UNITED STATES FOOD AND DRUG ADMINISTRATION

BLOOD PRODUCTS ADVISORY COMMITTEE MEETING

Tuesday, December 3, 2014

FDA White Oak Campus

Great Room (Rooms B&C), Building 31

10903 New Hampshire Avenue

Silver Spring, Maryland, 20993

The meeting was convened at 8:30 a.m.,

JAY BROOKS JACKSON, M.D., MBA, Chairman, presiding.

MEMBERS PRESENT:

JAY BROOKS JACKSON, M.D., MBA, CHAIRMAN, PRESIDING

SRIDHAR V. BASAVARAJU, M.D., FACEP

FRANCISCO A. BONILLA, M.D., Ph.D.

VALERIE DURKALSKI-MAULDIN, Ph.D., MPH

JOHN B. HOLCOMB, M.D., FACS

SUSAN F. LEITMAN, M.D.

NORMA B. LERNER, M.D., MPH

MARGARET V. RAGNI, M.D., MPH

PETER RHEE, M.D. MPH, FACS, FCCM

SONJA SANDBERG, S.B. Ph.D.

KATHERINE I. SCHEXNEIDER, M.D., CDR MC, USN

CHRISTOPHER P. STOWELL, M.D., Ph.D.

INDUSTRY REPRESENTATIVE:

TOBY L. SIMON, M.D.

CONSUMER REPRESENTATIVE:

COREY S. DUBIN

TEMPORARY VOTING MEMBERS:

JAMES ALLEN, M.D., MPH

LORI KNOWLES, LLB, BCL, MA, LLM

JOHN KNIGHT, Ph.D.

KENRAD NELSON, M.D.

MATTHEW KUEHNERT, M.D., FACP

MARK SKINNER

MONIQUE TURNER, Ph.D., M.A.

WILLIAM WARD, Ph.D., D(ABHI)

INVITED SPEAKERS:

MARJORIE SHULMAN, ODE, CDRH, FDA

DARCEL BIGELOW, MGA, MT, OBRR, FDA

MARIA RIOS, Ph.D., OBRR, FDA

MARK WALDERHAUGH, Ph.D., OBE, FDA

ALSO PRESENT:

BRYAN EMERY, R.N., LCDR, USPHS

Designated Federal Official

PROCEEDINGS

(8:30 a.m.)

CALL TO ORDER AND OPENING REMARKS

INTRODUCTION OF COMMITTEE

CHAIRMAN JACKSON: This is the second day of our 111th meeting of the Blood Products Advisory Committee. I'm Brooks Jackson. I'm the chair of the committee. We have a couple new members sitting in today for the topics today, so maybe we should go around the room once again and introduce ourselves. Mr. Emery, do you want to start?

MR. EMERY: My name is Bryan Emery. I'm the designated federal official for this meeting, and I welcome everybody in the audience, and I welcome the members in the FDA and the audiovisual.

DR. BONILLA: Francisco Bonilla, clinical allergist/immunologist at Boston Children's Hospital.

DR. LERNER: Norma Lerner, pediatric hematologist at HLBI.

DR. RHEE: Peter Rhee, University of Arizona, Department of Surgery.

DR. SIMON: Toby Simon, senior medical director at CSL Behring with a background in transfusion medicine hematology.

DR. SHEXNEIDER: Katherine Shexneider, Walter Reed Bethesda, transfusion medicine specialist.

MALE SPEAKER: [unintelligible]

DR. SANDBERG: Sonja Sandberg, professor of mathematics at Framingham State University.

DR. WARD: Bill Ward, deputy chief of the Department of Transfusion Medicine at the NIH Clinical Center

DR. STOWELL: Chris Stowell, director of the blood transfusion service at Massachusetts General Hospital.

DR. LEITMAN: Susan Leitman, director of the Medical Research Scholars Program at the NIH Clinical Center and formerly blood services chief in the Department of Transfusion Medicine at NIH.

DR. DURKALSKI-MAULDIN: Valerie Durkalski, professor of biostatistics at the Medical University of South Carolina.

DR. BASAVARAJU: Sridhar Basavaraju, medical officer with the CDC Office of Blood, Organ, and Other Tissue Safety.

CHAIRMAN JACKSON: Brooks Jackson, transfusion medicine physician and dean of the School of Medicine and the vice president for Health Sciences. Okay. Today, we have a very stimulating topic on classification of blood establishment computer software, known as BECS, accessories. But first, Mr. Emery will read the conflict of interest statement before we get started.

CONFLICT OF INTEREST STATEMENT

MR. EMERY: I'd like to remind the audience members to turn off your cellphones or put them on silence, and I'll read the COI statement. This announcement is in addition tot he conflict of interest statement read at the beginning of the meeting on December 2nd, 2014, and will be part of the public record for the Blood Products Advisory Committee meeting on December 3rd, 2014. The committee will discuss classification of blood establishment computer software, BECS, and accessories to BECS. This is a particular matter involving specific parties. The committee will also hear updates on (1) the emergence of chikungunya virus infections in the western hemisphere and potential implications for blood transfusion safety and (2) the first survey of the Rapid Donor Surveillance Project on Middle Eastern Respiratory Syndrome. These updates are non-particular matters based on the agenda and all financial interests reported by members and consultants. No conflict of interest waivers were issued under 18 U.S.C. 208. Dr. Toby Simon will serve as the industry representative. Dr. Simon is employed by CSL Behring in King of Prussia, Pennsylvania.

Industry representatives act on behalf of all related industry. Industry representatives are not special government employees, and do not vote. There may be regulated industry speakers and other outside organization speakers making presentations. These

speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflict of interest. This conflict of interest statement will be available for review at the registration table. We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not already on the agenda 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. FDA encourages all other participants to advise the committee of any financial relationships that you may have any firms; its products; and, if known, its direct competitors. Thank you.

TOPIC II: CLASSIFICATION OF BLOOD ESTABLISHMENT COMPUTER SOFTWARE (BECS) AND BECS ACCESSORIES

CLASSIFICATION OF MEDICAL DEVICES

CHAIRMAN JACKSON: Thank you. So our first speaker this morning will be Marjorie Shulman, who will be giving a presentation on the classification of medical devices regarding blood establishment computer software.

MS. SHULMAN: Good morning. Thank you. My name is Marjorie Shulman. I'm director of the Premarket Notification Program for the Center for Devices and Radiological Health, so I'm honored to be here with [unintelligible]. So what is the purpose of the panel meeting today? It's to provide input to the FDA on the appropriate regulatory classification -- so either Class I, two, or three -- for an unclassified pre-amendment device. So what is a pre-amendment device? It's a device that was introduced into commercial distribution prior to May 28th, 1976, the enactment date of the Medical Device Amendments. So how are the pre-amendment devices classified? We would -- the FDA would receive a recommendation from a device classification panel; we would publish the panel's recommendation for comment, along with a proposed rule classifying the device; and then we would issue a final rule classifying the device final after we review the

comments. It's not advancing. We're just building up the excitement here.

[laughter]

MS. SHULMAN: Oh, okay. Thanks [laughs]. So what are the device classes? So they're classified based on the controls necessary to mitigate the risks. So Class I are general controls, Class II are general and special controls, and Class III are premarket approval, and the overall goal is the device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness. So what are general controls? They include such things as prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing of the devices that are made there, recordkeeping, et cetera.

So special controls include such things as performance standards, post-market surveillance, patient registry, development, and dissemination of guidelines, et cetera. There's also -- Class I devices is for devices which general controls are sufficient to provide reasonable assurance of the safety and effectiveness, and Class I devices typically do not require premarket review prior to being marketed. What are Class I devices continued? So there's a little-known part of the regulations devices that cannot be classified into Class III

because they're not life-supporting, life-sustaining, or of substantial importance in preventing impairment of public health, and because they do not present a potential unreasonable risk of illness or injury, and they can't be classified into Class II because insufficient information exists to establish special controls to provide reasonable assurance of the safety and effectiveness.

