do incubate anaerobically to pick these up, and so far have not had any.

If growth is detected -- this is one of the most important parts of our procedure -- we keep the original aliquots so if we get growth, we can go back to that aliquot, re-culture it, and make sure whether we have a true positive or a false positive, and this has also allowed us to quantitate the bacteria over this time period. So, over the last 27 years, for 24 of those years, we have done this procedure on some or all of our platelet products, and that's approximately 150,000 times.

Our first paper came out in 1994, bacterial contamination due to increased surveillance. We then published more detail in 1993, prospective microbiologic surveillance program. We then published this more extensively in 2006, evolution of our surveillance methods to detect bacterial contamination. We also write several editorials. I've given you one example, written with Dr. Yomtovian and Dr. Tomasulo and myself, the quandaries in these issues. And I'm very disappointed to see that these same quandaries, if you go back and read this editorial, are the exact same ones we are discussing 11 years later. We have not solved them.

The next paper we had was relationship between bacterial load, species, and transfusion reactions. This was a key publication, and I'll show you some of that data. We also, I was the principal investigation of the Verax Pan Genera test, published in 2011, and I'll be showing those tests and the results of the study in more detail. And our most recent paper was the detection of septic reactions based on active versus passive surveillance; again, many speakers have referred to and shown you this data.

This is the summary of what we've done since 1991. We've cultured 12,700 apheresis units before culture was instituted, and we had 394 contaminants per million. In all the data I'm showing you, I'm using contaminants

rates per million, because when you get rates of .02 percent versus .025 percent, .03 percent, 0.1 percent, my head starts spinning, and I'm trying to avoid this issue. All my data is presented firstly as contamination rates per mission, and secondly, when I'm showing comparisons, I use 95 percent confidence intervals, calculated using the same method. This it much easier to compare data sets.

After culture was introduced, we had the same contamination rate for apheresis units. It did not change. This is not to say that culture was not beneficial, and I'll go into some of the benefits. The organisms changed, but the basic contamination rate did not change. This is an extremely important point.

However, when we looked at pooled platelets, there was a major, massive improvement. We went from 2,400, almost 2,500 contaminants per million pools, before culture was introduced. After this was introduced in 2007, when Acrodose units were used, this went down to less than 200. Big improvement.

We also were able to look at, because we quantitated all these units, the relationship between bacterial inoculum and what happened to patients. And note that I'm using the term bacterial inoculum, bacterial load. Several speakers up to now have called this bacterial concentration. Bacteria are not in solution. They do not

act as solutes, they act as particles, and this is a very important distinction which limits our early testing. And as you can see here, you get most of the severe reactions occur when they're greater than 10^5 organisms per ml. When the load was less than 10^5, we had 34, only 5 septic reactions. When the load was greater than 10^5, we had about an equal number, 21 septic reactions, and 11 serious septic reactions.

Also, some of this data has been referred to, bacterial contamination of platelets between 1991 and 2013. Detection of septic reactions was much lower by passive surveillance. During the first period we did active surveillance on part of our platelet inventory, about 100,000, versus 135,000 where we didn't culture them, and we found sepsis in 16, or 155 per million, when the active surveillance, versus a tenfold lower value when there was passive surveillance. There was one death in each arm, and this was recognized by active and passive surveillance.

During the culture period, which is predominantly after 2004, we had 5 cases of septic reactions, a slight decrease from 155 per million to about 100 per million, but the same number of deaths, well, no statistically significant difference.

What did this experience teach us? Or certainly, what it taught me. Firstly, that bacterial contamination

is real and continues to the present. Additional measures are needed to address this. We've been saying this for more than 10 years. Very little has been done to do this.

The second point, active bacterial surveillance by culture of platelets at time of issue is the key to understanding the extent of the problem and the effect of interventions, and I'll be showing you a lot of data to support this.

Thirdly, primary culture was effective in removing many of the fastest growing, most virulent bacterial species, but not in reducing contamination rate or eliminating septic reactions and fatalities completely.

Fourthly, recognition and reporting of septic reactions is poor. So assessment of the value of interventions based on septic reactions is of limited value, and this refers to many of the presentations you've heard up to date. We've heard interpretations, conclusions, based on septic reaction reports.

And the last point, which is a key one, and this was a game changer, was that clinical features of septic reactions changed after introduction of primary culture. They're now frequently delayed, less severe, and more difficult to differentiate from other transfusion reactions. So, again, comparing passively reported septic transfusion rates before and after culture were introduced

are greatly affected by this. And again, I'll be showing you the data in support of this.

Also, I was very disturbed to see this report, which came out last month. During August of 2017, two separate clusters of platelet transfusion-associated bacterial sepsis were reported. Two patients died in Utah after platelet transfusions from the same donation. Clostridium perfringens was isolated from one patient's blood and the other patient's platelet bag, and donor's skin swabs showed highly related organisms. And in California one patient died after a platelet transfusion contaminated with Klebsiella pneumoniae.

These cases reinforce the need for additional methods to prevent transfusion of bacteria-contaminated platelets, and the occurrence of two more fatal cases of Clostridium perfringens provides further evidence that primary culture should include an anaerobic culture bottle, going back to some of the previous discussion we heard.

My objectives for this presentation are to show the limitations of septic transfusion fatality reporting, show the limitations of primary culture, show that the proposed increases in primary culture volume do not increase detection rate, show that secondary testing is effective in detecting contaminated platelets missed by primary culture, and show that secondary testing has been

proven to be able to interdict contaminated platelets. These are the strategies that the committee was asked to address. My assessment will be based on these strategies.

My first objective, review evidence showing limitations of passive surveillance. These are the SHOT criteria used in the UK for septic transfusion reactions. Out of 616 reports of possible septic transfusion reactions, the committee adjudicated that one was definite sepsis. The issue with this is that septic reaction criteria have overly stringent criteria and requires the same bacterial species be cultured form the patient's blood and the component or the donor, and the problem is the committee will adjudicate that this is not a septic reaction if one of those cultures is not done.

Bacteremia can be transient, bags may not be available, and blood and product cultures may not have been performed. And this is a direct quote from the SHOT report. Hemovigilance systems for bacteria transfusion transmitted infections are passive, and as such rely on clinical colleagues to report suspected transfusion transmitted infections.

This is a compilation of reports of septic transfusion reactions based on active versus passive surveillance, and I am going to show you a number of charts where I'm showing you the rates per million -- again,

everything is per million, and the bars indicate the 95 percent confidence intervals, and they're all calculated using the same program.

As you can see on our apheresis units, by active surveillance, which is by bacterial surveillance, we found roughly 50 septic reactions per million. When we used apheresis or pre-pooled platelets, the rate was the same. At Johns Hopkins early experience before culture found very similar numbers, 40 septic reactions per million, confidence intervals overlapped entirely.

When we looked at septic transfusion reactions during the Verax study, and I'll refer back to this before, again, the septic transfusion reaction rate for this active study was no different, and I'll give you more detail on that when I discuss the test.

Conversely, if you look at the right-hand side, if you look at all the passive surveillance studies, all of these show septic transfusion rates about tenfold or more lower. Red Cross also showed a difference between reported rates, Amicus being higher than Trima. Kamel, Blood Systems, report 2008 to 2012 versus 2014 to 2016, showed the rate went from 5.3 to 3 per million, but again, this was not statistically significantly different. When you looked at the UK data from Dr. McDonald's data from the National Health Service, no pretesting went from 10 to 15,

if you include near misses. After pretesting went from 1 to 4, but again the big hook in this is how many of these were missed by passive surveillance and the change in the nature of septic reactions.

This is some of the evidence for the change in septic reactions. These are five cases we had that occurred after culture was introduced, and we had five severe septic reactions out of 20 contaminated platelets. None of these five transfusion reactions were reported to the transfusion service, due to lack of recognition, in case 2, or failure to report when delayed reactions occurred in outpatients.

This was a major breakdown of our system. Patients were transfused; as our patients went home, then developed transfusion reactions, came back in, and none of the medical personnel treating this patient through the emergency room, back to admission, back to transfer to our hospital, realized that this needed to be reported to the transfusion service. They were diagnosed as transfusion reactions, treated appropriately. The breakdown was it was not reported to the transfusion service, and without our active culture surveillance system, we would never have known that these transfusion reactions occurred.

The other issue that we had the opportunity of looking to in this paper was when patients do have

transfusion reactions, can you differentiate between septic and non-septic transfusion reactions? And the bottom line is that this distinction is not possible. There's complete overlap between signs and symptoms of septic reactions versus reactions caused due to other reasons, allergic reactions, ABO incompatibility, febrile nonhemolytic transfusion reactions, and so on.

The best positive predictive value we could come with using the AABB criteria was 12 percent. These calculations are based on the fact these five transfusion reactions would have been reported to the transfusion; based on the fact that none of them were reported, the actual sensitivity was zero.

Also, just to emphasize our active surveillance program, we account for 6 percent of fatalities during the period 2005 to 2016 reported to the FDA, yet we transfuse 0.4 percent of the 2 million platelets transfused annually in the United States. Again, emphasizing the difference between reported and actual reactions, both septic and fatal.

This brings up the main point that I want to bring out, that this is a very simple issue. You have a bag of platelets and plasma, you're infusing it into patients. If you want to know whether this is sterile, culture it. That's what we do for all nonblood products.

It's a very simple procedure, it's a very inexpensive procedure, and it gives you absolute data.

This is, to me, the gold standard for determining bacterial culture rates, is culture at time of use or outdate. The utility of interventions can be absolutely documented by such cultures. Other parameters, such as reported septic transfusion and mortality rates, result in rates being greatly underreported. Transfusion reactions cannot be accurately classified without appropriate cultures, as clinical features of septic and other reactions overlap.

My next objection is to show evidence that the U.S. primary culture alone is not adequate to interdict a sufficient proportion of bacterially contaminated platelets. We're all aware of this, but the point I'm going to make here is that variation in media, volumes, and time of testing makes very little difference.

These are all the studies, and I'm going to skip to the next slide to show the summary of these. You can see that all of these studies show apheresis contaminants missed by primary culture are independent of volume, time of testing, or test method. These all show overlapping 95 percent confidence intervals, 3 to 20 ml per collection were used for primary culture.

Now, this slide, to me, is one of the key cultures, so please keep your slide deck open at this when you have the printout, when you're referring to some of the other slides that I'm going to show, because I'm going to refer back to this slide. This shows a number of studies, because when we first started doing cultures, we were told that our site was unique. Well, we now have eight studies showing exactly the same thing. Our site is not unique. Our platelets are representative of the U.S. platelet supply.

The second point is, if you want to know how many platelets are contaminated, culture at time of use or outdate gives you this information. This was shown in the PASSPORT study. Four out of 6,000 platelets, the apheresis platelets with a higher volume, and 7-day out were shown to be contaminated. I've adjusted this down to two, because two of them were repeat positive, two of them showed different organisms, so it's possible that their rate was lower, but it's between 300 and 600 per million contaminated. And this was the reason that the PASSPORT study failed. This was the criterion set by the PASSPORT study and FDA mandate, that the contamination rate should be lower than this.

The next study is the Irish data published by Murphy, 2008, you've seen that. Plate culture results showing, again, 400 per million.

The next three studies that I've highlighted in red are intervention studies. These show how many were picked up by intervention. Again, the next principle that I want to introduce is that if you have an intervention study, that your detection rate is comparable to the missed cultures by primary culture, you have shown that that intervention is successful. And I can show you three interventions where this intervention was absolutely successful. We have absolute data; the detection rate was comparable to the missed rate.

The first one was the PGD test, where we found 9 out of 27,000 units were positive. Several of the previous speakers have referred to what's been missed by the study, leaving out what was detected by the study, and to me, the detection is extremely important. This has saved patients getting these 9 contaminated units. I'm going to show you more detail of that shortly.

The next study was presented in abstract form in 2015 at ISBT by Ladenheim, and this was experienced in Wisconsin over a seven- or eight-year period, where they did PCR on 85,000 platelet units. And guess what, they

found 300 contaminated platelet units by PCR, and they were able to interdict these.

Finally, on the extreme right, is the study that Dr. Bloch presented. This is the data Dr. Ness presented at AABB last year. He found 5 out of 17,000 platelet units were positive, a rate of roughly 300 per million, and he was able to interdict these. Dr. Bloch has given an update on these. The second last study was a study done in Canada reported by Sandra Ramirez using after-day-5 cultures. Seven out of 8,000 platelet units were found to be contaminated, again, missed by primary culture. So, I think there's no question that primary culture misses roughly 400 contaminated units per million, and that we can detect these with an adequate intervention system.

My next objective to look at the minimal proportional sampling volume and large volume delayed sampling are not equivalent to the current U.S. primary culture testing plus a secondary test, to interdict bacterially contaminated platelets. This is the key issue. Both speakers before me showed you the evidence they have that these methods are equivalent to primary and secondary testing.

If you look at what I call the gold standard, if you look at contamination rate per million, when they did culture outdated units, Vassallo presented this data and

noted himself that this was no different from the failed PASSPORT study. His contamination rate, depending on whether you use absolute proven or indeterminate results, were between 370 and 476 per million.

In McDonald's study, there's two issues with the data that Dr. McDonald presented from the National Health Service. One is he's showing you combined data of buffy coat pools, which are not used in the United States, and apheresis platelets. And during his early study, the ratio of buffy coat pools to apheresis was 2 to 1. During the time that they did culture the ratio was the reverse, 1 to 2. And we need Dr. McDonald to provide data, to do two things to their data.

One is, clearly differentiate, as Dr. Field did for the Irish study, between culture rates between apheresis and buffy coat pools, because in the United States we're only interested in the apheresis units -- we don't use buffy coat pools. And the second thing is to exclude anaerobes, mainly to exclude P. acnes, because those are of no clinical significance. Because the P. acnes does not grow, as was pointed out, in the aerobic platelet culture bag. If there are a few P. acnes in the bag, they just sit there until the unit expires, and don't cause any patient harm.

The rate that Dr. McDonald showed was 1 out of 6,000 platelets was contaminated. This is a very low number, and this is a very easy problem to solve. The UK has treated 2 million platelets. If that cost 20 pounds per platelet test, and Dr. McDonald can comment on whether that's a reasonable number or not, you spend 40 million pounds on this. Spend another million pounds on culturing your platelets to find out if your method actually works.

When you plot this data using low-volume versus these high-volume cultures, you can see that on these numbers that we have, these high-volume cultures have not been shown to successfully reduce the rate that we need. There is no statistically significant difference, and I believe that with the UK data, that when this is broken down and just shows apheresis units, that this difference will be even less. I think most of the difference seen in the UK was improvements in buffy coat, similar to the improvement we saw in the United States when we pooled single donor platelets.

Again, just to emphasize, there's no statistically significant difference between the minimum proportional volume and the large-volume delayed sampling and current primary culture methods.

When you look at the septic transfusion reactions are comparable after the introduction of primary culture in

the United States and UK. This was introduced in 2004 in the United States and 2011 by the National Health Service. By passive surveillance, septic reactions reported in the United States decreased by 72 percent to the Red Cross, and the National Health Service by 67 percent.

While septic reactions are notoriously underreported even the UK, the drops are comparable. Since the comparisons are within an organization, the percent decreases are important and are comparable, suggesting no advantage of the higher volume and later test time used by NHSBT. And I'm quoting Dr. Benjamin's publication and his comments at the last BPAC.

Going back to the high false negative rate of outdated culture. Outdate cultures in the minimum proportional sampling study done by BSI were done during the early phase of the 3.8 percent study. Eight thousand outdated units were culture and they showed either three or six contaminated units. Three confirmed and three indeterminate.

These data are not included in Dr. Kamel's publication, which was published in 2017, but predate the published data. This was, however, presented in abstract form. My question to this group is why was this not published? Why did BSI continue this program after they definitively showed that it did not work? At the BPAC

meeting in November last year, Dr. Vassallo compared these findings with the PASSPORT study, which had 300 to 600 per million, and noted that his result of 370 to 746 per million were not significantly different from the failed PASSPORT study, and again, he said the same thing today. This method should therefore be deemed unacceptable as well.

Data presented at the November BPAC showed a large decline in culture rates, however, as I mentioned before, data includes both apheresis and buffy coat pools, as well as anaerobes. The number of cultures performed after introduction is low, just over 6,000, considering 2 million platelets have been transfused with one positive in an apheresis unit. Much larger numbers as well as differentiation between apheresis and buffy coat pools are needed to provide a true indication of the efficacy of the large-volume delayed sampling method for each product. It's possible this method is superior but it needs to be shown. It has not been shown up to now.

Recent large-volume delayed sampling primary testing detection rate was no different from the rate rejected in the 2016 draft guidance. Dr. McDonald gave us an update today showing that their primary detection rate is .02 percent, or 200 per million. This was rejected by the draft guidance in 2016. Their subsequent reports

showed their contamination rate is exactly the same. It has not improved.

To try and come up with an explanation, primary culture misses contaminated doses for two reasons. One is the bacteria are not in solution. They are biologic organisms. They may be clustered along the wall of the bag, they may be stuck on a skin tag that gets into the bag, and bacteria decide when and where they're going to multiply at their own rate in the liquid phase.

In the simulation you can see here I've drawn a dotted line at roughly 1 CFU per ml. This is the limit of detection of taking an aliquot of 5 to 10 mls out of the bag into BacT/ALERT bottle. And you can see, if you look at day 1, you're going to miss many of the contaminated platelets. They haven't got to one CFU per ml.

If you go to day 2 you start picking up the faster growing organisms. By day 3, you're picking up most of the organisms within the simulation, and if you're not picking up an organism by day 3, chances are it's going to be very slow-growing and present in very low numbers even by the time the platelet unit outdates. This simulation coincides very well with the data Dr. Bloch presented where they're doing day 3 cultures, and showing a detection rate comparable to the detection rate we're finding at time of use or outdate.