So, what are some examples of Class I devices? General cardiovascular surgical instruments -- and remember, I'm from CDRH. That's why I'm giving you all device examples [laughs] -- adhesive bandages, manual stethoscopes, crutches. So Class II devices are for devices that can't be classified into Class I, because the general controls are insufficient by themselves to provide reasonable assurance of the safety and effectiveness, and there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification, also known as 510(k), prior to being marketed. Some examples of Class II devices include blood pressure cuffs, percutaneous catheters, electronic stethoscopes, vascular graph prosthesis, ECG, hemodialysis system, and syringes.

So how are special controls used? So, for an example, PTCA catheters were reclassified from Class III to Class II, putting them in special controls. FDA issued a special controls guidance

document to mitigate the risk to health, and it include such that would be required in the application, such as biocompatibility testing, bench testing, animal testing, sterility in shelf life, and labeling, warnings, precautions, adverse events, et cetera. These special controls in combination with the general controls provided reasonable assurance of the safety and effectiveness. So the companies had to provide evidence in their 510(k) submission on how the special controls were addressed.

Class III is for devices that cannot be classified into Class II, because insufficient information exists to determine that the general and special controls are sufficient to provide reasonable assurance of safety and effectiveness, and these devices are life-sustaining and/or life-supporting or of a substantial importance in preventing impairment of human health or present a potential unreasonable risk of illness or injury. Class III devices typically require premarket approval, also known as PMA, prior to being marketed.

Some examples of Class III devices are endovascular graphs, coronary and peripheral stents, percutaneous heart valves, LVADs, cardiac occluders, and implantable pacemakers. So here's just a chart for you to show that if you -- if general controls are sufficient in the green one up at the top that -- and they answer that as yes, it can go to Class I. If the answer to

that's that general controls are not sufficient, you go to the blue box next, and then -- sorry -- and then sufficient information exists for the special controls, and you can go into Class II. If the answer to that is no, then you can go into Class III for the device to classify it. Okay.

So what do we need today from the panel? We need input on the classification of the devices that are the subject of the panel session today, and the input should include the identification of the risk to health, if any, presented by the device, whether the device is life supporting, life sustaining, or of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury, whether sufficient information exists to develop special controls, the identification of those special controls. After the panel meeting, FDA will consider the available evidence, including the input of the panel. We will issue a proposed rule proposing the classification of the device and seeking public comment, and then issue a final rule identifying the appropriate class as either Class I, two, or three. If it's a Class I device, existing devices may remain on the market. If Class II, existing devices will be subject to any identified special controls and may continue to market. If Class III, existing devices will remain on the market, but must submit a premarket approval application by a specified time frame to continue

marketing. If the PMA, then, is not approved, devices will be consider misbranded, and must be removed from distribution. Thank you.

CHAIRMAN JACKSON: Thank you very much, Ms. Shulman. I think we're going to take questions after the next speaker, so if you'll be available then, that would be good. Okay, so as you all know, any device worth its salt must have accessories, and we're going to have Darcel Bigelow tell us about those accessories for blood establishment computer software.

MR. BIGELOW: Okay. Good morning. My name is Darcel Bigelow, and I'm the software team lead in the Devices Review Branch in the division of blood components and devices in the Office of Blood Research and Review at CBER. Okay. As you've already been told, the meeting today is for the classification panel to discuss and recommend the most appropriate classification for blood establishment computer software, which I'll refer to as BECS, and BECS accessories as Class I, two, or three devices based on the level of control necessary to provide a reasonable assurance of safety and effectiveness. And Ms. Shulman just explained to us in detail the classes. Basically, Class I devices pose the least risk to the patient and the user, Class II poses a moderate risk, and Class III poses the highest risk.

In order for the classification panel to discuss and recommend classification, I'm going to provide a description of BECS and BECS accessories, and explain how they're currently being regulated. Then I'll go over an overview of the regulatory history which spans over 20 years, the data on safety and effectiveness as reported in the literature, our evaluation of the medical device reports and device recalls, I'll experience through the 510(k) review, and the risk to health identified for BECS and BECS accessories, and how these risks can be mitigated.

And lastly, I'll present FDA's classification proposal for consideration to the panel.

BECS and BECS accessories are devices used in the manufacture of blood and blood components to assist in the prevention of disease in humans by four means, the first one being identifying unsuitable donors. BECS contains the data and logic to evaluate and track donor suitability based on information like test results, deferral information, responses to the donor health history questionnaire, and donation history. The second means is preventing the release of unsuitable blood and blood components for transfusion or for further manufacturing into products for human treatment or diagnosis. BECS performs blood release decisions, for example, based on test results. The third means is performing compatibility testing between the donor unit and recipient. And this is a computer-assisted analysis of the donor unit and the recipient test data through electronic cross match. The last means is performing the positive identification of the patient and the blood component. BECS contains the data and logic used to determine that there is a correct match between the patient and the blood component. In essence, BECS contains the logic to make decisions in the donor and transfusion management systems.

Now, a BECS accessory integrates with the BECS as part of a system and expands or modifies the function of the BECS and/or

the indications for use of the BECS device. These devices are intended for use with or capable of functioning with BECS as part of a system for the purpose of augmenting or supplementing the BECS performance. An example of a BECS accessory is the software that integrates with the BECS and sends test requests to an instrument, as well as sending test results back to the BECS. This software can analyze data and provide alerts if there are any problems with the data, for example, transmission errors or duplicate records. Another example is the use of biometric technology. The software used for fingerprint identification is integrated with BECS as a system to analyze the fingerprint and related it to a specific donor in the BECS.

Now that you have a description of BECS and BECS accessories, let's move on to how they're currently being regulated. BECS and BECS accessories have never been formally classified, and are regulated as unclassified devices. They are reviewed and cleared by FDA through the premarket notification process under the federal Food, Drug, and Cosmetic Act. This process primarily consists of determining substantial equivalence to another legally marketed device. We are here today because FDA law requires we classify medical devices -- [coughs] excuse me.

Now, to provide an overview of the regulatory history, we have to go back to the 1980s, when software began to play a more

important role in treating patients and preventing disease. In the late 1980s, the agency provided guidance to the blood establishments through two memoranda. This guidance provided information on validation, documentation, and confidentiality of computer systems. At this time, FDA focused regulation of BECS on the user end and not on the software development stage. A few months after the memoranda, the agency issued draft policy for the regulation of all computer products. This policy specifically called out for manufacturers of computer hardware and software devices intended for use in the blood bank that they would be required to register their facilities, list their devices, submit a premarket notification 510(k), report adverse events, and follow the current good manufacturing practice requirements.

Then, in the 1990s, FDA observed that unsuitable blood components had been released and distributed as a result of improper software design. These observations resulted in warning letter and recalls of the unsuitable blood components, and the defective software. This led to the awareness that additional regulation was needed at the software development stage. Therefore, FDA called for 510(k)s for these devices. Then, in 1996, FDA 510(k) cleared its first BECS. In 1998, FDA sought a classification recommendation for BECS. The panel at that time recommended the classification of Class II, but it was never

finalized.

In 2002 and 2005, FDA-issued guidances on software validation and the content for premarket submissions for all medical device software. Since the issuance of these guidances, FDA has conducted workshops and meetings with the blood industry and BECS manufacturers on the regulations of BECS and BECS accessories. Since 1996, FDA has cleared 204 BECS and BECS accessories under the 510(k) program. Over the years, there have been a number of technological advances: the use of biometric donor identification, which is the use of the fingerprint to identify the donor. Then we have the computer-aided self-interview, donor health history questionnaire, allowing the donor the privacy to answer questions by themselves and at a location they choose. We have the computer-assisted analysis of the donor unit and recipient sample test data through electronic cross-match, and we have software-controlled remote release of blood and blood components. And then we have the computer-based remote or bedside positive patient and component identification. These technological advances have improved the safety of the blood supply and compatibility between the donor unit and recipient.

Over the past two decades, the indications for use for these devices have varied in their content and complexity, but essentially, the indications for use has been to aid in the

prevention of disease by either identifying unsuitable donors of blood components or in preventing the release of unsuitable blood or blood components for transfusion or for further manufacturing. FDA conducted a literature review of the safety and effectiveness of BECS and BECS accessories; however, there was no single publication that comprehensively addressed the safety and effectiveness of BECS and all of its functions. A number of articles did assess the safety and effectiveness of key functions of BECS transfusion and donor management systems. We found literature on transfusion management systems that positively identify the patient and blood component prior to transfusion, electronic cross-match, and automated release of blood components. The donor management literature evaluated the effectiveness of the donor health history questionnaire administered by blood center personnel using paper and computer assisted.

Now, before automation, our transfusion and donor processes were conducted manually using a charter card and humans verifying everything. It is recognized in the literature that human error is the most frequent cause of errors in the transfusion process, and that automating the critical processes is an effective means to decrease the human error rate. It was reported in one study that between 1990 and 1999, an estimated one in 12,000 blood transfusions were given to the wrong

patient. Several studies concluded that automation throughout the transfusion system may lessen adverse events attributed to human error. The use of automation in transfusion and donor management has been increasing since the 1990s. So let's move on to the overview of literature for transfusion and donor management.

All of the literature reviewed assessed the safety and effectiveness of computer assisted transfusion management systems using barcode or radio frequency technology to ensure compatibility between the patient and the blood component. The literature shows that automating the transfusion management process improves patient safety. One study reported no missed transfusion after transfusion 50,000 units over four and a half years’ period using a barcode computer assisted transfusion management system. This was supported by a small study conducted in 2002 using a point of care barcode transfusion safety system in which there was 100 percent identification of the patient, their blood samples, and the blood components. The study concluded that barcode technology is an efficient approach to improving transfusion safety by eliminating errors in identifying patients, their blood samples, and blood components prior to transfusion.

In another study conducted using a network computer assisted barcode transfusion management system, it was reported

that 60,000 blood components were transfused without any ABO mismatch transfusions, leading to the conclusion that these systems greatly contribute to safe and efficient transfusion therapy. While barcode technology has been reported to reduce the potential for mis-transfusion and improving patient safety, radio frequency technology has also been reported to do the same. Transfusion management systems using the radio frequency transponder microchip can be used to standardize and document blood collections and transfusions, thereby reducing the potential for mis-transfusion and improving patient safety. With barcode and radio frequency positive identification, studies demonstrating incremental improvements in patient safety, other studies reveal that usability testing is integral to demonstrating the effectiveness of barcode scanning devices. A user needs analysis as well as a comprehensive hazard analysis is necessary to ensure effective design. The literature on transfusion management systems for positive patient and blood component identification demonstrated the ability of these systems to prevent human errors by monitoring the transfusion process. As I said earlier, transfusion management also includes electronic cross-match and automated remote release of blood components. This software performs compatibility testing between the donor unit and the recipient test data, and controls the ability to select and retrieve units or components from the

blood refrigerator.

What is important to note is that the selection of the compatible blood component occurs outside of the laboratory, and the release of the blood is performed by non-laboratory staffers utilizing a software-driven protocol. One study reported that out of 5,200 RBC units issued by this process, no units were incorrectly issued. All of the studies concluded that electronic remote blood release systems are safe. That is, they minimize incorrect issuance of units. Also, they are an efficient means of providing blood within the blood bank and at remote hospitals without blood bank services.

So now that we've discussed the functions of transfusion management, I would like to move on to the donor management systems. Donor management includes many functions, but the literature available addressed only the donor health history questionnaire. The donor health history questionnaire has advanced from a paper questionnaire administered by donor center personnel to a computer-assisted self interview. Several studies reported that when comparing computer-assisted self interview to face-to-face interviewing. There was a decline in the rate of occurrence of errors and omissions. Also, the identification of high risk behaviors among fist-time donors was greater using the computer-assisted self interview than the face to face. The use of these systems as systems protecting the blood supply by

preventing the collection of unsuitable blood at the interview stage. Thereby, the unsuitable blood is never in inventory and available for transfusion.

So, in summary, the literature demonstrates the safety and effectiveness of transfusion and donor management systems that assist in keeping the blood supply and patient safe. The widespread adoption of computer systems in blood establishments has resulted in greater accuracy in donor and patient identification, as well as a more efficient cross-matching and transfusion management. The failure or malfunction of these devices can adversely affect donors and/or patients.

So, in addition to what was -- has been reported in the literature, we investigated the available data within the agency, and that is the medical device reports and recalls. Medical device reports are submitted to the FDA database to report suspected device-associated deaths, serious injuries, and malfunctions. FDA uses these MDRs to monitor device performance and detect potential device-related safety issues. Although MDRs are a valuable source of information, this surveillance system has limitations. Events are typically under-reported, although mandatory for manufacturers, user facilities, and importers, and relies on voluntary reporting from health care professionals, patients, and consumers. Their rep are often delayed and are difficult to verify.

With respect to the barcode -- bar chart, we uncovered 201 events over the last 19 years that included one death, nine injuries, one invalid event, 173 malfunctions, and 17 other events. The one death occurred in 2002, and was attributed to a mechanical failure of a blood refrigerator. The BECS was not implicated in the death of the blood recipient. And for the nine reported injuries, the information provided is insufficient to accurately identify the nature of the injuries, but one of the nine injuries reported that hospitalization was required. The majority of the 173 malfunctions were attributed to software problems, with 93 being specific to software error and design problems.

An example of the malfunctions reported describe the test results and deferral information from two different patients were inappropriately merged when a user edited the name of the donor on a certain screen. This software malfunction could effect donor eligibility, as well as collection of an unsuitable blood component. Another report stated that the quarantine status applied by blood center staff was inadvertently overwritten when multiple donors' collection data were attempted to be synchronized from a thumb drive. This malfunction could lead to the distribution of an unsuitable blood component.

So, in conclusion, the malfunctions reported through MOD, which is FDA's database, could have potential to cause death or

serious injury. These medical device reports suggest that the current requirement for premarket notification 510(k) review, for BECS and BECS accessories, is an effective means of minimizing software malfunctions that could lead to death or serious injury. BECS and BECS accessories are complex devices, and the development process for software should be tightly controlled in order to prevent problems that cannot be easily detected until they are in distribution.

Additional risk of the device can be identified by the recalls that have been reported. A recall is an action taken to address a problem within a marketed medical device that violates FDA law. Recalls occur when a medical device is defective, when it could be a risk to health, or when it is both defective or -- and a risk to health. The data presented in the graph from January 1st, 2006, through December 31st, 2013, is a snapshot in time of BECS recalls. During that time, there were a total of 56 recalls. All of the deviations dealt with not meeting product specifications, including programming errors and design requirements that were not adequate.

The recalls included incidents like a programming loop error that allowed unwanted test results to be saved when the user selected "no" at the prompt, “Save? Yes or no.” The software's branching or decision logic that allows it to follow different paths during execution may hide some latent defects

until long after the software product has been introduced into the marketplace. Another recall reported a limitation in the character field for the antigen identification string. This resulted in the antigen results not being saved to the blood bank specimen or blood bank history records because e the antigen identification string exceeded a certain number of characters. This had the potential to cause a transfusion reaction. All of these recalls have potential to affect the safety of the blood supply and the patient. Often, recalls result after software is updated and changed. Such improvements sometimes lead to new defects from the change. So in conclusion, these recalls suggest that software development problems can be mitigated with proper verification and validation. These recalls suggest that the current requirement for premarket notification 510(k) helps insure that this is accomplished.

The 510(k) review is to ensure substantial equivalence tot he predicate device, and I've listed a few of the main items that we review. We compare the intended use and the differences in the technology to the predicate. We review the software requirements and the detail design to determine the functions of the device and how the device performs. Our evaluation of the hazard analysis allows us to determine if all the risks associated with the device are addressed and mitigated. The anomalies, which are bugs or defects in the software, allow us

to see how these defects affect the operation of the device. And lastly, we review the verification and validation testing to ensure that the specifications meet the requirements and the device performs as intended.