The second reason is that primary culture sampling during lag phase results in sampling error and false negative results. The bacteria may be sitting in a clump on the port or anywhere in the plastic, so that no matter how much of the contents you take out, it simply is not going to contain any bacteria. When the bacteria do get into the liquid phase and start multiplying, again, it's a numbers game, and the later you go and the more sensitive your method is, the greater your chance of detecting them.

My next objective is to show that rapid testing on the day of transfusion has been proven to be an effective means to interdict bacterially contaminated platelets. Two FDA-cleared methods are available, Verax platelet PGD test and the Immunetics BacTx test. They are able to interdict clinically significant levels of contamination on the day of transfusion, and they detect bacteria after they've grown in order to avoid sampling issues.

The Verax test, PGD test, is a single use qualitative test for the detection of aerobic and anaerobic gram positive and gram negative bacteria. It detects the presence of conserved bacteria surface-wall antigens, lipoteichoic acid, and lipopolysaccharide, using specific

antibodies. And the analytic sensitivity is between 10^4 and 10^5 CFU per ml for common bacterial contaminants.

The effectiveness of this method was studied in a multicenter study over two years, 18 U.S. hospitals. These were testing primary cultured negative apheresis platelets within 24 hours of transfusion with the PGD test, and units that were reactive were cultured. The study was done 2009 to 2010, published 2011.

What we found was that 9 contaminated units were found out of 27,000, 326 per million, and I've shown you in one of the previous slides that I asked you to make a note of, number 27, that this is comparable to other detection systems, as well as to what primary culture is missing, showing that this was an extremely successful study. Probably one of the most successful interdiction studies ever studied. The Hopkins experience and the PCR experience in Wisconsin were equally successful.

What was interesting as that this picked up four contaminants on day 3 platelets, two on day 4, three on day 5, for a total of nine. Six of them were coag negative staph, two of them were bacillus, and one was Enterococcus faecalis. Remember, again, these are on platelets that have already been tested by primary culture. This is secondary testing. The false positive rate was .5 percent, and I'll refer back to that false positive rate.

This study has been very unfairly presented, both by the agency FDA in their summary report and by several of the speakers before me. To quote from the summary report, based on one definite septic reaction and the possible septic reaction, both were false negative rapid test results, the septic transfusion reaction rate associated with the use of secondary testing rapid test on the day of transfusion following a negative primary culture is determined to be 1 in 27,000 to 1 in 13,000.

This comment caused a very negative view of the study, which was one of the most successful studies ever performed to interdict contaminated platelets released as negative after primary culture, detecting out of 9 out of 27,326 per million, and I'll be commenting further on the septic reactions.

In the study, 12 primary culture false negative doses were found amongst 27,000 apheresis platelets. So finding 9 out of 12 gives you a 75 percent detection rate. That's a lot better detecting 75 percent than detecting 0 percent by doing nothing.

Second point is that if you have a look, they confirmed the positive detected were, as I said, six coag negative staphs, two bacillus, one enterococcus, but if you look at the PGD negative test, the first one was Streptococcus oralis, was negative, and this patient was

transfused and had a septic reaction. This was a Streptococcus oralis. The PGD test at that time did not include reagents to detect strep oralis. This has now been added to the test.

There are three major antigenic groups of viridans streps. At the time the test was developed, two of them were included. Since finding this false negative, this has now been added to the test. So several speakers who present this as a false negative fail to point this out.

The second one that was missed was a coag negative staph at 400 CFU per ml, a level way below the level of detection of the test, and I'd expect would be positive, and also three logs below the bacterial load that's going to cause a transfusion reaction. So yes, it was a false negative, but it was of no clinical significance.

The final one also has caused a lot of confusion. This was a Streptococcus sanguinis, the PGD test was negative, patient had a reaction. The unit was cultured and gram stained, blood culture was done on the patient, the patient's blood culture was negative. Culture showed Streptococcus sanguinis. This was done in liquid culture medium. So unfortunately we have no quantitation, and gram stain was done, was found to be negative, was repeated and

found to have very rare organisms, and the most likely explanation is that this was just below the level of the test. Nevertheless, it was missed. Whether this caused a septic reaction or allergic reaction really doesn't affect the basic conclusions for this, and this has been very misrepresented both by the agency and several previous speakers.

So if you look at this, the Verax test picked up 9 out of 12, 75 percent of contaminated units. One that was missed has now been addressed by adding this reagent. The other two were probably below the level of detection. One did not cause a transfusion reaction. One may have caused a transfusion reaction. This is much better than, A, doing nothing and, B, several of the other methods that have been proposed.

So my conclusion about secondary testing is that the PGD study is one of the most successful bacterial interdiction studies ever performed, and I stand by that claim. These tests provide rapid results before transfusion to prevent the transfusion of contaminated doses. It's been proven to prevent transfusion of contaminated platelets. The 1 in 3,000 detection rate, 326 per million, and a culture negative apheresis inventory, and this detection is in addition to what the contamination was detected by primary culture.

I mentioned also that there was a .5 percent false positive rate in the study. This issue has been addressed by development of the second generation PGD test called the PGDprime. It's a simplified sample processing; no centrifugation is required. It has two additional capture lines for increased breadth of reactivity. It has improved specificity, fragmented antibodies, where the Fc fragment removed, to eliminate most false positive reactions.

Out of almost 2,500 platelet doses tested in in-house studies, no false positives have been found. So development of this product is complete and it's currently in validation studies, but it's still under development and has not been cleared by the FDA.

Switching to the second test, this is the BacTx assay. It's a rapid qualitative assay for detection of aerobic and anaerobic gram positive and gram negative bacteria in apheresis and pre-pooled, whole-blood derived platelets, the same as the PGD test. It has a different principle. It's based on peptidoglycan detection, using a chemical reaction that has a kit, which again requires similar steps to the PGD test, but its reading is in an analyzer after you do the reagent preparation. The tubes are put in the tube, this then incubates and shakes them over a 20-minute period, and reads the color reaction

automatically and gives you a positive versus a negative printout.

The analytic sensitivity has been determined in leukocyte-reduced apheresis and whole-blood derived platelet pools at two sites, and the lowest bacterial titer detected by 10 out of 10 replicate tests was taken as the limit of detection, and you can see here limits of detection for most organisms is between 10^3 and 10^4 CFU per ml, with little difference between platelet type.

It's now cleared for use with pre-storage pools, and its indications for use are as a quality control test in leukocyte-reduced apheresis platelets and pools of up to six leukocyte-reduced whole-blood derived platelets, and increased storage pools of up to six platelets.

This shows some of the detection in pooled platelets of the organisms that were inoculated in low inocula between 1 and 4 CFU per ml in platelet bags. It was detected for the organisms shown in green 7 out of the 10 at 48 hours, the remaining ones found at 72 hours, and all of them were also detected at 7 days.

So key points about rapid testing. Rapid testing has been proven to interdict contaminated platelets. Passive surveillance is inadequate and does not establish a residual risk of bacterial contamination of platelets,

particularly due to the nature of change in septic reactions following introduction of primary culture.

The large volume delayed sampling UK protocol has not been demonstrated to provide comparable safety to the current U.S. primary culture protocol followed by secondary test, and the minimum proportion Blood Systems protocol has similarly also not been demonstrated to provide comparable safety to primary testing plus a secondary test.

So going back to the issues that the committee has been asked to address, I've tried to make my presentation as evidence-based as possible and show you data in the same format so that you can easily compare them. So the first issue was primary culture followed by secondary rapid testing within 24 hours prior to transfusion. This is highly successful, detected 9 out of 97,000, 95 percent confidence interval is shown, and I've published this and I've shown you details of the study, and I'm showing you this as green. I agree with that.

The second one was primary culture followed by secondary culture on day 3, as presented by Dr. Bloch. This was highly successful, detected 217 per million, again 95 percent confidence interval, overlapped our known rens(?) that we're trying to detect. Caveat, culture at time of use data would be helpful in knowing whether we had

missed any in the study, and I encourage the Hopkins group to try to do this.

The next method is the minimum proportion sampling volume. Contamination rate at outdate was high, showing failure of this method, 3 to 6 out of 8,000, and I'm showing you the data on that, and to me, this -- I'm not sure why BSI continued using this method after they'd proven it did not work.

The next issue is pathogen reduction technology. I've shown you this in yellow as caution. Contamination rates at time of use or outdate have not been studied, and I think I would encourage the pathogen inactivation group to study this so that you can prove absolutely that you have sterilized your platelet units.

As far as 7-day platelets are concerned, primary culture followed by secondary rapid testing within 24 hours. Based on the highly successful detection study on day 5 platelets, with detection as early as day 3, this method is obviously valid and has FDA approval for use.

Primary culture followed by secondary culture on day 4, the Irish method, the Irish transfusion service approach was highly successful. Day 4 culture interdicted 5 out of 51,000, 95 percent confidence interval is shown, with no contamination in 2,000 units. Caveat,

contamination rate on day 4 was lower than in other studies.

Finally, the large volume delayed sampling contamination rate at outdate is high, showing failure of this method. However, caveat there is that very few outdated platelets have been studied, 6,000 out of 2 million. That's possible that with much larger numbers, if you get to 60,000, and you're still only 1, then the conclusion about this will change. But at the moment, this is the only data we have to work from.

My final slide is conclusion, opinion versus facts. Daniel Patrick Moynihan, who was a New York senator 1977 to 2001, quoted, everyone is entitled to his own opinion, but not to his own facts.

He obviously was a Democrat.

(Laughter.)

Fact number one, changes to primary culture volumes and times have not improved detection rates. If there was strong evidence that it did, why are we holding this advisory committee meeting? Second fact, secondary testing by a variety of methods has been proven to detect contaminated units missed by primary testing and considerably improve the safety of platelet transfusion, and FDA has given safety measure labels to two of these methods.

Fact, the efficacy of an intervention to decrease bacterial contamination is best documented by culture of products at time of transfusion. This is very easy and inexpensive.

Opinion, statistical parameters for determining the success of an intervention should be set so that the value of an intervention can be determined. I've shown you the statistical parameters. The guideline needs to consist of one paragraph. Do whatever intervention you want, culture your platelets at time of use, and show that you have either decreased your contamination rate to below the 95 percent confidence interval of the studies that have not had your intervention, or come up with an intervention that shows comparable detection to what's missed by primary detection.

Thank you for your attention.

DR. ALLEN: Thank you, Dr. Jacobs. That was a lot of data in 45 minutes. A lot to think about, as we have gotten from all of our other speakers.

We will open -- the panel is open for questions and comments to Dr. Jacobs on his presentation.

DR. LEITMAN: Just a simple question. What do you estimate the cost of the rapid test that your facility uses? I think we heard $25 to $35 per test, but it's used, maybe used more than once, of course, because it's used

within 24 hours of release. So both the cost of the materials and the labor? Do you have that?

DR. JACOBS: The cost of the test itself is, both the PGD test and the BacTx test, the test itself depending on volume is $25 to $30. If, again, it's a question of timing, because that test of that unit is not used that day, then you'd have to test at the next day. So a lot depends on your volume and your outdate, and how you stagger your inventory, for example; if you get in a batch of 50 platelet units, you may want to test 25 straightaway and then the other 25 the next day. But again, depends on your use.

DR. ALVING: Barbara Alving. Who performs the test? Do you train blood bank personnel? I would assume it would have to be someone available 24/7 or how do you work that?

DR. JACOBS: The test is designed to be done by blood bank personnel. This presents a lot of logistic issues, particularly with a lot of hospitals do not -- blood bank personnel do not manage the platelet inventory. It's managed by the blood supplier, and that puts a logistic issue into this, but most hospitals have their own blood transfusion service and they do the testing.

DR. ALLEN: All right, if there are no other questions or comments, thank you very much, Dr. Jacobs.

I will just add the comment to Senator Moynihan's quotation, a bumper sticker I saw here when visiting D.C. a few years ago was don't believe everything you think.

(Laughter.)

Seems to me the two quotes go very well together.

Our last speaker for this morning is Dr. Richard Benjamin, Cerus Corporation, pathogen reduction technology strategy.

Agenda Item: Pathogen Reduction Technology Strategy

DR. BENJAMIN: Good afternoon, Mr. Chairman and the committee. Thank you very much for the opportunity to address the committee on this important issue. I apologize; by now you should be used to a South African accent, but I'm think I'm the fourth South African ex-South African speaking today. I won't apologize for my accent.

My disclosures. I am an employer/employee and stockholder in Cerus Corporation, a maker of pathogen inactivation technologies.

Why don't I start off with my conclusions? The one thing I'd like the committee to take home is that no level of bacterial contamination of a blood product should be considered safe. Secondly, strongly encourage the FDA to finalize the bacterial guidance in order to improve patient safety. Those are the two most important points.

To my knowledge, the FDA has not set an acceptable level of bacterial contamination of any bacterial product, has not set a safe level of bacterial contamination. Indeed, I believe no patient deserves to get any bacteria in a blood product, and if you ask them, I think they would be surprised to hear that blood products are not required to be sterile. I think we have an opportunity to begin to address those issues here.

Second major point, I'm glad Dr. Jacobs brought up the MMWR report, because it brings up the fact that patients continue to develop sepsis from contaminated platelets. Since the 2012 BPAC was held, at least 13 patients have died, and many of those would probably have been avoidable with any of the technologies that we have discussed here today, including pathogen inactivation. So please, move forward. There's an urgent need for this final guidance to give direction to blood centers and hospitals so we can help to protect patients.

This MMWR report actually is interesting for more reasons then. It describes two apheresis platelet collections that gave rise to eight blood products: six platelets and two plasma products. Those two collections managed to kill three patients, two clostridia, one Klebsiella, kill another fourth patient that was actually ascribed as unrelated simply because the patient already

had Klebsiella sepsis, was on antibiotics for Klebsiella, died within five hours of transfusion, and the Klebsiella species they pulled out of the patient was the patient's own Klebsiella and not the one in the bag. So almost certainly this was a fourth death, had the patient already not been dying.

They salvaged a bag out of the trash that was outdated that was contaminated. That two plasma units which were frozen, which they cultured and were negative, but what they didn't do was remember that today plasma is frequently thawed and held for five days at 4 to 6 degrees in emergency rooms and may be transfused five days later. They didn't do that, and we don't know whether after five days at 4 degrees these products would have been safe or not.

Take-home message. There is an increasing risk to patients today, because of the move to increase split units in blood centers. Over the last 10 years, splitting is increasing tremendously. We have two collections, four deaths, eight components.

Subsequent to this publication, I am aware in the United States this year, and we're only halfway through the year, of another three collections that have given rise to seven components, seven septic transfusion reactions, including three deaths. So the issue is economic pressures

are driving splitting of units, when a unit is contaminated, they are killing more patients. We are seeing increased risk. We need final guidance from the FDA.

The other important point of this MMWR is the clostridium. When I was at the American Red Cross as chief medical officer, we reported, Dr. Anne Eder reported, two units we discovered at the bedside that were contaminated with clostridium. At that time, the Red Cross did not move to add anaerobic testing. Now we have two deaths. It's time anaerobic testing was put in place. It has to happen. It's been too long.

Now, let's get on to my topic. The INTERCEPT blood system. It's a pathogen reduction that offers a broad safety measure to reduce the risk of sepsis. It also helps with enveloped and unenveloped viruses, protozoa, babesia, malaria. Transfusion-associated graft versus host disease. It can replace CMV testing. It can replace bacterial culture screening. Can replace Zika testing and provide an extra layer of safety for platelet products.

I will talk briefly about some data showing that they are effective at treating and preventing hemorrhage and can be implemented broadly with little impact on platelet use when used in routine practice.

To remind you that the INTERCEPT blood system for platelets is the only FDA approved system for platelets, that it's gone through the rigorous FDA requirements of proving safety and efficacy, that it's based on amotosalen and UVA light that's targeted to nucleic acids, through crosslinking and preventing replication of DNA can prevent bacterial or protozoal or viral replication and leukocytes too; the bag system in front of you also shows that for many products, we can treat and then split products into multiple units, therefore decreasing the cost per unit to the patient.

There is extensive hemovigilance data, which I will go through. It is effective at inactivating bacteria. Not only at the time, if you contaminate a unit, but you can then take that unit to outdate and contrary to what Dr. Jacobs said, we in fact do routinely take them out to outdate when we contaminate them and show that they are persistently negative on culture at day 7 or day 5, when you do in vitro inoculation steps. They are functionally sterile.

Most important, that INTERCEPT process allows release of platelets much earlier than bacterial culture, especially much earlier than delayed large volume culture systems.

So let's think about the problem again. We believe that most platelet products on collection are in fact sterile. A proportion, probably a minority, but we don't really know, contain a small number of bacteria. Probably less than 10 units, colony forming units, or even clumps. Probably 1 or 2 at most.

Way beyond concentration that can be detected by culture. One CFU per 100 mls, you'd have to culture the whole bag. We hold the product and during storage a proportion of these start growing, and those that grow rapidly can reach higher concentrations. Those that grow slowly or have a long lag phase reach lower concentrations. The problem is there's always a small group that just sit there in prolonged lag phase, and that's your time bomb, because at any point in time during the life of that platelet, they can decide to start growing.

So what we have learned about point of issue testing is that you can detect the highest concentrations of bacteria, but you leave behind lower concentrations, and therefore you have to perform it as soon as, as close to transfusion as possible. Many patients are still getting contaminated units.

With delayed large volume culture, you can detect a larger proportion of the contaminated units. But again, you have the sitting time bomb here that if you have too

long a gap between your culture sample and your transfusion, a product can become -- get higher levels of bacteria.

Pathogen inactivation as used according to manufacturer's instructions, the ability to address all of these bacteria, plus give you protection against viruses, protozoa, and leukocytes.

So we have heard a number of different combinations today, and many of them, the clinical experience has been very limited. They have not been subjected to large national hemovigilance programs, and the reporting is doubtful or iffy at best. There are some exceptions. The delayed large volume culture systems in the United Kingdom, as reported by the SHOT system, and pathogen inactivation as reported by hemovigilance systems in Belgium, Switzerland, and France. I would like to briefly review some of these data.