During our review, we focus on the hazard analysis because it allows us to see that all hazards or risks have been identified, and that the mitigation measures are adequate. We have encountered submissions that the hazards and mitigation measures were not identified for functions like automatic transfer of information from the laboratory information system to the device, locking of the records, and duplicate records. But working with the manufacturers allow for reevaluation of the hazards, retesting, and resolution of the problems identified prior to release. Also, we focus on anomalies because they alter the way that the software performs. We have encountered software with numerous anomalies, like allowing two users to simultaneously edit the same patient's record, and the software may not always capture all of the changes made by each user. Such anomalies could have the potential to allow the collection from an unsuitable donor, or release of unsuitable blood for transfusion or for further manufacturing. In most cases, the manufacturer fixes most of the anomalies prior to clearance to ensure the safety and effectiveness of the device.

As I stated earlier, verification and validation ensures

that all functions are tested adequately. Over time, we have seen that testing at the user facility prior to clearance often uncovers problems that were unnoticed by a manufacturer. This is because the end-user tests the device according to their user needs, and in their environment. So we believe the premarket review process provides a vital opportunity for oversight of the performance of BECS and BECS accessories that will help ensure the safety of the blood supply and donors. I have discussed the safety and effectiveness of the devices and the potential risk assessed in the MDRs and recalls. Now, I would like to summarize what FDA has identified as the primary risk associated with BECS and BECS accessories.

The first one is transfusion reaction, injury, or death, and this can occur from the inadvertent release and transfusion of incompatible blood or blood components, or transfusion of inaccurately labeled and/or stored blood components. The second is transmission of infectious disease, and this can occur from inadvertent release of blood components that have tested positive for transfusion, transmitted agents, and the last is the donor health risks, which can occur from inappropriate or excessive donation of blood or blood components. I provided some examples of these risks earlier in MDRs and recalls. They all have the potential to threaten the safety of the blood supply, the patient, and the donor.

Now, one means to mitigate these risks is through special controls, and the special controls are usually device-specific, and may include device-specific performance standards, post-marketing surveillance, patient registries, special labeling requirements, premarket data requirements, and guidelines. So now that we've discussed the risks, I would like to provide the following mitigation measures specific to BECS and BECS accessories that FDA recommends. It's performance and functional requirements performance testing, and labeling, and I'll explain these mitigation measures in more detail in the next slides when I provide the special controls for these devices.

So FDA believes the BECS and BECS accessories should be subject to the following special controls. The first one is software performance and functional requirements are provided in the premarket submission, including detailed design specifications. For example, algorithms or control characteristics, alarms, device limitations, and safety requirements. The second is verification and validation testing and hazard analysis are to be performed and provided in the premarket submission. The labeling should include the software limitations which are functions that you would expect a device to perform that it doesn't, unresolved anomalies annotated with an explanation of the impact on safety and effectiveness, and these are design flaws that pose as defects and bugs in the

system, revision history, and hardware and peripheral specifications.

The traceability matrix performed and provided in the premarket submission, and performance testing is performed and provided in a premarket submission as necessary to ensure the safety and effectiveness of the system when adding new functional requirements. For example, electromagnetic compatibility or wireless coexistence. So in summary, based on the available information for BECS and BECS accessories, there is evidence that the benefits from the use of these devices outweigh the potential risk. The literature indicates that the computer-assisted transfusion management systems and donor service systems improve the safety and effectiveness of transfusion and donor management. However, medial device reports and device recalls data indicate that these devices present risk and that clear design requirements and extensive verification and validation are needed to ensure the safety and effectiveness of BECS and BECS accessories. We believe that the premarket review process provides a vital opportunity for oversight of the performances of BECS and BECS accessories that will help ensure the safety of the blood supply and donors.

Due to the risk associated with BECS and BECS accessories and their complexities, FDA proposes that general controls alone are not sufficient to ensure the safety and effectiveness of

these devices. So FDA proposes that special controls are required. So based on the safety and effectiveness of the information and the identified benefits and risks, FDA proposes a classification for BECS and BECS accessories as Class II devices with special controls, and the proposed regulation is as follows: Blood establishment computer software, BECS, and BECS accessories -- (A) Identification. Blood establishment computer software, BECS, and BECS accessories are devices used in the manufacture of blood and blood components to assist in the prevention if disease in humans by identifying unsuitable donors, presenting the release of unsuitable blood and blood components for transfusion or for further manufacturing into products for treatment or diagnosis, performing compatibility testing between the donor and recipient, performing positive identification of patients and blood components. A BECS accessory expands or modifies the function of the BECS and/or the indication for use of the BECS devices. These devices are intended for use with or capable of functioning with BECS for the purpose of augmenting or supplementing the BECS's performance. (B) Classification. Class II, special controls. As I stated earlier, the special controls are software performance and functional requirements, verification and validation testing and hazard analysis, specific labeling, the traceability matrix, and any additional performance testing necessary. Thank you very

much, and if you have any questions, I'll answer them now.

QUESTIONS FOR SPEAKERS

CHAIRMAN JACKSON: Thank you very much, Ms. Bigelow. I think also, if -- Marjorie Shulman will be available for questions, as well. So questions for our speakers. Mr. Dubin?

MR. DUBIN: Thank you, Mr. Chairman. I assume that more advanced antigen matching and sickle cell would fall under this classification?

MR. BIGELOW: Well, we do -- antigen testing is in BECS, but sickle cell, I don't know that we -- the sickle cell testing is --

MR. DUBIN: Did I miss that one?

MR. BIGELOW: Well, the antigen testing is in BECS.

MR. DUBIN: Didn't we do a session --

MR. BIGELOW: Antigen and antibody testing.

MR. DUBIN: I don't want to mess that one up.

MS. SHULMAN: So, the answer is no. Yes. You're right. We discussed the buy array precise type --

MR. DUBIN: Yes. Yes.

MS. SHULMAN: -- and that is revealed separately under a PMA.

MR. DUBIN: Okay.

MS. SHULMAN: Yeah. And --

MR. DUBIN: That's what I remember.

MS. SHULMAN: -- right, so including the device that does the interpretation of the genotype to phenotype.

MR. DUBIN: Right. And Larry and his son read this and asked me to raise it, so -- Larry Allen.

MS. SHULMAN: Right.

MR. DUBIN: Who represents sickle.

MS. SHULMAN: Yes. Now, the system's used for electronic cross-matching would fall under --

MR. DUBIN: Would fall here --

MS. SHULMAN: -- for discussion under the BECS.

MR. DUBIN: Okay. That's what I was trying to get at. I just wasn't real clear --

MS. SHULMAN: Right.

MR. DUBIN: About it. Thank you.

MS. SHULMAN: All right. You're welcome.

MR. DUBIN: And we -- and I think some of staff knows this. Magic to our ears as arm in the game is post market surveillance, and any time we see that codified in rule making or in procedure, we're very glad to see that, because if we had had that years ago, we just might have prevented some of what happened. Not all, but some. So it's good to see that word so many times in this presentation.

CHAIRMAN JACKSON: Dr. Simon.

DR. SIMON: Thank you. I appreciate the presentation. On

review of the documents before the meeting, one of the questions that I had, and some of us in industry have, is the definition of “BECS accessories,” which wasn't clear in the text of the document. However, you gave a couple of examples, so I think I understand it, but I wanted to ask a question about it to make sure, and for -- the example I would use and see if this works: we have a donor management system in our donor centers, and then our laboratory, which does the testing, has a laboratory management system. The laboratory management system sends the test results to the donor management system, which then determines whether the unit is suitable or not from that donor. Do I understand correctly, then, that the laboratory management system would be considered a BECS accessory, and similarly, any other systems that we had that we connected into our main donor management system?

MR. BIGELOW: No. The laboratory information system is regulated under its own regulation, but we're talking about the piece of software that you need to get the data to the BECS. The results to the BECS so that the BECS can make its determination of donor suitability of -- or unsuitable component. S normally, manufacturers submit their BECS with that piece of software already there. We only have a small few of accessories that come in as -- just on their own, but they're all for specific BECS and specific instruments. So it's the software piece, not the

laboratory information system. The software piece that you need to make that -- to pull that data over into the BECS.

DR. SIMON: So basically, this is an interface between your --

MR. BIGELOW: It's -- that --

CHAIRMAN JACKSON: -- instrument and your software --

MR. BIGELOW: Correct. Correct.

DR. SIMON: So the interface is considered the BECS accessory --

MR. BIGELOW: Accessory. Right.

CHAIRMAN JACKSON: Yeah.

DR. SIMON: Okay. Is that the only example? Are there other examples you could --

MR. BIGELOW: Well, for instance, for the fingerprint identification, now that's going to probably have hardware that also is included, but the software gets integrated into the BECS as a system. You know, you probably have a hard time distinguishing between the two, being separate, but it becomes part of the system in order to identify the patient from that fingerprint, and, you know, the patient in the BECS. So that becomes an accessory to the BECS device.

DR. SIMON: So, would the laboratory management system be considered a BECS?

MR. BIGELOW: No. The laboratory -- it's regulated on its

own.

DR. SIMON: So it's --

MR. BIGELOW: It meets -- they have, you know, requirements, but if you -- if the laboratory --

DR. SIMON: Okay.

MR. BIGELOW: -- information system meets that requirement, it's -- laboratory information system regulated under its own regulations.

DR. SIMON: So it's the interfaces --

MR. BIGELOW: That is the accessory.

DR. SIMON: Accessories. Okay. Thank you.

CHAIRMAN JACKSON: Dr. Stowell.

DR. STOWELL: I had a couple of definitions questions for you, but the first one is how does this fit in with the current 510(k) clearance process. I mean, many of those requirements for the special clearance looked like things which were done as part of 510(k)

MR. BIGELOW: Well, you're right, a lot of those things are in the 510(k), but where we're concerned is the content, it being adequately addressed. I mean, just like I gave the example of, yeah, you look and address your anomalies, but if you have a submission that has 300 anomalies and that gets put out on the market, then you have a safety issue. So while some of these thing are, you know, regular 510(k) information, but we're

trying to look at the content, how adequately these things have been addressed.

CHAIRMAN JACKSON: Yes [unintelligible].

MALE SPEAKER: I have a question about software updates. At which point would it be considered a new product? Sometimes, there are little patches --

MR. BIGELOW: Yeah.

MALE SPEAKER: -- sometimes there are new version.

MR. BIGELOW: The manufacturer looks at the guidance on when to submit when you revise your -- an existing 510(k). Small changes, they may not, but after they make so many changes, a lot of times they submit because it's the number of changes, and not just the -- you know, the impact of the changes. So they have a guidance that they look at, and they determine whether they need to submit a new 510(k)

MALE SPEAKER: Thank you.

CHAIRMAN JACKSON: Yes. Dr. Knight.

DR. KNIGHT: In the proposed regulatory language in paragraph two, you say, “verification and validations testing and hazard analysis are performed and provided in the premarket submission. I just wonder what the definition of that testing and hazard analysis actually is.

MR. BIGELOW: The --

DR. KNIGHT: Well, what testing is acceptable, and what

testing isn't acceptable?

MR. BIGELOW: Well, they have to provide -- they usually provide us a summary of their unit and integration testing, and then they do system testing to test all functionalities of a device, and that system testing is done at the manufacturer facility, as well as in an end-user facility prior to clearance.

DR. KNIGHT: Is there a required coverage metric on any of that?

CHAIRMAN JACKSON: Can you repeat your question again? I don't think she heard you.

DR. KNIGHT: Oh, I'm sorry. Is there a required coverage metric on any of the testing that's conducted?

MR. BIGELOW: [inaudible]

CHAIRMAN JACKSON: Coverage metric.

MR. BIGELOW: [inaudible]

DR. KNIGHT: An assessment of how much of the software was actually executed, for example.

MR. BIGELOW: Well, they should execute all of the functionality of the -- whatever the device is -- the intended use of device and all of the performance functions should be tested, and that's what we look at. They test it to what they feel, based on the risk of the device, they test based on what they feel is, you know, to the correct level, and then we look to make sure that all functionalities have been tested.

DR. KNIGHT: Okay, thanks.

CHAIRMAN JACKSON: Dr. Schexneider.

DR. SHEXNEIDER: Good morning. I think I just need some help in distinguishing these two phrases that would place a device in either Class II or Class III. In one of the read-aheads that we got, the FDA draft panel question, on page two, in paragraph B, we read that the FDA believes that BECS an BECS accessories are not life-supporting or life-sustaining, or of substantial importance in preventing impairment of human health, and then asks us if we agree with that. I guess I would see releasing antigen-positive blood, or blood that was infected as an impairment of human health, and that a computer could help prevent that. But the other term that it seems like the FDA has landed on is a device to still potentially Class III or two, if special controls so deem, if it presents a potential unreasonable risk of illness or injury. And so, if you get antigen-positive blood, and you have an antibody, or you get infected blood that's illness or injury, to me, those two are alike, and I'm -- do we need to make that distinction, or do we just say, you know, are we in either Class II if we feel that the special controls are adequate -- and to me, it sounds like they are -- or Class III if we believe that the special controls are inadequate?

MR. DUBIN: Yeah. If you could comment on -- I mean, I think

I had the same question on our pre-call that --

MR. BIGELOW: Right.

MR. DUBIN: -- I mean, under Class III, the way this is defined, if it falls into one of these categories that's under the definition of Class III, it would have to be Class III, so this is -- I think we're all struggling with this particular issue.

MR. BIGELOW: Yeah. Well, we felt that it fell under Class III for those two that you just mentioned, but because we had the special controls to mitigate the risk that it could be Class II with the special controls in place.

DR. SHEXNEIDER: Okay. I appreciate that. Do you make a significant distinction between preventing impairment of human health and a potential unreasonable risk of illness or injury?

MS. MORRIS: So I just need to be recognized by the Chair.

CHAIRMAN JACKSON: Yeah. Ms. Morris.

MS. MORRIS: Okay. This is Janine Morris. I'm with the CDRH, the Center for Devices and Radiological Health. So there was errata in your package this morning in which we clarified, we realized that we made an error in a paragraph on page 27, and it was replaced with, “Due to the risk associated with BECS and BECS accessories, and the complexities of this device type, FDA proposes general controls alone are not sufficient to ensure safety and effectiveness of BECS and BECS accessories. FDA

proposes that special controls are required. Under the statute, a device is potentially Class III if it is life supporting or life sustaining, or of substantial importance in preventing impairment of human health, or if it presents potential unreasonable risk of illness or injury. FDA believes that BECS and BECS accessories are not life-supporting and life-sustaining, but are of substantial importance in preventing impairment of human health, and present potential unreasonable risk of illness or injury. FDA believes, however, there is sufficient information to establish special controls to provide a reasonable assurance of safety and effectiveness as these devices could be classified as to."

DR. SHEXNEIDER: I wondered if the "or" was really meant to be "but." So I appreciate the clarification

MS. MORRIS: Yeah. Sure.

CHAIRMAN JACKSON: Yes, Mr. Dubin.

MR. DUBIN: Thank you, Mr. Chairman. I wanted to build on Sonja's point, and I want to use a radio analogy. In our studios, Digidesign has an automatic update right into our Pro Tools, but we had to intervene and write guidance because individual producers were mucking up the system, doing updates without any knowledge. So I assume that's kind of an analogy that holds true here, that the agency provides guidance to the manufacturers, and then they understand how it goes is that a

correct analogy?

MR. BIGELOW: Yeah. I would say that's correct. Yeah.

MR. DUBIN: Then I understand. Because we pulled our hair out trying to straighten it out. It took a year and a half. We lost four studios to complete failure because of the wrong updates. Thank you.

CHAIRMAN JACKSON: Dr. Leitman.

DR. LEITMAN: I want to address Dr. Knight's question earlier. Although the manufacturer of a BECS device is responsible for validation, verification, hazards analysis, functional and operational analysis, when the BECS is imported into a transfusion service or blood center, that center, of course, has its own obligation

MALE SPEAKER: Correct.