The SHOT program, Dr. McDonald spoke about the English experience. Well, SHOT covers the English experience. It also covers the Northern Irish experience, who also use delayed large volume culture. Slightly differently, but it is delayed. It's actually delayed more. It's also large volume.

As a small contribution from the Scottish blood systems and a small chunk of northern Wales, that they are

very small, so when you look at SHOT and we summarized five years of experience after delayed large volume culture was in place, and published that between 2011 and 2016, at that point in time it was 1.65 million distributed platelet products. That's 624 suspected septic transfusion reactions reported to SHOT. That's one in every 2,500 had a report that was investigated.

The vast majority of those were excluded or deemed unlikely. There was one septic transfusion reaction, in which case the same bacteria was found in the patient, in the bag, and in the donor. There was one possible septic reaction, where the same bacteria was found in the patient, and in the bag. Was deemed possible. No real explanation why it was only a possible.

There were at least 12 indeterminates where there was missing data, either didn't have a patient culture or a bag culture. They are lumped together as indeterminate.

There were eight near misses. Now, near misses are really important. Near misses are you have a closed bag that's full of bugs. There's only one way the bugs could have gotten into that bag, and that's at the time of collection. The moment you spike a bag to transfuse a patient, you have the possibility of having introduced bacteria at the time of spiking. There are many case reports of that happening. So these near misses are

important. They were clearly contaminated and are part of the potential risk to patients.

So if you add up definite septic reaction and the eight near misses, you come up actually to a number of less than 1 in 200,000, which is not that different to the U.S. risk today of 1 in 100,000, and clearly as Dr. Jacobs pointed out, not statistically different.

What about pathogen inactivation? Well, worldwide over 2.5 million INTERCEPT platelets have been transfused, most of them not in a defined hemovigilance program, but the company has not received any fatality reports worldwide with platelets made with INTERCEPT.

We also have had no near misses where a bag has been discovered with bacteria in it and the bag is still intact. There have, as Dr. Vassallo pointed out, been at least three what we deem as possible contaminations. That's using the SHOT definitions.

In each case, the bag integrity had already been broken by spiking the bags that sat around for a long period of time, and there was opportunity for retrograde contamination through the spiking. We have been very aggressive about publishing those cases so that you can make up your own mind. So the one case in Belgium and the one case in Switzerland, was published in Transfusion last year, and one case in the United States, we will move to

publish as soon as possible so that you can make up your own mind.

Having said that, there's no cases of definite sepsis or probable sepsis been reported in France, Switzerland, and Belgium who do have very good hemovigilance programs in place, during the same periods when multiple patients that were not receiving INTERCEPT platelets did report sepsis and did report fatalities. So during the same periods on 3.3 conventional platelets had 75 septic reactions and 13 deaths, and those parts of the countries that were using INTERCEPT, there were none. So we do believe that this is strongly supportive of the efficacy around bacterial sepsis related to INTERCEPT system.

What about efficacy? Cerus has a published a number of phase III clinical trials showing the safety and efficacy of INTERCEPT platelets. Some of the largest clinical trials in this area ever, including the SPRINT study. It was interesting very recently that a group of French investigators published the EFFIPAP study, which was independent of the company, Comparison of Hemostatic Efficacy of Pathogen-Reduced Platelets vs Untreated Platelets in Patients With Thrombocytopenia and Malignant Hematologic Diseases.

This study concluded that the hemostatic efficacy of INTERCEPT PAS platelets in thrombocytopenic patients with hematological malignancies was not inferior to control PAS platelets. The second part of the conclusion was that noninferiority was not achieved when comparing INTERCEPT PAS platelets with control plasma platelets. Mindful of these data, in November of last year the French blood system, EFS, decided to move to 100 percent adoption of the INTERCEPT blood system for 330,000 platelets per year.

Which draws attention to the second part of this conclusion. Noninferiority was not achieved. Interesting comment. They are not saying that something was inferior. They are just saying that noninferiority was not achieved. So it's worth looking at what that means.

What it means is that this the study had limitations. The study was powered around an 80 percent ability to prove noninferiority with 810 patients. But they only recruited 790 patients, and they were basically underpowered to prove noninferiority. Which means you should look at the data. What did they actually show?

The primary endpoint was bleeding of grade 2 or higher in these patients, and they found 47.9 percent of INTERCEPT PAS platelet patients, 45.3 of control PAS, and 43.5 control plasma patients, had this endpoint. They did

not provide a statistical analysis of the difference between those numbers.

If you do a post hoc analysis, what you find, actually there's no statistical significance between those numbers. The groups are too small. So they did not prove noninferiority, but they did not prove there was a difference either.

That's great, and they also went on to look at really clinically significant, meaning a grade 3 and grade 4. There they did show statistics. No difference. Days of bleeding, no difference. So we actually believe this is really supportive data around bleeding and the INTERCEPT system.

What about platelet usage? They found in the three arms that there was no statistical difference in the total platelet dose in these patients, or in the total red cell dose given to these patients, despite the fact that there was very meaningful differences in the CCIs. The CCIs were definitely lower with INTERCEPT platelets, but this had little or no effect on platelet usage in these patients, which is essentially what the experience has been with every hospital that has published around their experience of introducing INTERCEPT, and I will show you one hospital, a large academic hospital, in Innsbruck, Austria, who looked at 23 months before introduction and 23

months after introduction of INTERCEPT, some 8,000 platelet transfusions and about 1,800 patients, and showed essentially no difference in heme-onc patients, cardiac surgery patients, pediatric or neonatal patients, in platelet or red cell use, before or after introduction of INTERCEPT.

When they looked at their massively transfused patients, and they had 300 of those, defining massively transfused as greater than 10 units of red cells and at least one platelet within 24 hours, there was no difference in blood usage, and in fact, no difference in mortality, and for those that survived, for length of stay. So basically proven to be safe and efficacious.

So we've heard some question today whether pathogen inactivation is ready for primetime in the United States. Our experience has been that in many countries in Europe, they have been able to turn a light switch. So Switzerland, Belgium, France, have over a short period of time been able to go to universal pathogen inactivation.

In the United States, what we hear is that our tight INTERCEPT guard bands means my split rate will decrease, causing my center to lose product and revenue. Or, I can only supply a percentage of PRT product to my clients. Those are common comments we get. And our guard bands are a problem.

In order to use our system, you have to have a platelet of a certain volume, dose, and concentration. That is a constraint. We have been working with our blood centers, who when they first look at the inventories, realized, depending on the split rates, that they can only treat a proportion of their products. We have moved to helping them by either splitting triples into double and single or volume adjusting and then to collect, optimize their collections, what we found that centers with a lower split rate, many hospital self-collectors, can get to 100 percent with our current system.

Large centers can also get up to at least 75 percent, and there are some very large centers now in the United States that are doing this. Some of the major blood centers are now up to 70, 75 percent compatibility with our system, with maintaining the split rate. If you are prepared to compromise the split rate, you can get to 100 percent, but it does mean in a large center, you may have to compromise that 2.0 split rate.

So what's the way forward here? So what's the difference between Europe and the United States? In both sets of circumstances, we can treat Amicus platelets in PAS, Trima platelets in plasma, and we can do single and double unit treatments.

In Europe today, you can also do these other combinations of Amicus and Trima. You can do whole blood platelets and buffy coats. They have 7-day storage in many countries. They have a triple set. There's a CE mark triple set in use or available in Europe today. They also use, by the way, a lower platelet dose. The actual required dose of platelets is not 3.0 times 10^11. It's 2 to 2.5, which does help.

Because their systems are usually run as national systems where there's coherence between regulatory and safety decisions and funding decisions, they can put in place safety regulations and pay for them and move to 100 percent in one easy move.

In the United States, it's a little more complicated. We are working very hard with the agency to bring to the U.S. market these other combinations of products, to bring triple bags, to bring Trima in PAS and Amicus in plasma. These things will be very important to getting to 100 percent. We are working on 7-day platelets using the INTERCEPT system.

Today, and also I just have to draw attention to the fact that the dose of 3.0 times 10^11 platelets in the United States was perfectly arbitrarily set and is higher than any other country in the world and also -- the United States is a country that uses most platelets per capita and

has the highest dose per capita, which puts a strain on our donors, puts a strain on the availability of platelets, and also constrains INTERCEPT somewhat.

Today in the United States, the regulatory decisions and the funding decisions are not coherent. Blood centers and hospitals have to make decisions based on their environment, which is a competitive environment, and in the absence of guidance, economics has to play a part. Centers and hospitals cannot make decisions that make no economic sense to them if their competitors don't have to do it.

So without final guidance, I do not believe that we will be able to move forward to protect patients with our technology or any of the other technologies that have been discussed today, because they all have costs. So final guidance is the most important thing you can do today is to encourage the agency.

To summarize, no amount of bacteria in platelets should ever be considered acceptable or safe. We have to move to minimizing that risk to patients. The INTERCEPT pathogen reduction treatment system provides risk reduction against bacteria, viruses, and protozoa, can replace gamma irradiation, does not lead to excess use of platelets in routine practice. Treatment platelets may be released into inventory one to two days earlier than with delayed large

volume bacterial culture, allowing the use of fresher platelets.

Broad implementation is feasible, and final guidance is required and critical to provide clarity to hospitals in order to implement effective interventions to reduce exposure to contaminated platelets.

Thank you, Mr. Chairman.

DR. ALLEN: Thank you, Dr. Benjamin.

Questions from the panel or comments for Dr. Benjamin?

Yes, Dr. Kaufman?

DR. KAUFMAN: Richard Kaufman, Boston. So you had a couple of slides towards the end talking about sort of differences between the United States and Europe, and I just wanted to explore that a little further. New York Blood Center published an opinion piece suggesting that they could pathogen-reduce maybe 30 percent of their inventory, whereas Switzerland apparently pathogen-reduces all, and I was just wondering if you could speak specifically about how do the Swiss do it?

DR. BENJAMIN: Thank you for that question, Dr. Kaufman. I appreciate it. It would have been nice if that publication by the New York Blood Center had input, more input, from us. We could have assisted them to get to the 75 percent where larger blood centers producing more

platelets today than they do are at least 75 percent today. So I have to contest that number that was published; just because it's published doesn't necessarily mean I agree with it.

Places like -- Switzerland is a relatively small country. Let's talk about France, because France is 330,000 platelets, and I think it's in the range of 15 or 17 blood centers. I can't remember the exact number. But it is more comparable to here. You do need to adapt your collection process to the safety system and not expect the safety system to necessarily adapt to your economic reality. So it does come down to your priorities.

What is more important? France had a history of 18 years of more than 50 septic reactions and about 10 fatalities, and they decided that safety needed to be acted on. So that I think becomes the difference. What is your priorities and what -- you can argue that it might be reimbursement, but what is your priority here?

DR. SCHREIBER: Marty Schreiber from Oregon Health and Science University. We heard about rapid testing strategies from Dr. Jacobs. In light of the fact that only a very small percentage of the platelets are contaminated, what are your thoughts about combining these ideas? You -- do the rapid test. If it's positive, then do pathogen reduction, but not do broad pathogen reduction on a very

high percentage of the platelets that actually don't need it.

DR. BENJAMIN: That's an interesting concept. There are physical reasons why it's not practical, but there are also better reasons why we shouldn't do it.

Pathogen inactivation is not just about bacteria. Pathogen inactivation is providing a broad cover against Zika, Ebola, breakthrough cases of HIV, HPV, HCV, CMV, babesia, malaria, and all the other risks we don't yet know about. So that's probably the real reason to do pathogen inactivation. Sepsis is an important reason.

The practical reason you can't do that is that point of issue testing only works many days after collection, whereas pathogen inactivation needs to be done within 24 hours of collection to be effective. So you don't have that luxury of testing first. And also, testing has -- what you don't -- what the test misses, you will never know until you get a septic reaction.

DR. ALVING: Barbara Alving. I have two questions. Let's say that tomorrow it was mandated that pathogen inactivation occur throughout the United States. What is the capabilities of your organization to really take care of this mandate? The second question would be since there's so many public health personnel here, have

you penetrated the Latin American, South American, even Miami markets?

DR. BENJAMIN: The short answer is yes and yes. Having said that, can we supply the U.S. market? The process here, even if optimized, requires a draft guidance, comment period, a final guidance. I believe by the time, even if we expedite the guidance discussions with the FDA, that we can be ready in that time period. Nothing's a light switch overnight, but in the 12- to 18- to 24-month period, yes, because we need to plan for expansion of the production to meet that demand. We would love to take that challenge.

We are, on the other hand, the second part of the question, we have blood centers in Brazil that are using INTERCEPT today, and they have great interest because that's where Zika came from, that's where chikungunya came from, and that's where yellow fever is going to come from, because they have outbreaks today and that's almost certainly going to get into the Caribbean and three and a half Americans in Puerto Rico that are at high risk today.

DR. CALIENDO: Angie Caliendo, Brown. Do you have any data that this pathogen reduction works out to day 7? It's not approved for that, but have you accumulated data along the way?

DR. BENJAMIN: So let's talk about two types of data. Today, 7-day platelets with INTERCEPT are in regular use in Switzerland, and I believe in France now, too. So yes. It's in clinical use today in Europe.

If you are talking about the in vitro functionality of the platelets, we are working with the FDA on finalizing a protocol to allow us to do the recovery and survival studies to meet the U.S. standards. In terms of bacterial culture, there's extensive work published by others and by the company now, showing that if you inactivate within 24 hours, if you spike platelets with concentrations of bacteria, quite substantial concentrations, treat them at 24 hours, you can take them out to day 7 and re-culture, and they'll be functionally sterile, as long as you do the PI treatment within the package insert descriptions.

DR. LEITMAN: Every time I see this data, I'm struck by the fact that when the CCI, corrected count increment post-transfusion platelet CCI, goes down by 40 percent from 8.2 to 5, there's still not an increase in the number of platelets given to those recipients or the number of transfusions total, 22 times 10^11. A slightly cynical interpretation might be that since the majority of platelet transfusions are given for prophylactic purposes, the majority of platelet transfusions given both in Europe and

the United States are not clinically necessary. They are given to treat a number that wouldn't be associated with clinical bleeding.

So whether one goes from 12,000 to 17,000 post-transfusion or 12,000 to 22,000 doesn't particularly make a difference to the likelihood of having a clinically significant bleed. So when you're talking about setting a minimum platelet dose at 2 to 2.5 versus 3.0, and I think of the patient who has a platelet count of 3,000, I don't think three units of platelets is sufficient.

So it's clinical judgment, but I don't think one can make a blanket statement like that. The thing that we have to educate our users on again is the appropriate prophylactic use of platelet transfusions.

DR. BENJAMIN: May I respond to that? I think that's a very interesting comment. It does speak to how transfusion physicians use platelets and what they actually monitor, whether they are treating bleeding or a number, a CCI. I will point out to you that there's a difference here in Europe where countries use lower doses and use way fewer platelets than we do. The United States uses 7 platelet units per 1,000. Most of Europe is in the 4 range, and some are less.

Not only are they using lower doses, but they are using them less frequently, and I don't believe there's any

indication that they are treating their patients any less well than we are. So that does raise the issue in the United States whether our current dose of 3.0 and our current systems of prophylactic use is overusing platelets. That's quite possible. It's an indictment of the United States where other systems can use lower doses less frequently and have the same outcomes. So I have to agree with you.

DR. ALLEN: I think those are important points. I am not sure that the panel is prepared to address them fully today. But they certainly are issues that do deserve continued discussion and research and evaluation.

Other questions or comments? Dr. Stramer?

DR. STRAMER: I am going to add while this slide is up, I think it's really important to address the differences that occur in the United States and outside of the United States. So I think if our expectation is 100 percent PI platelets, mean a lot of things will have to change within the regulatory framework to make some of these things more widely available, such as triples, the use of collection devices with multiple -- whether it's additive solutions or plasma -- I mean, we're going to have to be more flexible to be able to allow more widespread use if that's what's indicated.

DR. ALLEN: Certainly I think that in our discussion session it is fair to raise these issues as ones that need to be considered.

Did you want to comment in any way?

DR. BENJAMIN: No, you know, we've worked very well with the agency and FDA to move forward with the agenda of enriching what's available to blood centers, and we are optimistic that we'll get past the current impasse and make these things available in the short term.

DR. ALLEN: Thank you very much for your presentation and discussion, Dr. Benjamin.

It's 12:45. On time for the scheduled lunch break. I want to first of all thank all of the presenters this morning. You did a wonderful job of staying on time and responding to the questions, and thank the panel. I think we had a very fruitful morning.

Committee members, during lunch break, once again, please do not discuss the meeting topic during lunch amongst ourselves, or with any member of the audience. We will reconvene in this room one hour from now. I would really like to have everybody back at 1:45 so we can start at 1:45. Panel members, please do return on time. Audience members, please remember to take any personal belongings with you at this time.

Any further?

MR. EMERY: I was just going to say panel members that have paid for your lunches, the lunches have been brought to a room directly behind us, and if you need help getting there, I can direct you there. Thank you.

(Luncheon recess.)

AFTERNOON SESSION

Agenda Item: Open Public Hearing

DR. ALLEN: The committee will come back to order. We will proceed with the open public hearing portion of the meeting, during which public attendees are given an opportunity to address the panel, to present data, information, or views relevant to the meeting agenda. I will now read the open public hearing disclosure process statement.

This is an open public hearing announcement about particular matters of general applicability. Welcome to the open public hearing session. If you wish to speak, please state your name and your affiliation, if relevant to this meeting. 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 meetings, 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, as you begin, to state if you have any financial interest relevant to this meeting, such as a financial relationship with any company or group that may be affected by the topic of this meeting. If you do not have any such interests, also, FDA encourages you to state

that for the record. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking, and you may still give your comments.

For the record, we have received, as of the beginning of this meeting this morning we had five formal requests, and we have a few more, to speak for today's meeting. Each scheduled speaker will be given five minutes to address the panel. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

The panel appreciates that each speaker remains cognizant of their speaking time, and we have had to restrict it a bit. Some of you may have been told you would have a few more minutes. It's because of the number of people that we have who have come forward and wish to address the meeting, and the length of time that we have available to us. Also, if you have a written statement you may certainly give it to Joanne Lipkind at the table outside, and it will be made available, not necessarily this afternoon.

Our first speaker is Dr. Ed Snyder, with Yale Transfusion Service, and he will present some data.

DR. SNYDER: Thank you very much. My name is Ed Snyder. I'm from Yale University, and I want to talk about

how we integrated pathogen-reduced platelets into Yale University. I am PI on the phase IV PIPER study for Cerus, and also the phase III ReCePI study. I have no personal remuneration, I have no stock, I've not any relation with the company. All monies have gone through Yale contracts.

Yale-New Haven Hospital has about 1,600 beds. We treat about 10,000 patients, with about 40,000 blood products. Over the past year, too, we've increased our single-donor products, and decreased the number of pooled random donor platelets dramatically. Most of the single-donor products are now pathogen-reduced, as we will see.

The way we integrated, we started with deciding to move forward internally, and then contacted almost the entire institutional org chart so that everyone was aware of how we were going to move to 100 percent pathogen-reduced platelets, and all the way down to the C suite individuals.

We did this because the bags look different. As you can see, the conventional bag versus the psoralen-treated bag has a different configuration, the outlet ports are different, the labels are different, and if we didn't do this, there would be all kinds of confusion that we eliminated by training everyone well in advance.

We decided that all demographics within the institution would receive pathogen-reduced products. We

were not going to give them specifically. We weren't quite sure which was considered to be the better product, so we considered they would be equivalent. So everyone at Yale-New Haven hospital gets pathogen-reduced products as necessary. Jehovah's Witnesses, of course, for religious beliefs, this doesn't affect them.

This shows the platelet usage at Yale, starting from October 2016, going to May of this year, and as you can see, the red line is the pathogen-reduced. The green line at the top is the total platelet usage, and the blue is PL5 and others, non-pathogen-reduced single-donor. We're at about 80 percent. And the reason we're not at 100 percent, we believe, is probably because our supplier, the Red Cross, has not yet received the BLA, and the guard bands are a concern, and also triples are not available as well. So, we're at about 80 percent.

The way we treated dual inventory is we considered, and we went through the ethics committee and discussed it extensively, we consider pathogen-reduced platelets to be essentially equivalent to conventional product plus a safety measure done on day 4 and 5. And that's why we used them interchangeably, we don't specially give one group one product or another. They're considered equivalent, and as we decrease the number of conventional, we're going more toward the pathogen-reduced.

These are the metrics that we have looked at. We looked at transfusion reactions between November 2016, when we started, to December 2017. On the left side is the number of type of reaction. The conventional there were almost 4,000 products, versus 2,700. These were not paired, these were all comers evaluated, for all age groups. You can see, on the right side, is the ages that are listed.

The bottom line is that there were 46 reactions with the conventional, and 18 with the pathogen-reduced, which is 1.16 and .66 respectively. Most of the drop in reactions was due to the decrease in allergic reactions and febrile, which we believe is probably due to the removal of about 65 ml of plasma from the PR, and replaced with the PAS-C.

We looked at our neonates. Again, all comers. Neonates, specifically, that received phototherapy and PR platelets. The wavelength of concern is 375 nanometers. Our device, and most of the devices in the Western world are well above that. We're at 458. There were no reported rashes by any of the neonatologists taking care of these infants. We're now up to about 40 children, and there have been no reports of rashes there, either.

We looked at the transfusion-associated GVH, because we do not irradiate INTERCEPT products. This was

the group, which was our part of the PIPER study. These are chemotherapy patients, some being transplanted, some not. There were conventional products. There were 161 patients, none of them was GVHD reported, they were all irradiated, and we had 159 INTERCEPT receipt, no transfusion-associated GVH without irradiation, in this very susceptible population.

Again, these are small numbers, but that's where we are today. We then looked at the efficacy -- these are the components. This was, again, part of the PIPER study, our part of it. How many platelets were given -- 161 conventional platelets, 3.65 platelet units were given to patients who were enrolled, over the roughly the month period they were on the study. The INTERCEPT arm was 3.19 for the mean number of red cell units, which we took as a surrogate for whether the patients continued to bleed, 1.8 units versus 1.12. We did not consider these to be significant, but this, again, is part of an ongoing PIPER study. This is just our snapshot of what it is.

Very quickly, the top part are neonates, or children 4 months to 18 years, in yellow. The bottom, the pink, is 0 to 4 month, conventional versus PR. These are all comers. We looked at those children who received conventional platelets that were 4 months to 18 years, there were 175 ml during the period of time, which was

November to January 2018, 175 versus 115, which was about a .05 level, and the number of transfusions -- this was mls per patient, and these were the number of transfusions for these children -- 1.3 versus 1.6, not significant, and looking at the 0 to 4 month level, 84 versus 80 mls, 1.4 versus 1.8, and these numbers were not significant, as well, as seen over on the side.

And the last slide, we decided to go for early adoption because our concern was not just for bacteria, but for babesia and Zika and diseases endemic in Connecticut, and those other areas we thought bacteria alone was not the concern. We obtained approval from everyone. We have had several near misses, including a very recent one. We have had a death, as well, from platelets. We educated everyone from the top down.

This is a global integration, it wasn't something that is just done quickly. We established a dual standard of care for all service lines until we got full PR. Our auditing, I just went over the data, and as far as financial considerations, it is about $200 more than a pooled random donor, because it's $100 more, roughly, for the single donor, and another $100 for pathogen reduction. But the hospital believes that safety eclipses costs. We believe that it's an improvement in safety for our patients.

Thank you, Mr. Chairman.

DR. ALLEN: Thank you for the information. Any burning questions? If not, we'll move on. Thank you.

Dr. Michael Petrini, representing Terumo PCT.

DR. MARSCHNER: Michael Petrini submitted the slides. I am Susanne Marschner with Terumo PCT. I am an employee of Terumo PCT. I will be presenting you some data on minimal proportional sample volume and large-volume sampling that depends on the apheresis device the products are collected on.

We'll go through the definitions of those sampling strategies, the key message, and then also the data for septic transfusion reactions based on collection device. We heard some of this already this morning. There are differences that are significant between the Amicus and the Trima devices.

Also, I have a slide about the cost and the result of the mitigation strategies in the conclusions.

Minimal proportional sampling volume means that at least 3.8 percent of the total platelet collection volume is taken, 24 hours to 26 hours post-collection. Versus large-volume delayed sampling, is a sample of 16 ml per split platelet product, that is taken more than 36 hours post-collection.

To improve the safety of platelet transfusions, approval of minimal proportional sample volume, large-volume delayed sampling, and other bacterial contamination mitigation strategies must use an evidence-based standard. For example, clinical evidence, which includes data on specific apheresis collection devices.

Septic transfusion reaction data that has been published over the last few years includes data on the Amicus and the Trima device, data from the American Red Cross, published by Eder at al., showed an overall transfusion reaction rate of 13 per million. However, 17 per million is the rate that was observed with Amicus. This is using a standard-volume sampling technique.

This compares to 4 in a million reactions with a Trima device. In supplemental analysis in regions that used only Trima or Amicus devices, these reaction rates were 18 per million for the Amicus device, and 2 per million for the Trima device. Again, this is with a standard-volume sampling strategy.

BSI, and this is what we heard this morning, switched from standard volume sampling to the minimal proportional sampling volume, and did not observe a significant decrease in the transfusion reactions. It was 5 in a million before the switch to the minimal proportional sample volume, and 6 in a million afterwards.

At NHSBT, the rate of septic transfusion reactions also with a Trima Accel device, is less than 1 in a million. There were no transfusion reactions with products collected on the Trima platform, and this is published by Carl McDonald in Transfusion.

This data supports that minimal proportional sample volume and large volume delayed sampling on Trima Accel is the only supported device. Data for Amicus needs to still be generated in support of these sampling techniques.

The cost associated with these strategies, large-volume sampling and minimal proportional sampling, has no additional cost for the hospital. Point-of-issue testing in comparison what we heard this morning, also, is a $25 to $30 premium, and pathogen reduction has an about $100 premium per product, as we have heard these septic transfusion reactions with Trima are 2 in a million, and with large-volume sampling there have been no reports of any septic transfusion reactions with the Trima device.

In conclusion, there are statistically significant differences in septic transfusion reactions for the two primary apheresis collection devices. The rates were significantly lower with a Trima Accel device. Data supporting the use of minimal proportional sample volume and large-volume delayed sampling were all collected on the

Trima Accel device. Data on the Amicus device has not been generated, or not published at this point.

The FDA's recommendations of minimal proportional sample volume and large-volume delayed sampling must use an evidence-based standard, and take into consideration the impact of the Trima Accel apheresis system on bacterial contamination.

Thank you.

DR. ALLEN: Thank you for your presentation. Our next speaker is Dr. Nancy Dunbar, from the Geisel School of Medicine, Dartmouth College.

DR. DUNBAR: Thank you. Good afternoon, my name is Nancy Dunbar, and I'm the medical director for the blood bank at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire. I'm here today to share our transfusion service perspective on the use of rapid testing to enhance the safety of apheresis platelet transfusion and routinely extend that shelf life to seven days. I will also share my personal perspective on the large-volume delayed sampling approach, a potential alternative for 7-day outdating.

I disclose that I serve on the scientific advisory board for Verax Biomedical, which financially supported my presence here today.

Dartmouth-Hitchcock Medical Center is an FDA-registered facility that supports a 400-bed academic

tertiary care medical center, which includes a level 1 trauma center, neonatal, intensive care unit, and hematopoietic stem cell transplant program.

We transfuse approximately 2,500 apheresis platelets annually. Our hospital-based donor center provides almost 40 percent of our apheresis platelet inventory, while the rest is provided by three external blood suppliers. Due to our rural location, our closest external supplier is approximately 100 miles away from our hospital. This means that during times of unanticipated demand that lead to unexpected platelet shortages, it can take three to four hours to fill our urgent ad hoc orders for more platelets, assuming more platelets are even available. This means that patients at risk for bleeding due to thrombocytopenia, particularly our hematology-oncology patients, may experience delays in necessary transfusions as they wait for ad hoc orders to arrive.

Dartmouth-Hitchcock was one of the first hospitals to introduce pre-storage bacterial culture platelets starting in May 1999 and most likely the first to enhance the safety of platelet transfusion by performing additional rapid testing on previously cultured platelets starting in July 2008.

From February 2016, we've used rapid testing to extend the shelf life of all apheresis platelet units from

all of our blood suppliers to seven days as described in the current draft guidance. We've shared our experience using rapid testing to enhance platelet safety in a manuscript published electronically in Transfusion on April 17, 2018. From July 2008 through November 2017, we performed rapid testing on over 9,000 apheresis platelets. We've not identified any true positive results, nor have we seen any units with initial negative rapid test results that subsequently converted to a true positive on repeat testing. We have observed a low false positive rate of less than 1 percent, as reported by others using this method.

Since implementation of pre-storage culture of platelets in 1999, we have not identified a septic transfusion reaction at our institution. We also recently reported changes observed in platelet transfusion practice and inventory management, one year after routine implementation of 7-day platelets, compared to the year before implementation, in another manuscript published in Transfusion in April 2018.

Since implementation of routine use of 7-day platelets, we have not observed any change in hospital length-of-stay, or in the mean number of platelet transfusions per patient transfused, compared to the year prior to implementation of 7-day platelets. Our platelet

outdate rate has decreased significantly, from 5 percent to 2 percent, which offsets the cost associated with performing rapid testing.

Additionally, ad hoc ordering, which is generally a reflection of urgent need for platelets at our hospital, significantly from 21 percent to 9 percent. As mentioned previously, ad hoc orders reflect urgent need for platelets during times of unanticipated increased platelet utilization, when our regular standing order and delivery schedule is not able to meet the needs of our patients. Given the distance from our blood suppliers, the situations requiring ad hoc ordering can be stressful and delay necessary patient care, as platelets take several hours to arrive.

Thus the use of rapid testing to extend the platelet outdate to day 7 has allowed our transfusion service to better tolerate fluctuations in platelet supply and demand, and better meet the needs of our patients. Although alternative options exist for enhancing apheresis platelet transfusion safety, such as pathogen inactivation, which currently only allows for 5-day outdate, our institution has chosen rapid testing, due to the ability to extend platelet outdating to seven days and increase availability for our patients.

Alternative options for 7-day storage of apheresis platelets, such as large-volume delayed sampling, are currently under consideration. I remain unconvinced that large-volume delayed sampling provides increased or even equivalent safety, when compared to our current approach of primary culture followed by secondary testing later in the shelf life of the unit.

Further, large-volume delayed sampling approach would require a larger sample volume taken at 36 to 48 hours after collection, with a product hold of six to 12 hours after sampling, before distribution to the hospital transfusion service. Thus, it could effectively reduce the time for platelet availability in our inventory by 12 to 24 hours, or up to half the time we gained by implementing 7-day outdating using rapid testing.

Our hospital transfusion service will continue to perform rapid testing to enhance platelet safety and availability, until other equal or better methods that allow for 7-day outdating are available and feasible.

Thank you.

DR. ALLEN: Thank you for your presentation, information. The next speaker is Dr. Peyton Metzel. I don't have an organization there. If you would please give us any affiliation.

DR. METZEL: Peyton Metzel, retired. Up until a month ago, successfully. I spent about 22, 23 years with Baxter, with the Fenwal division, and then as Fenwal incorporated, the spinoff from Baxter Healthcare. During that time I had the opportunity of working on what we called at the time pathogen inactivation, which is now of course the Cerus INTERCEPT program. I worked on PASSPORT, which has been mentioned a couple of times. I worked on platelet additive solutions. And it's exciting for me to come back and see that there's as many people standing as there were when I left five-and-a-half years ago.

Before I get too far into the presentation, I'd like to personally apologize to Dr. Snyder for some comments I made four years ago. I apologize.

Five years ago, and we can do the math, three or four people every year died as a result of contaminated platelets. That's minimally, 20 people, in those five years. I would suggest that if it were CJD, or HIV, the chairs would be filled. I think Mo Blackman made that same comment in the paper that was reviewed in 2013. So, for me to be gone for five years, and to find out that I'm even close to being relevant, is shocking. But also kind of disappointing that we are still in the place that we are.

We've looked at several options today and heard people passionately speak about those options. I don't

have any slides, but during your discussion, if you might draw a timeline of the platelet starting at day 0 and going through day 5 or day 7 and look at these different methods of what their interventions are, what time are samples taken? Twenty-four hours, 36 hours. How much volume is taken? Eight mls, 12 mls, up to 25 ml. And statistically, how much do those volumes really make a difference in terms of detection?

And more importantly, when you look at secondary methods, whether it be culture at day 3 or day 4, as we heard from Hopkins, or the intervention using a rapid point of issue, those, in fact, represent additional platelet units that are detected. So, we have a day 1 that, for example, might detect 200 per million -- and I'll pull this right out of PASSPORT -- and then subsequently, a day 8 platelet was 500, 600 per million.

So that indicated that that primary method for culture really represented 25 percent of the total platelets contaminated. So, is there a way that we can move with a secondary method, whether it be culture or point of issue, to close in on those number of platelets that actually get released and transfused?

I found it really interesting in Dr. Jacobs's presentation that passive surveillance can also miss deaths, which I was shocked. If you look at his data, he

accounted for 0.6 percent of the platelets, or 0.4 percent of the platelets transfused, yet 6 percent of the platelet-related deaths. So, that would indicate that sometimes with the delayed scenario of these platelet reactions, don't get associated with the platelet itself. It gets associated with something else. I think that's a slide that the committee might revisit.

I come back to, like I said, the PASSPORT scenario, where we ran about 200 per million in the initial culture, and then day 8 culture, about 500 to 600 per million more, in addition. And it would be my hope that with the intervention of either culture, at day 4, 5, for a 5-day platelet, or a point-of-issue test at day 4 or 5, 6 or 7, would reduce that number and hence reduce deaths.

As kind of a personal aside, several years ago I lost a very close friend. He received platelet transfusions and early on in his treatment he died of unknown causes, and I spoke with his family and what they described to me appeared to be one of those rare deaths that occurs, and it's not until a personal friend or family member that's receiving a platelet that you look up there and you wonder if an intervention such as a culture, or in the case of INTERCEPT platelets, which also would be effective in eliminating that bacterial risk, would have made a difference, and that's just one life.

Thank you.

DR. ALLEN: Thank you for your comments.

Our next speaker is Dr. Mark Brecher, emeritus UNC.

DR. BRECHER: Thank you. Like Dr. Jacobs, I have historically lots of conflicts, which may mean I have no conflicts. But I wanted to take 30 seconds to address the question of anaerobic bottles. It was my laboratory that did the initial validation work with the BacT/ALERT. Back then it was Organon Teknika, the 3Ds, and in our initial experiments we chose to include Clostridium perfringens, because we had known that in the literature there were cases of Clostridium perfringens deaths.

The second thing is, contrary to what the committee has been told today, the formulations of the broth in the two bottles, while they're similar, they are different. So, that's one possible explanation why you see a difference.

The third thing is, we observed, through many iterations of inoculation experiments, faster growth with streptococcus, and in some cases, staph species, with the anaerobic bottle.

The final point I wanted to make, quickly with that, was that the plastic bags -- yes, they do breathe, Susan, but they breathe very slowly. So that the

environment in a platelet is not really an aerobic environment and it's not really an anaerobic environment. It's something in between.