DR. LEITMAN: -- to validate in its environment with its staff, with its operations, and verify, and usually it sets up test cases --

MR. BIGELOW: Correct.

DR. LEITMAN: -- anywhere from a couple to dozens to make sure that there's no loopholes for how they use the BECS. Is that subject to FDA -- what goes on at the center when it incorporates the BECS?

MR. BIGELOW: We have a user guidance, a guidance for validation, and a user facility, but -- and they -- they do

inspections at user facilities, I think, as well. But you're right, that's basically the same way that the manufacturer, he writes his test scripts, and sometimes, he even gives those test scripts to the user facility, who then modifies them based on the way that they intend to use the device.

DR. LEITMAN: The problem with BECS as I see it is that humans will still make errors, so it has to -- one has to test all the potential for human error in use of BECS.

MR. BIGELOW: Correct.

CHAIRMAN JACKSON: Dr. Stowell.

DR. STOWELL: I'm still perseverating on the 510(k) business. It would help me if I could understand what would be the difference in the requirements for performing -- the manufacturer performing these special controls, or seeing that in place, compared to what is reviewed or what is required for the 510(k) process? A number of things that you've mentioned look quite reasonable and, I think, are already done, and so I'm -- you know, I'm perfectly happy calling us a -- these Class II devices, but I'm not sure what the distinction is between 510(k) process and what you're doing here.

CHAIRMAN JACKSON: Yes, Ms. Morris. Dr. Morris.

MS. MORRIS: Yeah. Janine Morris, CDRH. So I think -- I believe I understand your question and the confusion. CBER has been reviewing and regulating these products under 510(k)

already, and they ask certain requirements. The special controls, because now we're formally classifying them, and if you -- you know, we're proposing a classification of two with special controls. They're essentially the same thing we are already asking for in the 510(k)s now, but they're not formally classified, so this is a formality that we have to go through. To my knowledge, there isn't anything new from what they're already doing.

DR. STOWELL: Yeah. There was a concern, is that there might -- these might be --

MS. MORRIS: No.

DR. STOWELL: -- additional burdens on what's already --

MS. MORRIS: No. No.

CHAIRMAN JACKSON: Any other -- Mr. Dubin?

MR. DUBIN: I'm just stretching. I assume that this will facilitate post-market surveillance because of the --

[inaudible]

MR. DUBIN: I can project, Jay. I assume this will help drive post-market surveillance with new classifications that makes it easier for the agency to do that post-market.

[inaudible]

MR. DUBIN: On devices like software.

[inaudible]

MR. DUBIN: Thank you.

CHAIRMAN JACKSON: Ms. Morris.

MS. MORRIS: Yes. Janine Morris, CDRH. I don't quite understand the question. Driving post-market. Post-market has --

MR. DUBIN: Well, so facilitate a more clear path because you've reclassified some things in ways that it seems would facilitate better post-market surveillance of, for instance, software --

MS. MORRIS: I believe it would remain the same. Post-market surveillance has existed already for BECS --

MR. DUBIN: Right.

MS. MORRIS: -- because they're regulated as medical device.

MR. DUBIN: Thank you.

CHAIRMAN JACKSON: So, Ms. Morris, could I ask a question, then? So, as I understand it, if you're submitting for a Class I device classification, you don't need to submit a premarket application, but for Class II and Class III, you do, and at that point the FDA will decide whether it fits into Class II or Class III, or does the industry submit -- request one of those designations so they would -- for BECS, for example, you're asking that they be considered Class II so they would all be submitted as Class II. Is that right, or do you then look at it and decide, “Well, this one, maybe we'll do Class III”? How does that work?

MS. MORRIS: So -- Janine Morris, CDRH. We're seeking your

input. We're proposing a Class II classification. The majority -- the vast majority of Class I medical devices are exempt from premarket notification. There is a small group that are reserved and require premarket notification, but the burden of data is much lower compared to a Class II. Class IIIs are premarket approvals. Yes, it's a premarket submission, but entirely different from a 510(k) premarket notification. So based on your recommendations, and based on the available information, we'll decide which is the appropriate class, and then we'll issue a proposed rule, and then receive comments from the public so there's more opportunity for the public to give us comments about our proposed classification, and then deliberate on that, and then make a final classification under a rule. Does that answer your question?

CHAIRMAN JACKSON: Yes. Yes. It does. Dr. Simon.

MS. MORRIS: Okay --

CHAIRMAN JACKSON: Go ahead, Ms. Morris.

MS. MORRIS: Was the question, “What happens if we -- if you disagree with our proposal?”

MALE SPEAKER: No.

CHAIRMAN JACKSON: No.

[inaudible]

MS. MORRIS: Okay. You answer.

MS. SHULMAN: Hi. Marjorie Shulman, CDRH. In answer to your

question, if it goes into Class II, w require premarket notification. The 510(k) would come in and be reviewed. If there is a significant difference, or a new intended use, or a change in the technology that would cause it to go not substantial equivalent, that device could go -- it would be classified as a Class III device.

CHAIRMAN JACKSON: I see.

MS. SHULMAN: So if it's equivalent, it would be equivalent to the Class II device. If it's not equivalent, it would be a Class III device, so if there's a significant change.

CHAIRMAN JACKSON: Okay. Thank you. Dr. Simon.

DR. SIMON: Yeah, I was just going to speak to the point Mr. Dubin brought up about surveillance. I think one effective method of surveillance, at least in my experience -- [coughs] excuse me -- over the years has been that the inspectors, when they come into the blood centers, or to the donor centers, look at the performance of the donor management system, and if they have issues, at least in the past, and I assume it's still true, they can bring in a specialist --

MALE SPEAKER: [affirmative]

DR. SIMON: -- on computer, so there is a continued surveillance through the inspection mechanism.

CHAIRMAN JACKSON: Yes, Dr. Ward.

DR. WARD: Just a clarification if you would, please. I'm

not clear on exactly what is traceability matrix as a special control.

MR. BIGELOW: Oh. Okay. The traceability matrix is sort of like -- it documents the requirement. It traces us to where the design is. It takes us to any hazards in this design, and then shows us where the hazards have been mitigated through the testing. So it's like a roadmap that you can go through the submission and find almost anything. It's really important in identifying problems and seeing where the main factor has identified risk, and that we see that they've mitigated them.

CHAIRMAN JACKSON: Other questions? Dr. Knight.

DR. KNIGHT: On slide number 24, I think, in your presentation, you have a table, a graph, showing the number of recalls of BECS and BECS accessories per year. Was any root cause analysis conducted on any of those recalls to see why they occurred in the first place, and why they weren't detected before these devices were put into practice?

MR. BIGELOW: We just, you know, obtained the data from the recall group. I don't know what analysis they actually do on the data.

DR. KNIGHT: Well, your previous slide indicates what a recall is, and --

MR. BIGELOW: What --

DR. KNIGHT: -- the reason for recalls is a defective

medical device, and I'm just wondering whether -- if a device is determined to be defective, whether any analysis was done to find out why the device ended up being developed with that defect, and why the defect wasn't caught before the system was put into operation.

MR. BIGELOW: Well, yeah, these -- they do do an analysis once they have the recall, and, they, you know, make the adjustments. They modify their software and then send out, you know, replacement software for -- or upgrades to their software once they've done the analysis to find out what the problem was, if it was a program error, was it a design defect, or something like that. Is that the question?

DR. KNIGHT: Well, but if a correction has to be made --

MR. BIGELOW: Yeah.

DR. KNIGHT: -- is there any effort to determine why the defect entered the product in the first place?

MR. BIGELOW: Yeah. The manufacturer, I assume they go back because they -- the report that we see that they do their analysis and come up with, like I said, is it a programming error, did they have a design flaw, the requirements weren't clear, they make the adjustment, they recall the software that they have and send out modified software to make the adjustment to the product.

DR. KNIGHT: Okay. Thank you.

CHAIRMAN JACKSON: Ms. Morris. Did you have --

MS. MORRIS: Yeah. Janine Morris, CDRH. I just wanted to clarify that these recalls were voluntary recalls, and the manufacturers are bound to the quality system regulations in which they typically would go and do a root cause analysis, and make any necessary modifications. It's -- depending on the class of recall, they might withdraw it from the market and replace it with some -- a corrective action, but it's mainly up to the manufacturer to follow the quality system regulations.