Looking at FDA data from before the era of bacterial detection, was about six cases, six deaths per year, and the majority of the deaths were from gram-negative organisms.

Looking at studies from the United States, United Kingdom, and France, and sort of pulling all the data together during that period, that gram-negatives accounted for 82 percent of the reported deaths. So, gram-negatives are the really bad actors, and the risk of a gram-negative death with gram-negative sepsis was 45 percent, in this aggregated data. But a gram-positive was only 10 percent. And the early culture method is very good with gram-negative detection.

How good is it? Do we have success or failure? It's already been said.

Red Cross data. There was a 75 percent drop in septic reactions reported. If you look at -- this is a slide I got from Anne Eder a couple of years ago -- if you look at fatalities, Red Cross data, there's been about a 80 percent reduction in fatalities, with all the interventions we've made over the years.

FDA data being reported for apheresis platelets. We went from about eight deaths per year down to about one per year, now. That's an 87.5 percent reduction in fatalities. So, we've been very successful. Not to say we can't do better, but I think we have to acknowledge how well we have done.

Some gram-negative cases do continue to slip through. This is just a couple cases, there's some Morqanella, two deaths, with Walter Reed and the NIH. Some E. coli death out of Kansas City. You could say that these were operational issues, human error. Some gram-negative cases do continue to slip through. But the same thing could be said for pathogen reduction. Where humans are involved, errors will happen.

I think an interesting point that we had not talked about here -- actually, there's two. Let me just back up for a second. I meant to say that with all these bacteria in the bag, in the old days we used to talk about why can't we just add antibiotics to the bags? Small amounts. I'm disappointed to hear that that hasn't come back up again. That was 25 years ago. It would be a simple quick fix.

But the other question that I wanted to address is are older platelets less safe than younger platelets? We've already seen many slides about slow-growing bacteria

increasing concentration over time. We've also alluded to the step graphs where, with the day of storage, you start to see more cases of sepsis and fatalities. However, these are not true rate slides. We really don't have a denominator. We don't know how many platelets were transfused on day 5. How many were transfused on day 4. So, we don't have a true rate.

Recently, in Transfusion, there was a study from Denmark, Kreuger et al., that finally tried to look at this, and he cut the data several different ways, but the bottom line, he concluded that contrary to current thinking, transfusion of a single old platelet actually seemed to be protective.

We don't have that kind of data in the United States. We just don't know what the date of our platelets. What about pathogen reduction? It was alluded to today that platelets don't like to be put under UV lights and treated, so the survival and recovery takes a hit with these platelets. Dr. Benjamin said, we owe our patients the safest platelets. Well, you could also argue we owe them the healthiest platelets, and unfortunately, the two goals are mutually -- they're not mutually possible.

He did show you a slide from the study in Austria, but this is a U.S. slide of the pathogen reduction. This is the SPRINT trial, the number of

platelet transfusions, and in the treated arm there were 35 percent more platelets needed, so that's something we have to think about.

DR. ALLEN: Thank you very much, Dr. Brecher.

Dr. Louis Katz, from America's Blood Centers.

DR. KATZ: Dr. Louis Katz. I am the chief medical officer of America's Blood Centers. My remarks today are a joint statement from AABB, America's Blood Centers, and the American Red Cross. Accordingly, I am not allowed to extemporize.

I am the paid chair of data safety monitoring boards at Terumo BCT, evaluating the Mirasol pathogen reduction technology. We appreciate the opportunity to present this joint statement to the FDA as it finalizes recommendations for bacterial risk control strategies, for platelet transfusion. The statement updates the FDA on the current thinking of our organizations since November 30, 2017, when this topic was discussed at the BPAC. We believe these comments will assist the 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 current interventions which interdict 30 to 50 percent of contaminated platelet units, transfusion-associated sepsis remains the most common infectious cause

of recipient mortality reported to the agency. Nineteen fatalities have been recognized and reported in the last decade to FDA, but as has been pointed out during the meeting, surveillance is passive, and the clinical burden is believed to be greater. Hence, our organizations support the 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 post-collection.

While calibrating our efforts to enhance platelet safety is intrinsically difficult without an a priori threshold of tolerable risk, we strongly endorse providing multiple options based on both demonstrable enhanced safety and operational considerations for collection facilities and hospitals across the United States, depending upon their ability to implement one or more of the allowable interventions.

This statement expresses and implies no preference for a specific mitigation option over others, nor does it commit any blood collector or hospital to a specific approach or combination of interventions. That must be the result of consultation and collaboration between the collectors and transfusion services within FDA rules and guidance. The options available to achieve this goal include enhancing the sensitivity of testing for

bacteria, and the use of pathogen inactivation. We favor making multiple approaches available while surveillance data accrued on their relative clinical values.

Regarding bacterial culture approaches, these include rapid point-of-care tests on days 3 or 4 and beyond, re-culturing during the shelf life of the product, and implementing changes in the approach to primary culture. Data are available for each of these approaches to support increased safety relative to the current intervention using early culture alone.

Increased sensitivity of primary culture can be achieved with three options. Increasing the inoculated platelet volume, using aerobic culture only without increasing platelet hold time, or changing other parameters, increasing the inoculated volume without changing the platelet hold time, but using both aerobic and anaerobic culture, the latter for detection both of obligate anaerobes and for enhanced growth for facultative anaerobes and microaerophilic organisms. And finally, increasing the inoculated volume using both aerobic and anaerobic culture, in addition to a longer hold time for platelets prior to culture, greater than or equal to 36 hours.

Published data from the National Health Service Blood and Transplant in the United Kingdom, and emerging

data provided by our Canadian colleagues at Hema-Quebec and Canadian Blood Services, suggest that a combination of large-volume and delayed sampling into both an aerobic and anaerobic culture medium, is effective. Two-culture approaches during platelet storage presented today have shown improved bacterial yield, and in one case, reduced septic transfusion events.

The method defined by the Hopkins group for 5-day platelets using secondary culture at day 3 describes improved yield and improved outcomes, recognizing that only five mls was inoculated into a single aerobic bottle. The Irish have described improved yield during their experience with aerobic and anaerobic cultures on days 1 and 4, with extension of platelet shelf life to seven days.

Some enhanced testing options can be implemented with 5-day stored platelets, but with the extension of storage to seven days all enhancement improve operational efficiency and platelet availability, and this particularly true with large-volume delayed sampling, which results in the loss of up to one day of committed shelf life that is mitigated by expiration extension to seven days.

Based on published reports and hemovigilance data from outside the United States, pathogen inactivation has been shown to provide bacterial safety for platelets, while also effectively reducing the risk of transmitting other

blood-borne pathogens and other adverse reactions from transfusion. In the United States, the capacity to produce PI platelets is limited by restrictive guard bands for qualifying apheresis products as eligible and lack of a license system for triple-apheresis products, or for whole-blood-derived platelets. In order to overcome limitations to the PI platelet supply, we urge the manufacture with FDA to collaborate aggressively in pursuit of the goals of expanding the guard bands and providing data in support of triple collections.

Further, we ask the FDA to make regulatory process more conducive to timely implementation of this technology. We understand the limitations of the data for evaluating the clinical efficacy of U.S. licensed PI platelets. Robust data on their effectiveness are largely derived from hematology-oncology patients, and patients with active hemorrhage from trauma and other conditions may be underrepresented.

In summary, morbidity/mortality due to transfusion-transmitted bacterial infection will still occur, does still occur, and it is necessary to pursue enhanced safety to protect patients. The allowance for multiple approaches that enhance bacterial safety balances the need to improve safety with economic and logistic

considerations that may influence decision-making in different institutions.

Thank you.

DR. ALLEN: Thank you, Dr. Katz.

I would remind speakers, please, to stick to your time. If you have a written statement that can be submitted and distributed, but we must keep to our time.

The next speaker is Dr. Heather Pidcoke, chief medical officer of Cellphire.

DR. PIDCOKE: Good afternoon, I'm Heather Pidcoke. I'm chief medical officer of Cellphire, which is a biotechnology company that is developing lyophilized platelets. I have two statements, one on my behalf and that of my company. The other was from a colleague, Dr. and Colonel Andre Capp, who is an active duty physician with the U.S. Army.

Beginning with my statement, my disclosures, including the work that I do for Cellphire. I'm a former employee of Terumo BCT, which has received government funding for both cold-stored platelets and for pathogen-reduced platelets.

I'd like to thank the BPAC committee for giving us the opportunity to offer some comments on bacterial contamination, which became an important topic when room temperature storage of platelets was adopted as the

standard of care in the early 1980s. This change in product handling was made to address a proceeding change in clinical practice, in which transfusion for bleeding was replaced by prophylactic transfusion.

Both changes were made without the rigorous data that would be required today. Room temperature stored platelets have a higher incidence of bacterial contamination compared to other blood products by at least a factor of 10. In addition, there's a well-documented platelet storage lesion with consequences for immediate hemostasis. In order to prevent bacterial contamination from leading to sepsis and/or death, blood centers and hospitals must expend significant resources ensuring that bacterially contaminated units are identified and discarded. This has created a financial and operational burden that is straining blood center resources.

In summary, managing the very short duration of room temperature stored platelet products is costly, places a strain on blood centers, and increases risks for patients. Today the committee has primarily focus don options to address the risk to patients that would add to that complexity and that burden. We urge the members of BPAC to consider expanding the analysis to consider how the choice of the product is related to the clinical treatment.

There are several other ways to approach platelet storage, both approved and in development. Cold-stored platelets are approved for three days in plasma, and existing data suggest that the storage duration could be extended. Frozen and lyophilized platelets have much longer storage potential and are also under development, and these could carry a much lower risk of bacterial contamination.

These products have not been considered because a room-temperature stored product is thought to be required for prophylactic transfusion. But prophylactic versus therapeutic platelet transfusion strategies have been recently compared in large randomized trials with not a hemostatically active platelet product as one of the arms. We suggest that a randomized controlled trial that compared prophylactic transfusion with a room-temperature platelet product versus a therapeutic strategy with a hemostatically active platelet product is needed. Such a trial, to evaluate the problem of bacterial contamination, would be the additional data required.

This is from Andre Capp. His disclosures -- he has no financial disclosures to make. He is an active-duty colonel in the military and is currently on service in the hematology department of the Brook Armory Medical Center in San Antonio, which is why he could not be here. He does

have the disclosure that he does not speak for the U.S. Army, for the U.S. Department of Defense, or for any other U.S. government agency.

Dr. Capp would like to remind the committee that a randomized controlled trial, the Norwegian cold-stored platelet trial, although pilot in scope, presented results at AABB that there were decreased blood loss in the cold-stored platelet arm, and these results are consistent with what we know about cold-stored platelets from trials performed in the 1970s, better hemostatic function for treatment of acute bleeding than room-temperature platelets.

These results are also consistent with results for cryo-preserved platelets, as demonstrated by Bob Valeri in a randomized controlled trial in Cardiac Surgery in the 1990s. There exists a substantial body of data demonstrating that alternatives to room-temperature platelets, such as cold-stored platelets, thermocycle platelets, cryo-preserved platelets, and lyophilized platelets, offer functional advantages to room-temperature platelets for acute bleeding.

We should keep in mind that trauma is the number one cause of death in patients under the age of 44, and the third leading cause of death overall. The number one of cause of preventable death in trauma is hemorrhage. It is

time for the transfusion medicine community to acknowledge the need for innovation to address this important public health problem. We need hemostatically active platelets with shelf life adequate to supply America's hospitals both in the United States and deployed with our soldiers overseas.

Alternatives to room-temperature platelets exist now, such as cold-stored platelets. The shelf life of these should be expanded now to 15 days, as supported by available data. We must continue to develop more products to meet our patients' needs. Thank you to the committee for this opportunity.

DR. ALLEN: Thank you for your presentations. Our next speaker is Dr. Steve Wagner, from the American Red Cross.

DR. WAGNER: Steve Wagner, American Red Cross. In addition, I've participated in three scientific advisory meetings for bioMerieux. At the end of Dr. Bloch's presentation, Dr. Allen suggested that blood centers, such as ARC, could do secondary culture instead of a large hospital, for example, at day 3. For example, we could sample with immediate release on day 3, at blood centers, let's say, ARC blood centers, but because we have to transport the platelets, sometimes to places like New Hampshire or Vermont, for example, we would lose one to two

days of storage on a 5-day storage time, and so that makes it difficult routinely to get platelets everywhere, especially rural areas, where they're far away from the blood center.

There was also a suggestion that extending the hold time, for example, to 36 or 48 hours, might necessarily be efficacious to get results similar to those that were described in Dr. Bloch's study, but I just wanted to caution that the data, if you were to get data on that maneuver, might not be as good as what Dr. Bloch reported, because of slow-growing bacteria that may have lag times that are longer than the time period when sampling took place.

In the same way, and that's for 5-day storage, and for 7-day storage, the same is true. Extending the storage to seven days might introduce more slow-growing organisms that you would not necessarily see on day 5, because they're there, but they haven't had time to grow up yet. So, I think that there's really not enough scientific data to make claims that the blood center could do secondary testing and get similar data to those that were presented by Dr. Bloch at Johns Hopkins.

Thank you very much.

DR. ALLEN: Thank you for your comments.

The next speaker is Dr. Laurence Corash, Cerus and UC San Francisco.

DR. CORASH: Thank you, Mr. Chairman. I am Laurence Corash, I'm the chief scientific officer at Cerus Corporation, and professor of laboratory medicine at the University of California in San Francisco. I am an employee of Cerus and have an equity interest in Cerus Corporation. I started to work on the INTERCEPT pathogen inactivation technology in 1982 in response to patients acquiring transfusion-transmitted infections in our hematology service.

I want to urge the committee and the FDA to issue a final guidance, because as I talk to hospitals and clinicians around the United States about how to reduce the risk of transfusion-transmitted bacterial infection, they need clarity. Draft guidance doesn't give them sufficient clarity, and they want options, and they need specific codification of these options so they know what to do and how to use the technology.

There are several points that I would like to amplify, based on comments that were made during various presentations today. We tend to focus on septic transfusion reactions and deaths, and they are undoubtedly very important, but as Richard Benjamin commented, there really is no level of bacterial contamination which is

acceptable, and we need to think about delayed infectious events.

Any of us who have taken care of hematology-oncology patients have chased febrile neutropenia and dealt with catheter-related infections, and you have to think about the possibility that low levels of contamination in all blood products can lead to colonization by biofilms and catheter-related infections. So, I urge you to keep that in mind as you think about the various options and how rigorous these options need to be.

I think also it's very important to think about this from the patient's perspective. Everybody tends to look at the per-component risk, but think about the fact that a newly diagnosed acute leukemic will on average receive six to eight platelet products in the first 30 days, and so that patient is looking at their total risk during that period of time, and I think it's very important to bear that in mind.

In the United States, we have largely neglected whole blood-derived platelets. I think one of the things that pathogen inactivation technology and also the various detection technologies, when used appropriately as they have been described in some of the European countries, can clearly make whole-blood derived platelets more available, which gives elasticity to the platelet supply, and will

improve availability and the adoption of these technologies.

There was a comment made this morning about the possibility of combining or using pathogen reduction technology after some type of initial screening, and I would like to point out that the two approaches are diametrically opposed, in the sense that detection, to have adequate sensitivity, needs delay for time for the bacteria to multiply before they can be detected, whereas the pathogen reduction technologies are specifically designed to be used early after collection of the product, to prevent proliferation and production of endotoxins. So, we need to keep that in mind.

The comment was also made about the lower CCI responses. I would point out that in clinical trials that have been conducted with adequate hemostasis evaluation mechanisms, that bleeding -- grade 2 bleeding, in particular -- occurs in approximately 50 to 60 percent of patients. Generally only on one or two days, which shows us the prophylaxis is working. And this is despite lowered CCI responses. So I think that we're transfusing enough platelets, and the CCI responses don't necessarily correlate directly with hemostasis and despite these lower CCI responses, we're not seeing increased utilization.

I think that the committee faces a very important task, and that hospitals and treating physicians need a final guidance. Thank you for your attention.

DR. ALLEN: Thank you, Dr. Corash.

Our next speaker is Dr. Ralph Vassallo, from Blood Systems Incorporated. Chief medical officer.

DR. VASSALLO: Thank you to the committee for entertaining a brief response. I wanted to address the comments that Dr. Jacobs made, and make sure that the committee is aware of all the facts.

One of his contentions in the failure of enhanced primary detection was the assertion that the residual risk of bacterial contamination at day 7, for both of those technologies, was the same, statistically, as historic rates in 3 to 10 ml cultures. What he failed to put on that slide was the day 5 Verax residual contamination rate -- not septic transfusion -- residual contamination, which had a higher point value than any of the other four on that slide, and was probably also not statistically significantly different. So, using that criterion to suggest the failure of enhanced culture, so too must secondary testing with Verax similarly fail.

He also asked us to focus on the success rate of Verax interdicting. They interdicted nine in a 27,000-some transfusion study, and that that was a rate of 326 per

million, but again he neglected to mention the interdiction rate of minimal proportional sample volume, which we showed had risen 107 per million as we increased from 8 to 10 mls, to a 3.8 percent sample volume.

That, on top of the fact that we're using Trima alone, which as Susanne Marschner has read into the record, based on the Eder paper, was already 130 percent lower than Amicus platelets, which formed the predominant platelet in the Verax study. So, of course the Verax study had more contaminated platelets to find in that study, so I would suspect that if you do the math there, you would find about a 220-some per million interdiction rate, with the minimal proportional sample volume 320-some per million interdiction rate with secondary testing with Verax, which are likely statistically the same. So, by that criterion, minimal proportional sample volume is as successful as Verax.

I just wanted to not leave the committee with that incorrect perception, so thank you.

DR. ALLEN: Thank you, Dr. Vassallo. The last speaker that we have on our list is Dr. Carl McDonald, with the National Health Service Blood and Transplant, United Kingdom.

DR. MCDONALD: Thank you for giving the opportunity to reply to some of the things said this

morning. I'd just like to make a point to the committee about the SHOT surveillance system. In 2015, our regulators at MHR, Medicine and Healthcare Products Registry, actually MHRA, came to the FDA, it became mandatory to report all transfusion reactions back. In 2015, they started to inspect the hospital blood banks. So, it may not be perfect, but it is quite a stringent system.

Also, the committee probably need to think on the clinical outcomes we've achieved. Mark Brecher mentioned we've had a considerable reduction in clinical reactions since the implementation of bacterial screening, and I think that appropriate application of bacterial screening, and indeed, pathogen inactivation, used appropriately, will cause a significant reduction in transfusion reactions, which is obviously what everybody's after.

Thank you.

DR. ALLEN: Thank you very much, Dr. McDonald.

Does anyone else in attendance wish to address the panel? If so, you will be granted five minutes.

(No response.)

All right, we will close the open discussion section, and at this point move on to the question to the committee.

Dr. Nicole Verdun from OBRR, FDA, will be presenting the question.

Agenda Item: Question for the Committee

DR. VERDUN: Thank you. I just wanted to take one moment to just thank the committee, thank the presenters, and thank you for the compelling discussion that has followed thus far. As we move into the open committee discussion, I just wanted to restate the question, since it's been some time since this morning's presentation.

The question for the committee is please comment on the advantages and disadvantages of each of the various strategies to control the risk of bacterial contamination in platelets, including the scientific evidence and the operational considerations involved.

Thank you.

DR. ALLEN: All right. So, we will open the floor to the experts on the panel to begin deliberating any issues that you may have heard the data for today or that you haven't heard data for and think we ought to have heard, and bring those. We'll focus, in addition, our discussion on the FDA question presented by Dr. Verdun. Copies of the question are in your panel folders.

This is a deliberation period among the panel members only. Our task at hand is to answer the FDA question based on the data, the presentations, and the

expertise around the table. I would ask that each panel member identify him- or herself each time he or she speaks in order to facilitate the transcription. You may ask questions of the presenters that we heard this morning if you like. Please address the question or comment directly to them, and they may come to the microphone, identify themselves, and respond to that question.

The overhead that is up there now is the strategies for discussion. We will look at each of these in turn, the 5-day storage, and there are four different scenarios presented there, and 7-day storage, and an additional three scenarios for us to discuss. And, as I believe has been said, opportunities, if you see other issue or items that you want to add, you certainly may do so.

We'll start by discussing for under 5-day storage, primary culture plus secondary culture, predominantly on day 3.

Agenda Item: Open Committee Discussion

DR. LEWIS: Roger Lewis, Harbor-UCLA Medical Center. With the permission of the chair, I'd like to make some general comments about the challenges facing us, rather than specifically addressing just one of the options.

DR. ALLEN: Absolutely, that's quite appropriate to begin that way. We have time, and yes, we need to get all the information that we as the panel believe the FDA should consider and help them move forward, as you heard many of the speakers speak about the need to get this guidance finalized and out. Feel free.

DR. LEWIS: As one of the token non-blood bank people here, but someone who spends a lot of time thinking about sparse data, what struck me is how incredibly sparse the data was. It's the equivalent of a statistical Rorschach test, in that anybody can see in it what they want to see in it. To me, that really poses a number of challenges regarding how we just think about this, and it will directly relate to the question posed to the committee.

One of the challenges is the variability. There's clearly variability in the lag phase of the different pathogens of interest. There is unknown variability in the doubling time of the pathogens once they exit the lag phase and enter the log phase, and it's clear that there are clinically important contaminants that at the time of initial collection, or even at 24 hours, are below the limit of detection for the initial testing.

The strategies that are based on enhanced initial sampling can fundamentally only have a linear effect on the

sensitivity of detection, because we may talk about a doubling or a tripling or a quadrupling of the sample volume, or small changes in the timing, but those are really going to have linear effects, and what we're trying to achieve here seems to me it's more of an exponential or a log change in the risk of a clinical event a number of days later.

To me, there's a very close analogy between what we're trying to do here, which is basically a surveillance problem, and the challenges that have faced those looking at the data for the improvement in mortality that was expected with surveillance in cancer screening. And as I think, as many members of the audience and the committee know, that the actual reduction in deaths from many cancers for which we actively screen has been a lot smaller than we would have hoped for.

One of the key insights related to that observation is that cancer, even within a particular histologic type, is in fact very heterogeneous with respect to the speed with which it grows or metastasizes, and I think the lessons that were learned from that area, where there is very rich data, can inform the way we think about this area in which the bacteria are the heterogeneous thing, and there are very sparse data. If we were only interested in catching the rapidly growing pathogens, we

could just culture initially, or one time at a fixed time point. If we knew they were all going to be slow, we could culture later. But since we don't know, we have to have an enhanced strategy.

In my mind, what this means, that if one accepts that the current risk of contaminated platelet units is too high, there's really no escaping the need for one of two approaches. One is a sequential testing strategy, because you have to do better than just a linear change in the sensitivity at the initial test. Or, a pathogen reduction strategy that essentially reduces of any contamination at all below the level that you're willing to detect.

If one is comparing sequential testing strategies, it's either an additional test at four days, or a just-in-time rapid test. What the committee, I think, should understand that the just-in-time rapid test will be statistically superior if the sensitivity of that test is larger than the fraction of all contaminated units -- meaning, those that will ultimately turn out to be contaminated that have turned have turned positive by day 4.

Thank you.

DR. ALLEN: Thank you, Dr. Lewis. We are going to take a quick break here. Dr. Jones has lost his telephone contact with us, and we need to reset that, so if you want

to get up and stretch, get a quick drink of water, but we will reconvene in four, at most five, minutes.

(Break.)

DR. ALLEN: We will reconvene the discussion.

Dr. Jones, just quickly, we've finished the public session and we have just had about three or four minutes of discussion under the committee's discussion format, and we're going to open it first of all for some general discussion, and questions the committee members may have. Our speakers from this morning are here, and if you want to address a question to any of them, you're certainly welcome to do so.

DR. ALVING: Barbara Alving. I just wanted to make a few general comments. First of all, I think there are some things that perhaps could be agreed upon, and from my reading and the comments today, it seems that the AABB criteria for STRs seem to be one that appeared to be very strong, and I think that could be explored further, if one is looking at definitions for STRs. So that that could lend a little more clarity to physicians in the field. But I would also agree that I think it's very unlikely that we're going to get robust reporting systems from actual clinicians, because they work in such complex situations.

Secondly, I think every one of these hospitals or blood centers is probably moving forward. In other words,

this is a dynamic moving field. It's just not going to stay put. So, I think we have to have -- I would recommend the FDA have flexibility in looking at what is known, but keeping the door very much open for going forward.

Thirdly, I would say that our country is incredibly complicated, for example, I don't even begin to know of all the operational issues. In other words, what works for Johns Hopkins with the American Red Cross, or Johns Hopkins in Baltimore, may not work for Fargo, North Dakota, with Arizona -- is it Arizona supplying Fargo's? Fargo's a long, long way away from Arizona.

It's an incredible network of systems that we haven't really heard about, and I think somehow, and you brought that in, in terms of operational considerations, these are things that need to be respected and perhaps can only be understood in terms of those blood centers that are supplying the platelets and having their other ideas about moving forward.

DR. ALLEN: Thank you.

DR. SCHREIBER: Marty Schreiber, from Oregon Health and Science University. I wanted to expand on the comments made by Heather Pidcoke and Colonel Capp. I didn't mention it earlier, but I'm also a reservist, United States Army, I've been deployed three times to Iraq and Afghanistan. I work in Portland in a big city, but it's

primarily a rural state, and this platelet problem affects me and all the places I work.

I think it's critical to talk about this -- everybody's here today for one simple reason, and that simple reason is we're leaving the milk out of the refrigerator. And everybody knows that if you leave the milk out of the refrigerator, bacteria grows in it. This leaving the milk out of the refrigerator is making us have a 5-day product. What does that mean? In theater, what it means is, you can't get platelets from CONUS. You have to get platelets from theater.

Right now, when operational tempo is low, there are not people to get platelets from. So, the military is using cold-stored platelets out of necessity. What does it mean in rural Oregon? What it means is our entire, the vast majority of our geographic state, doesn't have platelets. If you're injured on the coast of Oregon and you're hemorrhaging and you need your spleen out, you're not going to get platelets, and you're going to die. Mortality is double in rural places. You can't store platelets in a rural hospital when you can only store them for five days.

On top of all that storage issue, the truth of the matter is cold-stored platelets have greater activity and are more hemostatic than room temperature platelets,

and we know from data in the 1970s that the cold-stored platelets come out of circulation much more quickly, however, you don't need the platelets to stay in circulation if you're bleeding to death. You need to give a platelet transfusion, stop the bleeding, the patient survives, and you move on. There may not be one solution for all the patients.

So, maybe the cancer patients who are thrombocytopenic, maybe they're going to get a warm product, and we're going to do one of these things. But our trauma patients who are hemorrhaging to death need cold-stored platelets so they can be used throughout the world on our patients, and they're more effective, they'll stop bleeding, and save lives. We need to extend the FDA approval for the time that cold-stored platelets are approved. Right now it's three days. There's no reason for that. They should be approved for 15 days.

DR. DE MARIA: It is sort of related to the last few comments. I think with all of the material provided to us, the discussion at the last meeting, the discussion here, the presentations, I have a good sense of what it might take to get to zero in terms of septic reactions. What I don't know, and was alluded to earlier in the meeting, was what are the unintended consequences related to operationalizing these various interventions?

In terms of what the consequences -- it's hard for me, because I don't collect blood and I don't transfuse blood, it's hard for me to imagine what those are, but I have to imagine that there's a certain downside in terms of the consequences of implementing one or more of these strategies in terms of what it means to people who need platelets, what it means to the supply of platelets, and some of the other things that were discussed here. That's what I would like to see more information.

The other things is these strategies -- I think we're considering these particular strategies because they were studied, and after this discussion I can see a lot of combining some of the interventions within these strategies with each other, and the possibility of coming up with another algorithm for testing, or an algorithm even related to pathogen reduction, and what are the options for other potential strategies?

DR. LEITMAN: I would like to make a plea for continued hemovigilance no matter what the larger blood collection centers decide to implement after our recommendations and discussion are published. Large collection organizations -- Red Cross, UBS, consortia of AABB centers, perhaps -- continue to engage in studies, perhaps NIH-funded studies, of active surveillance of what's going in the product, detectable by transfusion at

the point of issue, or at the point of outdates, so we know how successful all these interventions are and we can compare apples to apples, when it's all done.

DR. ALLEN: Dr. Leitman, there are people here who are not -- including myself, certainly -- who are not primary blood bankers. Do you want to give a very brief description of the term hemovigilance, because it's one I hear thrown around a lot, and I've never really heard it well defined? I think I have my own definition. Or anyone else who might want to add it. But I think just a 30-second definition so we're all at least talking about the same term.

DR. LEITMAN: I think it is a systematic study and analysis of the safety of transfusions, not only infectious safety; it's safety from all sorts of adverse effects of transfusion. One does that systematic analysis both by analyzing the safety and efficacy of the product, safety would be infectious with a culture point of issue, as well as outcomes in the recipient.

In order to implement that kind of system, you have to have codified definitions of each type of the clinical adverse reactions that you collect and analyze. Septic transfusion reactions, someone needs codified definitions, you need systematic collection of the data, both on the product and the patient, in multiple areas of

the country -- urban, suburban, multiple collection centers and hospitals. I would ask those doing this if they want to supplement that definition. Maybe Sue Stramer could help with that.

DR. STRAMER: Well, I think, as Dr. Leitman said, it's a system of really collecting patient outcomes, and I would just add, since as long as we've been talking about the problem with bacteria, we've been talking about a national hemovigilance system in the United States, and until one is required or supported, it's going to be very difficult to implement on a voluntary basis. Going back to the remarks that Dr. McDonald made about the NHSBT, that's not the case. Even though SHOT is a passive reporting system, because they're not culturing every single product at outdate, it is not the passive surveillance that we have in the United States.

There are dedicated and trained staff in hospitals who do nothing but monitor reactions. These programs are inspected for consistency in following their SOPs. And they're supported by government. So, we have none of those systems available in the United States, and although the CDC may have NHSN, the reporting into NHSN is sparse at best, and even if we use a centralized collection of definitions, until we have support for a required system

of reporting patient outcomes in the United States, nothing will happen.

So I made a listing of a couple of observations that I had during the day that I wanted to comment on, but one of them is probably a more objective criteria, although there are costs associated with anything we discuss, and where that money comes from is unknown, but outdate culture, I think, that was one of Dr. Jacobs's points, is really the most objective criteria to determine the efficacy of what we have today, which we really don't know, or the efficacy of any changes that we make.

So unless we do something like outdate culture, which of course costs money, and one could argue, if I'm going to spend this kind of money, why wouldn't I spend it on the intervention rather than a monitoring device? So, to answer the original question, hemovigilance is a way to monitor what we have going on, whether it's in patients or donors, but in this case it's really to assess the effectiveness of any strategy we use based on patient outcome.

DR. ALLEN: Thank you.

Dr. Jones.

DR. JONES: I am Jefferson Jones, CDC. First, a comment on CDC's NHS and hemovigilance module, which is, those who don't know, it's an online module that hospitals

can opt in to, to report adverse events with a blood product. Currently, one of the difficulties with bacterial contamination of platelets is that they're grouped into transfused transmitted infections, having specific criteria for fever and heart rate and symptom onset that might be more specific to sepsis from bacteria. It's difficult to group in with the viral infections that we also look for as transfused transmitted infections. That's a current difficulty in NHSN, looking specifically for bacteria.

A couple other comments. There's been a few comments about small changes in volume or timing, and needing a secondary test as opposed to primary. I don't know if I have seen enough data where when we're talking about logarithmic changes, particularly about delayed culturing, whether a delayed culture, say 36 to 48 hours, versus a secondary test at four days, if I've seen enough data to know where the appropriate cutoff is to allow for that proliferative phase of bacteria to be detected.

A third comment is to the question about when we do get to each of these individual strategies and we're talking about them, I don't know if we want to address anaerobic, whether anaerobic testing would be recommended for all strategies, or only for those strategies that have been demonstrated through studies.

We have had comments on both sides about increased false positivity, but we've also had the comments about, most in the UK, about organisms that have only been picked up just on anaerobic bottles. We have the recent MMWR that talks about C. perfringens, and even the Klebs pneumonia, the facultative anaerobe, and we have concerns that both of those might have been prevented if anaerobic testing had been available. Thank you.

DR. ALLEN: Thank you.

DR. STRAMER: In response to Jefferson's comments, or comments that have been made by the committee, for any of these interventions, we have the data that we have, and if we want more data, or perfect data, it's going to take years to collect, and probably in permutations that may not be optimal. I think, you know, it's time to cut the -- or to facilitate doing something even though the data may not be perfect, but in order to move things along, determine ways to determine if they're efficacious, and then to do fine-tuning as we move forward.

I don't know that we want to meet once to twice a year to talk about contamination of platelets. I would say it's time to take action, whether it's finalizing guidance, as has been suggested, knowing what interventions we can use, do refinements of those as we figure out a way to really collect data, and move on.

I would also say that I agree with those presenters who commented that we don't want any bacterial contamination in platelets, because given any recipient on any given day, depending on the condition of the recipient, I think any bacterium could cause havoc, certainly, in that recipient.

I think the only other comment that I wanted to make was we talked about device differences, and there are collection device differences, as has been shown. Regardless, both of them will need ongoing bacterial enhancements. It doesn't really matter. And I was actually hoping that Fenwal or Fresenius Kabi, they have made a software change in their collection device for the Amicus, so I was hoping that they would present some of their data, although their licensed claim is not for reduction of bacterial intervention. The software allows another 100 mls of the initial collection to be diverted, so that potentially has the ability to further reduce bacterial contamination rates.

DR. ALLEN: The assumption on that being that the first collection, the initial collection, after penetration of the skin, is the one that allows a lot of the bacteria that enter to do so. I agree with you. I had made a note myself, as I prepared for this meeting, and heard the presentations today, that yes, we need to go back and take

a look at skin antisepsis, we need to take a good look at what we might do to first to reduce the ability of any skin bacteria to get into the system at any point, and certainly even the simple -- any needle puncturing it has a potential risk.

We need to make certain that we've got the best systems available that technology can develop, and that probably hasn't been given much thought recently and probably needs to be kind of on a continuing development basis.

DR. ESCOBAR: Miguel Escobar, in Houston. I think we can get as complicated as we want today, but that's not really what we want. Here, at the end, we've got to make a recommendation. The way I see this, we have a practice which is not perfect, which is platelet transfusion, it's given morbidity and mortality, and we've got some strategies to try to decrease that. It's not perfect, the data, but we have to work with what we have, like it was said.

So at the end, we're just going to have to make some recommendations, putting those strategies in combination to bring that to minimal or zero. That's the way I see it. Collect data, then prospectively, from then on, to try to get more information.

DR. ALLEN: Are there other general comments that any of the committee members would like to make? Then we'll get into the discussion of the specific strategies.

DR. CALIENDO: Angie Caliendo. I think, maybe it's just my perspective, I understand driving risk to zero, but at what cost? We haven't really talked a lot about false positive results and discarding units that are otherwise, maybe discarding units incorrectly, and limiting access to platelets because of that, and some of the data that we saw today, the numbers, if you do the math, are high. You're really dumping a lot of potentially useful units.

So I don't know how -- I'm not a blood banker, so I don't know how you guys weigh the pros and cons of that, or whether the goal is we're going to a zero risk no matter what. So I appreciate from some of the people in the panel who are transfusion experts to giving that perspective.