CHAIRMAN JACKSON: Mr. Dubin?

MR. DUBIN: So, is a patch considered a new device that starts in the beginning? I may have missed that point. It may have already been covered.

MR. BIGELOW: I didn't hear you. Is a --

MR. DUBIN: Well, frequently, like, Pro Tools will give us a patch to get around some problem we're having --

MR. BIGELOW: Right.

MR. DUBIN: -- and they'll send it -- well, it ended up being sent to the program director so I could control it.

MR. BIGELOW: Right.

MR. DUBIN: Is it considered a new device? A patch?

MR. BIGELOW: No. Would be a modification to the device.

MS. MORRIS: It depends upon the impact of the patch.

MR. DUBIN: How strong the impact is. How far-reaching.

MS. MORRIS: Yeah. Janine Morris, CDRH. Yeah. The --

MR. DUBIN: That makes sense. Thank you, Jenny.

MS. MORRIS: -- whether or not it impacts the safety and effectiveness, and, again --

MR. DUBIN: Right.

MS. MORRIS: -- Darcel mentioned the guidance for when to submit a new 510(k).

MR. DUBIN: Right. For us, it represented how much it altered outcome at the end, whether or not we considered it an addition, or just a patch. Thank you.

CHAIRMAN JACKSON: Yes. Dr. Bonilla.

DR. BONILLA: If there's an adverse event that occurs with the use of a BECS or BECS accessory, who is notified? The manufacturer, or the FDA, or both? And what is the path of notification?

MR. BIGELOW: I can't hear the question --

DR. BONILLA: My question was if an adverse event occurs with the use of a BECS or BECS accessory, who is notified of that? The manufacturer, the FDA, or both, and what is the path of notification?

MR. BIGELOW: [inaudible] I think FDA is -- the blood establishment would probably notify the manufacturer, but just like I told you, the MDRs, they -- voluntary for some, and mandatory for others. They would report it to the FDA, whoever

was the mandatory person, and voluntary person could. So it would be reported to the manufacturer, and then the manufacturer should report it to the FDA, or it could be both people, you know, alerting the FDA.

CHAIRMAN JACKSON: Yes, Dr. Simon.

DR. SIMON: Just -- but there are FDA requirements for reporting upon the blood establishment, so I think, it makes --

CHAIRMAN JACKSON: Yeah.

DR. SIMON: -- if there certain adverse events, the blood establishment would have to report it to FDA.

MR. BIGELOW: [affirmative]

DR. SIMON: Is that not correct? Yeah.

CHAIRMAN JACKSON: Dr. Leitman.

DR. LEITMAN: I had a slightly tangential question. If a blood center or transfusion service has historically written its own BECS for internal use only by its own facility IT team, and that BECS is not for sale, barter, or trade, it's only for use in that establishment, is that still subject to 510(k)?

MR. BIGELOW: That's going to be something we need to discuss at, I guess, another forum. I think it's --

CHAIRMAN JACKSON: Yes.

MS. BICHO: Jeanette [spelled phonetically] Bicho [spelled phonetically], FDA. Even though the product that you've developed is not in interstate commerce, there's a presumption

of interstate commerce, so that is a medical device subject to the regulations of FDA, and you had another question. And we have stated that in-house developed BECS are subject to oversight by FDA, as well.

CHAIRMAN JACKSON: Ms. Bicho or Morris, perhaps I could ask, the difference with a Class II and a Class III device in terms of, you know, the whole process of getting something submitted and approved, could you just sort of describe what the difference is? I mean, is it a lot more time, effort, more data? I mean, what's involved there?

MS. BICHO: This is Jeanette Bicho from FDA. I won't go into great detail, but it's, I think, accepted among industry and FDA that the premarket notification 510(k) submission is a much lesser burden on the manufacturer than is the premarket application for -- the premarket approval. The user fees are vastly different, much more expensive when you're submitting it -- a Class III device for review. The amount of information, the type of information that's required is much vaster as well for the PMA, and so there is quite a difference in regulatory burden. Also in terms of inspections, the much more frequent inspections of facilities that manufacture Class III devices. So there are distinctions, and we generally have greater regulatory control over a Class III device, but there are many devices, and, in fact, the majority of medical devices are regulated as

Class II or Class I, where we have found that that level of oversight is adequate to ensure the safety and effectiveness of those products.

CHAIRMAN JACKSON: So three really does present more significant, more burden, not just to the manufacturer, but to the FDA, as well.

MS. BICHO: Absolutely. So we try to -- we make efforts in these classification exercises to propose the lowest level, the lowest class that still is adequate to allow the proper oversight, and you've heard here this morning that we're proposing a Class II, but with special controls. These special controls under the regulations are requirements. It's not up to the manufacturer to decide whether or not they want to comply with those special controls. They become a requirement. So that also brings a control in place to ensure that these products are safe and effective.

CHAIRMAN JACKSON: Do you have a question? Okay. Any other questions? Well, thank you both -- everyone for this information. We're going to take a break now. Then we'll come back, and we'll have some open public hearing and discussion on this topic addressing the questions the FDA has asked us to look at. So 15 minutes.

OPEN PUBLIC HEARING

CHAIRMAN JACKSON: So at this time is the time for the open public hearing, and first, I will need to read the hearing announcement for particular matters, matters involving specific parties.

"So both the Food and Drug Administration (FDA) and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor; its product; and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

So we have a couple individuals who have asked to speak,

and there are some materials, I believe, at your table from some groups that may not be speaking but provided some information here. Our first presentation will be from -- I believe its Christine Silcox from the National Center for Health Research. Not sure what the topic is but…

DR. SILCOX: Thank you [inaudible]. I'm Dr. Christina Silcox. I have a Ph.D. in medical engineering and medical physics from MIT, and I'm a senior fellow at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective health information to patients, providers, and policy makers. Those are the perspectives I bring with me today. We do not accept funding from device companies, so I have no conflicts of interest.

In the 1990s, the FDA found numerous problems with BECS software, including the potential release of infectious blood. Part of the problem was that as the programs added complexity, the software testing utilized by the software companies became inadequate. In response, CBER started regulating BECS with 510(k) premarket reviews in August of 1996. We believe that the FDA's regulation of BECS has been an important improvement. However, it should be noted that the statistics we have to measure safety are based on a passive reporting system. Analysis of the CDC's National Blood Collection Utilization Survey in 2009 suggested that it underestimates a number of adverse

events. Another study showed a thirtyfold increase in bedside transfusion errors using active tracking instead of the current passive tracking. In addition, studies have shown that the number of near misses is nearly 18 times higher than the number of adverse events. Human error is the cause of many of these near misses and adverse events. Blood Establishment Computer Software and accessories, meanwhile, have greatly reduced these adverse events and near misses. With that in mind, we strongly support the FDA-suggested special controls for BECS and BECS accessories. We would like to emphasize the importance of verification, validation, and hazard analysis. We urge you to ensure that this should include substantial system security testing. We are concerned that the special controls do not specify the need for validation at the user facility. Numerous studies have emphasized the importance of training and usability for the success of BECS.

Unsurprisingly, it turns out that human error can overcome even the best automation. One example illustrates this well: a user hands over unlabeled specimen bottles to a colleague because he finds the printing process confusing. Another common example is when users override the systems because they don’t think it's correct. The FDA itself has a guidance to industry titled "Blood Establishment and Computer System Validation in the User's Facility," which suggest that the agency recognizes

the importance of this sort of testing. We agree and urge you to recommend that the agency explicitly specify this type of validation testing in the special controls, as usability of the system is critical to its safety and effectiveness.

In summary, we recommend that the advisory panel vote to classify BECS and BECS accessories as Class II, with well-designed and carefully monitored special controls. Validation in the users' facility should be required as one of the special controls listed. Thank you.

CHAIRMAN JACKSON: Thank you. Next, we have Allene Carr-Greer from the American Association of Blood Banks.