DR. ALVING: Barbara Alving. I just wanted to -- I think one of the little elephants in the room is this anaerobic testing, and I am wondering if there could be some different approaches to that. For example, let's say an organization like Hopkins does their secondary culturing, but they are using aerobic, but what if instead of instituting also anaerobic, they could do a rapid test that would be good enough? In other words, you would be

picking up anaerobes and aerobes, since they seem to be growing faster, and that could suffice. That could be a surrogate for an anaerobic culture. So I'm wondering if there are ways to think about this at all, if it would be easier.

DR. ALLEN: Maybe somebody will answer that. Dr. Harrell, do you -- I don't see another hand responding to that. I was just going to move on, because I know you have had your hand up, Dr. Stramer has, so let's go ahead but that is a question that clearly is important and needs to be addressed.

Dr. Harrell?

DR. HARRELL: Lizzie Harrell, Duke. My general comment is that the biggest challenge for me in trying to decide what to recommend here is that I'm having a hard time comparing the data from the various studies, because of the volumes used and again, aerobe versus anaerobe, and also the time period. Are we going for five or seven days, and also when are we going to do the secondary testing? So what I was wondering is if we are going to look at five days, should we look at the 5-day protocol, then try to narrow it down and agree on something that could be done by several different large centers for at least a while so we could get some data to see where to go from here?

DR. ALLEN: I am a little surprised we haven't heard more from NHLBI at this meeting, because I would think that in terms of the research side of it, that they might be good partners to be listening to the discussion here. That's just a comment to throw out there. Yes, we will come back and in just a few minutes begin the discussion of those.

Dr. Stramer?

DR. STRAMER: I wanted to respond to the earlier questions. I don't think anyone is presuming that we would get to zero risk or achieving zero risk with bacteria. I think we're still looking for the optimal incremental improvements over what we are doing today, and just to remind us that donors are healthy, asymptomatic individuals. So when we do screening for any marker, the vast majority of results, over 90 percent of the results, are false positive versus true positive. So every day we sit here, whether it's HIV or HPV or Zika virus or whatever the agent is, we vastly discard many, many units from healthy individuals who then desperately ask us to be reentered as a donor. So this type of issue is not new.

DR. CALIENDO: Angie Caliendo. I'm not -- I understand exactly what you're saying. I guess what I'm trying to get is a number around it where this benefit is not worth this side effect of sending away this many units,

and do you guys have those kinds of cutoffs in your head, or not. Do you know what I'm saying?

Like to drive it down to one per million less for throwing away another 300 units, what's your cutoff? How do you think about that? Because I understand exactly what you're saying. But I'm wondering if there's a cutoff to which you're like, oh, this is -- we're wasting good material here at this point.

DR. STRAMER: I don't think we have that number. That's what Dr. Katz read from the AABB statement. We don't have a number a priori. We just know why we're here today is we don't want to be here six months from now. So we need to advise FDA which of these strategies they should move forward with, based on whatever data are available, which are sparse and not able to be compared one method to another.

DR. ALLEN: Dr. Katz, you have one minute. This is the committee's time.

DR. KATZ: When we wrote our statement, we forgot that most of the people at the table are civilians, as opposed to blood bankers. So let me make the point very clearly, that the nature of the comments about 7-day dating, it more than compensates for what you lose in false positives. Before PASSPORT at my center, the outdate rate for platelets was 12 percent. With 7-day dating during

PASSPORT, it went to below 5 percent. So the platelet supply expands with 7-day dating. That's important for you to understand.

DR. ALLEN: Thank you. Any more general comments? If not, it's moving on, 3:30. So I'd like to get to the discussion of these individual items because the FDA is very interested in our specific comments. So for the 5-day storage period, let's first of all consider the approach of primary culture plus secondary culture on about day 3, and you can also make any comments you want about volume collected and -- well, we'll get to rapid testing in the next discussion. So this is two cultures. The second one being about day 3. Any comments?

DR. KAUFMAN: This is partially a general comment, but one thing that people on the committee that are not blood bankers may not think about is that some of the interventions that are being discussed really apply just to blood collection facilities, and some, such as secondary rapid testing or secondary culture, really apply to transfusion services only.

So they really in some ways have to be considered very, very differently. An ideal intervention, honestly, would be something that would be done right up front by the collection center, and then you would have a perfectly good product to go to the patients. Anything that is done at

the level of a transfusion service or hospital immediately presents both costs and challenges, and the same can be said for the blood collection interventions as well.

One of the things that was really, I thought, intriguing about this secondary culture that was done at Hopkins, one of the reasons that this was done, frankly, was it was practical. We saw some data that, while not perfect, it did interdict some contaminated units that otherwise would likely have been transfused and may have caused harm to patients.

It was done at a relatively low cost. It did require the addition of a single FTE, so not at all a trivial amount of work, but certainly less expensive than some of the other interventions that we'll be talking about. So anyway, I guess I think some of the advantages are really, I would categorize as operational.

DR. ALLEN: I think you have raised some very important points here, because the Hopkins system, while it worked very well there, probably would not work at all at the vast majority of community hospitals, and in fact, it's not discussed -- people still have the concept. I think the majority of the citizens or residents in our country probably believe that if they go to the hospital in their community in their area that they will be getting blood donated by their friends and neighbors to the local blood

center. That just isn't the way that it works anymore, and it's going to continue to evolve.

The fact is, blood moves and blood components move all over the country by air every single night, and we're getting to the point where there are going to be large regional distribution centers, and so where it's collected, it will go to a distribution center, perhaps some of the processing will be done there, and then it's going to go to area hospitals out there where it's needed and collections will be enhanced where it's less expensive to do so rather than where it's more expensive to do so.

There's going to be all kinds of changes and whatever testing system is put into place has got to be -- we have to look at how the test is going to be done, when it's going to be done, and how the results of the data are going to follow the unit of blood. So it's getting -- the logistics of that are enhancing the complications of it.

Dr. Leitman?

DR. LEITMAN: If we are going to go through all seven of those one by one, which is a reasonable approach, then we don't really have to comment on whether it's operationally feasible to every center, rural transfusion medicine centers, tertiary care centers, huge collection organizations like Red Cross. Just have to say does it do

something that we think significantly adds to safety in terms of bacterial contamination.

So what I heard this morning presented by the investigator from Hopkins was that primary culture, the typically 8 to 10 ml aerobic, at 24 hours, followed by a day 3 culture, which was in their case 5 ml in an aerobic bottle, if one chooses to do more, 8 ml or whatever one chooses as more is only going to add more, but will also cause you to lose more product, probably.

But the 5 ml in an aerobic I thought significantly enhanced the safety of that product, and was a highly efficacious intervention. I think Hopkins data -- I may be misquoting them -- is 1 to 3,000 initially positive products at their 24 hours, and then 1 in 4,600 were captured later. That is the vast majority of what you would expect to be clinically significant to cover day 3, 4, and 5. So I find that to be a very fine intervention at a reasonable cost that significantly improves the safety of platelets in terms of bacterial contamination. As to whether you can implement it, it depends on your center.

DR. STRAMER: I thought what was significant about the Hopkins data is that they showed a certain rate of septic transfusion events prior to and then zero in the subsequent 13 months. So I thought most importantly they showed clinical efficacy without doing outdate culture, at

least within their own system, using their own consistent definitions.

DR. BAKER: Something that I saw, this might be a little bit more general, but I think it was the EU had some common technical specifications that were published for HIV diagnostic tests that articulate the requirements, standards and criteria that must be met, so that concept, that general concept, I think might -- I would recommend that the FDA consider in moving forward to final guidance. I mean, there was so much talk about apples and oranges and anaerobic/aerobic and near miss was often not in some of the studies.

So the general concept of placing some common technical specifications, not to lock or limit future studies, but for them to be considered as being valuable to all future studies. I think if that was clarified, that could help future study designers and help us with the available data.

DR. ALLEN: Thank you. Other comments on this? Anybody else want to expand on Dr. Leitman's overview for the primary culture plus secondary culture day 3?

Okay, are we ready to move on to the second option, primary culture plus secondary rapid testing?

DR. DE MARIA: Al DeMaria from Massachusetts Department of Public Health. To me, from what was

presented today, it seems like either/or. You're going to do a primary culture regardless, unless you go to one of these other strategies, but for these two strategies, secondary culture and secondary rapid testing seem to be, from the data, equally effective at reducing risks. So I sort of see them as either/or.

DR. KAUFMAN: Actually, this is a question maybe for Dr. Jacobs. One of the -- first of all, I agree with what Dr. DeMaria says, and I think that there's a clear efficacy in the secondary testing approach and with the Verax test specifically. One of the challenges, though, is just the format of the test to set up for sort of one platelet at a time, whereas often at least larger centers like mine would definitely want to test a batch. So this is sort of another operational question, but is there a batch format forthcoming, or can you comment on that?

DR. JACOBS: That is a good question. Michael Jacobs, Case Western Reserve University, Cleveland. That's a very good question. When we have run the Verax test, we typically do it in batches of 6 or 12, and they have little stands that hold six units. You do 6 at a time or 12 at a time, and the timing works out very well.

DR. JONES: This comment refers to kind of the three top, the three first items. These are the besides pathogen reduction technology, anyone that does not include

anaerobic bacteria tests in this time. We in Office of Blood Safety here at CDC have talked about the imposing or requiring anaerobic testing or maybe changing these methodologies. We agree with the earlier comment that the efficacy from what the level of data, slightly smaller studies compared to national hemovigilance studies, look to be efficacious; given the rarity of the event, it's difficult to prove, but given what we have discussed so far, the anaerobic testing would be recommended.

DR. ALVING: Barbara Alving. My question would be would the rapid -- I said this earlier -- could the rapid testing be a surrogate for anaerobic culture? I know you said that you're adding one more antigen to the test, but could that take the place of an anaerobic culture? It would be interesting to compare those two.

And then my other thought would be secondary rapid testing is good only for 24 hours and you have to keep repeating it if you haven't transfused the platelets. Does that make sense? Does that give you any additional information, or could you say you have done the secondary rapid testing and that's good for the next three days? You know, what are the data that say you have to do it every 24 hours? Because that really is very difficult with trauma situations, et cetera.

DR. LEWIS: I don't know the answer to the question, but my impression was that it was in the slide that showed that this limit of detection for the rapid test was in the range of 10^4 to 10^5. So you are already in the exponential phase. So another day could be a much higher number.

DR. STRAMER: If I may -- Susan Stramer -- a negative at day 4 doesn't guarantee a negative at day 5, et cetera, based on exactly the points that we just made.

DR. EDER: Anne Eder. I am actually with the FDA, but I'm representing myself. To answer your question, in our paper that described the septic transfusion reaction from clostridia, the rapid test did not detect it. So it can't be thought of as a surrogate. They offer different advantages. But they both offer advantages, but they're not -- one doesn't serve as a surrogate for the other.

DR. ALLEN: Thank you. Again, however, my guess would be that, given the right incentives, that the rapid testing technology could be developed very quickly and I have enough faith in human innovation when properly rewarded to come up with systems, given the right incentives to do so. So we will see things in five years and ten years that don't even begin to exist today.

Do any of our speakers from this morning want to address the issue, additionally?

DR. DE MARIA: Al DeMaria from Massachusetts Department of Public Health. Could I just speak in favor of the anaerobic culture? Just from the fact that I think the strict anaerobes are very rare in causing septic reactions, so I would like to see more in terms of expanding the potential for identifying organisms. Also, I don't remember -- I may have missed it -- that there wasn't data about rapidity, time to positivity, that might be better in an anaerobic bottle than aerobic bottles.

So I think there may be advantages just -- I think already been suggested -- there might be advantages beyond picking up strict anaerobes to having anaerobic bottle. Whenever I didn't have enough blood for both bottles, I always put it in the anaerobic bottle.

DR. ALLEN: Dr. Jones?

DR. JONES: I would just like to reiterate that I think for the anaerobic question that currently there's not data that would convince me that it's a good -- that the rapid test is a good surrogate, and I think in the McDonald publication in table 4, I do -- there may be a good additional data beyond this, but find that some of that data is helpful for the discussion and seeing which -- seeing some time to detection and which organisms were detected in England and one bottle, only one bottle versus the other, anaerobic versus aerobic.

DR. SANDERS: Joe Sanders with Verax Biomedical. The test does in fact detect anaerobes. The sensitivity of the first generation test across all species wasn't identical, but our second generation test offers pretty significant enhancements that has already been developed and is now in validation. But the test detects both aerobes and anaerobe species.

DR. ALLEN: Thank you.

Okay, and again, this is discussion for the panel members.

DR. LEITMAN: Could I ask a technical question to the microbiologists here? So Clostridium perfringens, when it's in the exponential replicative phase after three or four days in a platelet component, is that picked up in an anaerobic bottle when it's replicating so rapidly, or is it really strict and will it never be picked up in an aerobic bottle, only anaerobic, if you are doing culture?

DR. HARRELL: Lizzie Harrell, Duke. It is rare for it to be picked up in an aerobic bottle, but occasionally it has happened if it's in the exponential phase, just because it grows so rapidly that it reduces the oxygen in the bottle and also will allow it to grow -- C. perfringens, even though it's an anaerobe, it is not one of the most strict anaerobes.

DR. ALLEN: So thank you. Basically, what you are saying is it's all very complicated and it depends on a whole bunch of what's getting together at the same time. Okay, thank you.

Other discussion on the primary culture and secondary rapid testing? Again, I think this is an area that will develop further, and certainly one I would not want to see eliminated at this basis even though I think it's got limitations to it.

Dr. Jones?

DR. JONES: No additional comments at this time.

DR. LEITMAN: I think my comments are exactly the same as those of the first procedure that we talked about. The data suggests that primary culture plus secondary rapid testing and then release within 24 hours of that rapid testing, using the currently licensed improved test, significantly reduces the incidence of serious -- the kind of bacterial contamination that will lead to a serious clinical reaction. It makes the product significantly safer in terms of bacterial contamination.

DR. ALLEN: I would agree with you. I was more skeptical when I started preparing for this session, and was very intrigued with the data that are available. Suggesting that.

DR. SCHREIBER: I think the obvious -- Marty Schreiber, OHSU. I think the obvious limitation is that you have to know when the transfusion is going to be, right? So you're going to have to test it every time if you go beyond 24 hours, and certainly in my environment, I don't know when I'm going to give a platelet transfusion.

DR. LEITMAN: Leitman, NIH. That is a very significant operational question, and for large transfusion centers, they'll figure that out, and for moderate transfusion centers they'll figure it out, too.

The ones that use platelets, need them in emergency, use them less often, the smaller centers, the rural centers, the in theater centers, maybe perhaps that won't work for them. But it is acceptable to significantly decrease the likelihood of bacterial contamination, which is I think what the advice and the discussion we're offering to FDA.

DR. ALLEN: Any other comments on the primary culture secondary rapid testing?

We will move on to the third one then under 5-day storage, minimal proportional sampling volume, which is based as you heard in the discussion on a larger proportion of the base, but the volume depending on the amount of the unit that is being tested.

Any comments or discussion on this approach or comments?

DR. LEWIS: As I said in my general comments, I see this approach as giving a sort of linear several-fold advantage, and the question is whether that is the kind of reduction that gets us where we think we need to be, and to me it's a less promising strategy than any of the prior two that we have discussed.

DR. ALVING: I think, again, we have to look at this maybe in the context -- I mean, now we have switched over to an actual blood donor system, that's sending its platelets out, again, to Fargo. That's one of my favorite towns. And maybe also to Oregon, where you're going to need to give it to your trauma patients. So here they have done something that they have taken the responsibility at the blood center, and they said this is how we are going to mitigate this issue.

So if you look at it as a primary, then presumably the recipient hospitals wouldn't do anything further, but they must have very good informatic systems so that if they get a notice from Arizona, that look, this has turned positive, do not transfuse it. Then they can do that.

DR. CALIENDO: Angie Caliendo. Several of the people who spoke today asked for flexibility in how we

would -- how this could be implemented. If this isn't the most effective way, it does give sites some flexibility, because then they don't have to do anything onsite. It's all done at the central site, and then they can just use the product.

DR. ALLEN: I think there's certainly an argument if the level of contamination is extremely low to begin with, that certainly gives you a much better opportunity to capture the organism, and again, often I think this was the larger volume was then split into multiple bottles, one of which -- one or more of which -- might be anaerobic. So it clearly offers some flexibility and options that aren't available when you're doing what truly is a minimum sample collection from the unit.

DR. LEITMAN: So I think this is one of the most operationally attractive methods, because the blood center, the collection center, does everything, releases a component with a 5-day shelf life that the transfusing service doesn't have to do anything else to, and in the hands of the collection facility, their number of true positives doubled during that time, but this was not a randomized concurrent study. It was one period followed by another period, and we all know that things change. Anything could have changed.

So their collection instrument did not change, but we know that things change over different time periods. That bothered me, that it wasn't concurrent, that it was two different periods. So that study compared within institution, two periods, with a different technique, but as has been critiqued by another presenter this morning, the residual contamination was still quite high. That bothers me.

So I find this to be perhaps -- it's hard to compare apples to oranges. There was no outdate sampling at point of large volume outdate sampling here to know for sure what the residual risk was. So find this likely to decrease the level of bacterial contamination, but I'm not as excited about it.

DR. KAUFMAN: I think I would echo those comments. I would allow that if you sample more volume, you're likely to increase your sensitivity to detect bacteria some, but unlike the first two strategies that we have talked about, this is one that just will miss the delayed exponential growth of bacteria, which is really the problem.

DR. LEWIS: Roger Lewis. I would like to ask a question about the kinds of advice the committee can or can't give. So if we were in a situation where one strategy that would work better in a more dense urban area, different types of hospital sizes, volume, and those sorts

of things, but was infeasible or not cost-effective or had negative consequences like an adverse effect on the adequacy of the product supply in a more rural area, what are the rules, if you will, about having two different frankly standards of safety based on location?

DR. ALLEN: Basically our guidance for today is that we do not -- the committee does not need to recommend a specific strategy but to discuss pros and cons of the options up there. What that suggests to me is that perhaps the FDA will come out with a guidance that offers options. I think our job is -- in other words, if you feel that there are operational issues that mitigate against certain options up there, be free to say that. On the other hand, if there are circumstances that make that a reasonable or a better choice, feel free to say that.

DR. LEWIS: My impression both from the data shown and some of the comments that have been made by the committee is that there's a direct tradeoff between the degree of safety with respect to bacterial contamination that can be achieved and the logistical difficulties, both in terms of the complexity at the transfusion service, the transportation issues, the shelf life and therefore on the blood supply, or the component supply, and obviously the lack of components can also cause harm to patients. So these are competing risks, and so what I'm hearing is that

the committee might support some strategies in a setting in which those logistical constraints are less impactful and allow for other strategies to be admissible or acceptable in settings in which those logistical or distribution issues become paramount.

DR. ALLEN: Absolutely. I think that is a very fair statement and certainly Dr. Schreiber has spoken passionately about the need in rural settings where trauma rather than treatment of patients with specialized treatment of patients with cancers, you know, is the real need. The product that is needed may be very different, and the speed with which, the rapidity with which it's needed, and the volume with which it's needed may be quite different.

So I think the committee should feel quite free to comment on all of those areas.

DR. LEITMAN: So I'm still, getting back to it, troubled by the residual contamination rate at the time of a secondary experimental culture with the large proportional volume tests. So for institutions, I would like to recommend that for institutions choosing to use their proportional volume, aerobic culture, 24 to 36 hours, they have an ongoing -- not hemovigilance, because that's too broad a term, but an ongoing outdate culture system of

a reasonable proportion of their units to keep track of what's being missed.

DR. ALLEN: Certainly that's why this strategy is still -- or this option -- is still within the 5-day storage, rather than the 7-day storage. Certainly it is an area where perhaps further research is very important. I would be fascinated to see what organisms are showing up at the time of outdate and then look at the profile of those organisms over time, because we might find that -- well, it's an area where there's I think some opportunities for research to help clarify what's going on.

Dr. Stramer?

DR. STRAMER: Yes, thank you. Sue Stramer. There may be other flavors of this type of blood center providing a ready-to-use platelet, whether it's within five days or seven days, in the absence of secondary culture or rapid testing that we haven't explored yet. I mean, this is only one example. So it's one example that used the 3.8 percent volume in an aerobic bottle only. So there may be equal or better permutations of what a blood center can and should do.

DR. ALLEN: Any further discussion on this option? Let's move on then to the 5-day storage, pathogen reduction technology.

Dr. Jones, do you want to speak before we move onto the next?

DR. JONES: Sorry, yes. Before we move on, I had a question about kind of comparing the operation-ability of what blood centers might -- blood collection facilities for minimal proportion sample volume versus large volume delayed sampling, talk about flexibility is important, given those options, but given that going to a 7-day storage decreases outdating and perhaps we could talk about it when we get to that, but get to large volume delayed sampling, that the data appears to be more plentiful and robust with the large volume delayed sampling, are there blood collection facilities that would still prefer operationally minimal proportion sample volume over large volume delayed sampling?

DR. ALLEN: I think you have raised an interesting question.

Dr. Stramer, do you want to address that?

DR. STRAMER: Well, I think the answer is completely dependent on dating. You delay culture, it's not really feasible with five days. It all really depends on how creative you want to be, because we talked about the way primary culture is done now. There's 24-hour platelet hold, and then 12 hours post-inoculation, which coincidentally adds up to 36 hours.

So if one negated the hold after inoculation of platelets, I mean, I'm just talking about other options, one could have a 36-hour hold, but the vast majority of blood centers prefer to control platelets, see what grows out in culture before distribution, to provide the nightmare of having to recall platelets from hospitals or hospital inventory, and hope that it wasn't transfused yet.

So I think the answer to Jefferson's question really depends on dating. This is what the AABB statement said. In order to include all three options for enhancement of culture, doubling volume, anaerobic culture, and delayed volume, you really need to go to a 7-day dating.

DR. ALLEN: Dr. Jones, do you have another question?

DR. JONES: I just wanted to add that bringing up the point that some of these require something to be done by the hospitals in terms of secondary testing and making sure that we do have including minimal proportion sample volume pathogen reduction technology and large volume delayed sampling options that allow for the rural and small hospitals to not require a burden on their part, and including the recommendations considering those hospitals, as well. So included in this comparison I just mentioned, taking that into account as well.

Thank you.

DR. ALLEN: Thank you. All right, we are ready to move on to pathogen reduction technology.

DR. LEITMAN: It certainly seems extremely safe in terms of maximum insurance of not having any pathogens, bacterial, viral, parasite, things you don't even think about right now may come up in the future. So in terms of safety, it's the most attractive method. But it's not ready for primetime at many centers for all the reasons that were discussed. It adds significantly to the cost and to the labor involved in preparing the components. There's a lot of labor involved in pathogen reduction.

So I don't know how many FTE have to be added, but certainly some. So again, another advantage is that it's done at the collection center and large collection centers can of course absorb increases in FTE more than smaller transfusion services. Certainly there's no objection to implementing pathogen reduction technology in terms of safety. It's an operation -- it's a cost and operational consideration, I would think, for the facility.

DR. ALLEN: The cost issue is obviously -- it's a strange one in our country, because we talk so much about how healthcare is too expensive and we can't afford -- people can't afford the insurance premiums and so on. So it really is an insurer decision in a way, whether they're

going to cover it, and I think we need some big -- some open public discussion about what do we do? What are the choices? How do we get there?

I was impressed with what I read and heard in preparation for this and in the meeting today. I think it's an exciting technology to move forward, but there seem to be some drawbacks, and those probably need to be addressed openly.

DR. SCHREIBER: When the conversation moved on to other pathogens beyond just the bacterial pathogens, the discussion about malaria and all these other diseases, that -- if we recommended on that basis, then we would have to recommend it for all blood products, because those issues of malaria are going to be potentially problematic in red cells and plasma and that's an argument to do it to every single component.

DR. LEITMAN: There is no technical ability to do that for red cells right now. So you can't require it. But that's the -- the problem with this is you're doing it to one component and not to the others. So if you are only collecting a platelet apheresis component from a donor on that collection procedure, it makes sense. But if you are also collecting red cells in one of these instruments that collects red cells, you can program it to do platelets,

plasma, or red cells. You're really not protecting the red cells.

If you could not do testing, transfusion-transmitted testing for the seven or eight other organisms that you test for, there would certainly be a monetary savings for platelet apheresis components if you could collect by pathogen-reduction technology and then not do all that safety testing.

DR. ESCOBAR: Miguel Escobar, from University of Texas. So I do agree with this technology. I think the data that they show from Europe is very robust. I think from even 205 coming data. I don't think we should really put it on the side. I think it should still be an option here in the United States. I understand the cost, but again, what is the benefit of having something like that? I think it might be the future, and I think it should be part of the options to be put here as a strategy to prevent any morbidity and mortality for the transfusion of platelets.

DR. ALLEN: Thank you. Any other comments on that point?

Dr. Jones?

DR. JONES: Just a quick comment that we support it being an option, one of the included options, based on the data available.

DR. ALLEN: Thank you.

Dr. Stramer?

DR. STRAMER: I think as discussed earlier, there are many things that need to happen to make pathogen inactivation more accessible. So those have already been stated, but I think it's worth just mentioning it again.

DR. ALLEN: Other comments or discussion on pathogen reduction?

We'll move on to 7-day storage options. First is primary culture plus secondary culture on day 4.

Dr. Leitman?

DR. LEITMAN: It does not address that particular method, but I'd like to say that the survival studies, the autologous indium or other radiolabeled in-vivo survival studies of 7-day stored platelets showed this significant drop-off in recovery and survival compared to 5-day and 5-day compared to 3-day. So you're not transfusing a product that's hemostatically as efficacious as a 5-day stored product.

But it does have some hemostatic efficacy. So I don't think that the committee should accept that a 7-day stored platelet is terrific, because it's not. It's not as good as 5, which is not as good as 3, which is not as good as 2, which can't be transfused anyway, because you have to store it for so long. But we have lost hemostatic efficacy

in the last 20 years of making platelet transfusions safer, and 7 days is another hit.

So that doesn't answer the question of -- this is the Irish blood transfusion data that primary culture plus secondary culture on day 4. So this is a blood center in that case testing their residual inventory and their data was very convincing that that method significantly reduces the likelihood of distributing a bacterially-contaminated product.

So I think that that is an excellent option for a blood center to perform. I think it would be -- the transfusion service could do it as well. There's no data on the transfusion service doing it, but they can establish a secondary culture system as well, and then take it out to day 7. I would again urge, as I did for the prior methods, that there be a method for outdate culture, to continue to look at the efficacy of that method.

DR. ALLEN: I think that's a very important statement. Your earlier statements in terms of always we need to look at how do we have the most effective platelet transfusions possible? Safety is one part of that. Freshness is one part of that. So all of these need to be considered, and again, as I said earlier today, if I were a patient who needed a platelet transfusion, I would want the freshest ones available, for a variety of reasons.

DR. KAUFMAN: Actually, I think it might in some ways depend a lot on the clinical context. So most of the platelets that we give are for prophylaxis for patients with having stem cell transplants or chemotherapy, and we know for example if you give half a dose, that you get actually the same rate of grade 2 or higher bleeding as if you gave a whole dose or even a double dose, and we've seen from some of the data from pathogen reduction studies that essentially, even though we know that the CCI is lower and there seems to be some damage to platelets in going through pathogen reduction, the clinical outcomes in that population are more or less the same as if you gave a conventional component.

What there's less data on and where there really may be a difference is in other situations more like treating trauma patients or patients who are really acutely bleeding, and there we are just starting to see some data, but maybe chilled platelets work better than anything that's kept at room temp and so on. But for the majority of the platelets, going to the patients where they are just getting a transfusion to a nonbleeding patient based on the morning count, I guess I don't worry so much about the platelet quality as I do for the acute bleeders.

DR. CALIENDO: Angie Caliendo, Brown. I would say that if the center is going to think about doing either the

primary culture and secondary culture or secondary rapid testing, they should really think long and hard about why they would do that for only five days when they could do it for seven days, and I think the point made about the discussion about the quality of the platelet is one, but the point made earlier, that's one of the values of all this secondary testing is that it gives you a longer shelf life. So I think that's an important consideration is if you're going to do this and you're going to go through all this work and all this expense, can you get the best bang for your buck out of it by doing it for -- allowing the storage to go for seven days.

DR. ALLEN: Dr. Jones?

DR. JONES: I just wanted to add support to previous comments that using the data presented today, including this as one of the options, we support that.

DR. ALLEN: Could you repeat that, the last portion of your statement?

DR. JONES: With the current data that's been presented today, we support this strategy as one of the options.

DR. ALLEN: Thank you.

DR. LEITMAN: I might just point out the Irish blood transfusion service did aerobic and anaerobic bottles, both at primary and secondary. So if we think

that this is acceptable and considerably increases safety, it does so in the context in which the Irish blood transfusion service did it.

DR. ALLEN: Thank you.

Other discussion on the primary and secondary culture 7-day?

All right, primary culture plus secondary rapid testing, for 7-day. Comments? Much of what we already said, it's an alternative option, it will probably become better over time. Certainly something that is a viable consideration, should not be excluded at this point. Other comments? Okay.

And the last option there is large volume delayed sampling, and again, this is -- they were taking what, 7 to 8 percent I think, of the total volume for testing at a somewhat later period of time, single test, and again, doing -- if I remember correctly -- both aerobic and anaerobic culture.

Yes, Dr. Lewis?

DR. LEWIS: This again just strikes me as something in which it is subject to false negatives due to the lag phase and that the lag phase is more of an issue with a longer period of storage. So whereas I think it's possible -- it has been demonstrated that this decreases the risk of contamination at the time of transfusion, I

think it's unlikely that this strategy can achieve the same level of safety of some of the other strategies considered.

DR. ALLEN: Other comments or questions?

DR. HARRELL: Lizzie Harrell, Duke. I didn't quite understand your comment; are you saying that if you stored the sample, the platelets, for a longer period of time, that they are not going -- I was thinking at the organisms in the sample actually may proliferate over time at room temperature over three or four days. I missed the point. I was trying to make sure I understood you.

DR. LEWIS: Roger Lewis. My point is that the variability in the lag phase means that at the time the large volume delayed sampling is done, I believe there may be clinically important pathogens that have not started to replicate to a level that they'll be detected. So whereas it's clear that you do increase your sensitivity with a large volume delayed sampling, I think it's going to be a relatively incremental improvement in safety and not get us the same degree of additional safety that is at least potentially achievable with secondary testing approaches on the unit.

DR. ALVING: But on the other hand, they then release it six hours -- they culture it 36 to 48 hours, then release it at six hours after the culture, and then continue to culture throughout seven days, with

notification to the hospitals if anything becomes positive. So I guess that's what they're attempting to do. Or that's what they are doing.

DR. LEWIS: Then I'm -- this is Roger Lewis. I think I need to be corrected. My understanding of this strategy was a larger volume at 36 hours and that was the only test, and if that was the strategy, then I stand by my comment, and if that was not the strategy and it includes additional cultures, then I misspoke, misunderstood and misspoke.

DR. ALVING: This is Barbara Alving. More continued culture, not new cultures, but the continued culture and surveillance.

Also, like to say that in the last, the closing slide of the presentation from the Irish blood center, is that they are considering a one-test 7-day strategy because they feel that evidence suggests it's also safe, and there would be time and cost saving advantages. So they are looking at this for, you know, as well.

DR. FIELD: Dr. Field, Irish Blood Transfusion Service. Consideration, we're always reviewing what we do and always critical of what we're doing and review doesn't mean to say we'll change.

DR. ALLEN: Thank you for the clarification.

DR. Jones?

DR. JONES: Jefferson Jones, CDC. I agree with the theoretical comment that this is -- and it's not just 36 hours. It's 36 to 48 hours, and we didn't discuss the Hema-Quebec data necessarily as well, but it's in our packets, that we don't have the data to really know how much delay you need to catch the lag phase and the data coming from NHSBT is some of the largest data that we have, and given the rarity of the event, having as much as data as has been accumulated in the UK, I think this strategy is more convincing.

DR. ALLEN: Thank you.

Dr. Stramer?

DR. STRAMER: I was just going to add as the industry rep that industry does support all three of the 7-day storage options.

DR. ALLEN: Thank you.

Any other comments or questions from the committee? Dr. Leitman?

DR. LEITMAN: I have a question. So when a secondary culture is done in the two studies that are up there, one was day 3 for 5-day shelf life, one was day 4 for 7-day shelf life. For the secondary rapid testing, the recommendation is within 24 hours of transfusion. Is that starting on day 3 for both 5- and 7-day so one would test day 3, day 4, day 5, day 6, and potentially day 7? Any of

those days, if one were planning on releasing, or is there a hold until day 4 because that's similar to primary culture plus secondary culture on day 4? When does the rapid testing start? Either day 3, 4? Definitely day 3? Doing -- can we advise based on the data we've seen?

DR. ALLEN: I don't have the answer. Dr. Jacobs, you want to --

DR. JACOBS: Michael Jacobs, Case Western Reserve University. At the 2012 ADCOM, the committee voted to do secondary testing on day 4 and day 5. They were not considering 7-day. They specifically voted not to do secondary testing on day 3.

DR. CALIENDO: Angie Caliendo. So what about day 6 and 7? So you start on day 4, but if you want to use it on day 7, do you keep testing every day?

DR. JACOBS: Again, that was not considered by the committee, but the point to me is if you have 50 platelets in inventory and you typically use 25 a day, you'll test 20 of them. When those 20 are used, you'll test another 20. So it's not a question of testing all your platelets in inventory. Conversely, if you go through them very fast, you can test them as you use them.

DR. CALIENDO: Right, but I am concerned with something Dr. Stramer said, which is it's clear there's more growth at day 7 than at day 5. So if you were going

to do that, you would be in the position of potentially having to test every day after day 4, depending on how you manage your inventory. Is that right?

DR. JACOBS: The way the test is currently approved, that is the case, but with each day, the number of organisms is going to increase. That's certainly possible if there's data to support this, which there isn't at this stage. That you could test on day 5 and that platelet would be good until day 7. But at this stage, the requirement is every 24 hours.

DR. ALLEN: We are going to let the committee wrap this discussion up, thank you.

Any other comments or questions? Dr. Leitman.

DR. LEITMAN: So this is an answer to this question. Operationally, if you have a certain number of day 7 units in inventory, just because you want to be cost effective, you'll test those first and try to release them that day. Then you'll go to day 6 stored. So first in, it's FIFO, first in, first out. So you want to be smart in terms of managing your inventory and operations. So on day 4, you would never test everything in inventory for that day.

DR. ALLEN: Dr. Verdun? Any questions or anything additional that you would like the committee to address?

No? Okay.

Dr. Jones, any final comment?

DR. JONES: No, thank you.

DR. ALLEN: All right, thank you for participating. Any other comments from committee members?

Well, thank you all for your attendance, for your diligent work. I think this has been both an enlightening and fun session. I hope it's been useful to the FDA as they move forward on their guidance. I think certainly they heard that everyone who spoke was in favor of getting the guidance completed as expeditiously as possible.

So again, thank you all for your work on this.

Mr. Emery, any final?

MR. EMERY: This is Bryan. I just wanted to thank the committee and the speakers for their great information that has been gathered into the FDA, and I appreciate everyone coming. If there's anybody that needs help with travel, Joanne outside will help you with the travel. Anybody that needs help with the transportation to and from the hotel, also Joanne has that information outside.

I hope to see everybody in the morning. We'll be starting at 8 o'clock for July 19. Thank you.

DR. ALLEN: I now pronounce the July 19, 2018 Blood Products Advisory Committee adjourned for the day. Thank you.

(Whereupon, the meeting was adjourned at 4:30 p.m.)