MS. CARR-GREER: Good morning. Thank you. AABB is pleased to have this opportunity to provide comment to the FDA on the classification process for BECS and BECS accessories and agrees that the proposal made by the FDA to classify BECS as Class II is reasonable. The difficulty today is determining, what is a BECS accessory. The FDA executive summary does not specifically define BECS accessories and frequently uses the phrase "BECS/BECS accessory," making it difficult to interpret what is a BECS and what is a BECS accessory. Without a specific definition, the combination of identifying unsuitable donors and evaluate, determine, and track donor screening information and component history, two phrases found in the device description portion of the executive summary introduction found on pages six

and seven, potentially makes all equipment or devices that could have results electronically transferred or uploaded to the BECS or BECS accessory. AABB strongly recommends that the FDA provide more clarity or perhaps its education around the definition of a BECS accessory before providing to rulemaking.

And just this morning, in some of the questions and answers that were exchanged between the panel and the speakers, we heard that the interface between a laboratory information system and the BECS was a BECS accessory, but I can tell you that in industry, we think that’s an MDDS, and I think the executive summary says that MDDSs are not BECS accessories. So whether that’s clarification or education or some point of conflict, I'm not certain, but I think that needs some attention. Also, this morning, as another example, one of the speakers mentioned barcode scanners being BECS accessories, but I think in executive summary, that’s also a device listed as a peripheral and also an example of something that’s not a BECS accessory.

One further point regarding FDA proposals for performance testing, found in Section 9.3, which I think is one of the final pages of the executive summary, we say that focusing on wireless networks seems unnecessary at this point. The networks are widely used and many hours already invested in exercises testing use of devices through network -- wireless networks have not yielded benefit. Thank you.

CHAIRMAN JACKSON: Thank you. Good points. Perhaps we'll bring some of that up in the discussion. Is there anyone else in the audience who would like a couple minutes to address the committee?

MS. SYLVESTER: Good morning.

CHAIRMAN JACKSON: Just please identify yourself.

MS. SYLVESTER: I'm Ruth Sylvester, the Director of Regulatory Services with America's Blood Center; it's also known as ABC. I am a paid employee, and they paid my travel here. ABC was founded in 1962. It's North America's largest alliance of community-based, independent blood programs. Our members provide over half of the U.S. and a quarter of the Canadian blood supply. Thank you for the opportunity to comment on the issue of Blood Establishment Computer Software systems, or BECS, and BECS accessories. We thank the FDA and specifically CBER for taking on the issues of BECS accessories because it had been a topic of confusion for our industry, so we appreciate CBER bringing it up and allowing for the dialogue.

ABC agrees with the risks identified for BECS by the FDA, as described in the classification of BECS and BECS accessories executive summary. Likewise, ABC concurs with the interpretation that general controls alone are most likely not sufficient to provide a reasonable assurance of safety and effectiveness for BECS. Hence, we agree with FDA's classification recommendation

of BECS as a Class II medical device. However, we do not agree that BECS and BECS accessories are synonymous, as described throughout the executive summary and as Allene just described in her statement. The definition of BECS accessories, "An entity that expands or modifies the function of a BECS and/or indications for use of a BECS device," is not sufficiently detailed to allow the industry to determine, what is and what is not a BECS accessory? It is overly broad, such that anything that connects to a BECS could be considered a BECS accessory. A clear and thorough definition for the industry is essential. Examples of what is and what is not a BECS accessory can be used to augment or bring greater clarity but should not substitute for a clear and concise definition.

ABC endorses the statements in the executive summary that clearly state that Medical Device Data Systems, or MDDS, are not BECS accessories. And Allene also brought up that point in -- from the description earlier this morning with the OIS interface to a BECS. Additionally, ABC endorses the exclusion of components used with BECS, such as operating software, hardware, and peripherals, in the definition of a BECS accessory. Thanks -- thank you to the committee for allowing the statement.

CHAIRMAN JACKSON: Thank you very much. Is there anyone else in the audience who would like to make a statement? Okay, thank you.

OPEN COMMITTEE DISCUSSION

QUESTIONS FOR THE COMMITTEE

CHAIRMAN JACKSON: Then we will move to the questions for the panel and discussion. Is there someone from the FDA who is going to walk us through these and provide some clarifying information here? Oh, okay, Janine Morris.

MS. MORRIS: Good morning, Janine Morris, CDRH. So I'm going to try to walk you through these questions. Essentially, there are just two questions, but there are multiple parts to the questions. Marjorie Shulman kind of explained early on what they'll entail. It's talking about the risks of the device and then talking about what is the appropriate regulatory control for the device, in terms of Class I, II, or III. Part of the classification process I'll explain in detail, and if you have questions, again, I'm happy to elaborate or enrich past descriptions of the process as best as I can.

So the first panel question is: FDA has identified the following risks to health for BECS and BECS accessories based upon FDA's review of the literature, information available to FDA regarding cleared devices and recalls reported, available standards on medical device software, and FDA MAUDE databases on adverse events associate with BECS and BECS accessories. So you heard these already, but just to review, risks to health would

include transfusion reaction, injury, or death -- for example, inadvertent release and transfusion of incompatible blood or blood components or transfusion of inaccurately labeled and/or stored blood components. The next one is transmission of infectious disease, such as inadvertent release of blood components that have tested positive for transfusion transmitted disease agents. And finally, donor health risk, such as inappropriate or excessive donation of blood or blood components.

So I'll read this first part, both A and B together, because they kind of go together once you enter into a discussion. So first, please comment on whether this is a complete and accurate list of the risks to health presented by BECS and BECS accessories. If you disagree, please comment on what additional risks should be included or explained or explain which, if any, of the risks should not be included in the overall risk assessment of BECS and BECS accessories. So at this point, we would like to hear any comments, suggestions, changes with respect to the risks.

CHAIRMAN JACKSON: Dr. Simon.

DR. SIMON: Yes, I'll comment on behalf of the industry point of view, and I think that--talked with some of my colleagues and we believe the FDA has done a reasonably good job of indicating what the risks are and would not have any either

additions or subtractions from the list. We think it's basically a good description.

CHAIRMAN JACKSON: Others?

MS. MORRIS: Okay.

CHAIRMAN JACKSON: Okay.

MS. MORRIS: Okay. Question two is rather involved. I'm first going to describe going through what a Class III is, what a Class II is, and what a Class I is, and if there remains any uncertainty about the differences, I'm open to your questions regarding it. But let me first run through one more time. So under the statute, Section 513 of the Food, Drug, and Cosmetic Act, it states a device should be a Class III if insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness or that application of special controls would provide such assurance and the device is life supporting or life sustaining or for a use which is of substantial importance in preventing impairment of human health or if the device presents potential unreasonable risk of illness or injury. So that's a Class III. So just high level, general controls is not enough. Special controls is not enough. And it's one of the four criteria that we spoke to.

A Class II device--a device should be Class II if general controls by themselves are insufficient to provide reasonable

assurance of safety and effectiveness and there is sufficient information to establish special controls to provide such assurance. So any of the prior categories -- life supporting, life sustaining, whether it is impairment to human health or unreasonable risk of injury -- those could still be a Class II if there's adequate information to establish special controls. Marjorie brought up an example of PTCA catheters. Early on, PTCA catheters were Class III devices, but once the technology and the understanding of those devices matured, they were reclassified as Class II because special controls could be written to have reasonable assurance of safety and effectiveness.

Class I is where just general controls are adequate or sufficient to provide that reasonable assurance of the safety and effectiveness or insufficient information exists to determine that special controls are sufficient. Special controls can establish or provide reasonable assurance of safety and effectiveness, but the device is not purported or represented to be the four criteria for use in supporting sustaining human life or is for a use which is of substantial importance in preventing impairment of human health, and does not present a potential unreasonable risk of illness and injury. That’s for a Class I.

So we described before some examples of what general controls are: good manufacturing practices, registration of the

facilities, listing of the device types, record keeping. So the first part of question two is: FDA believes that general controls alone are not sufficient to provide reasonable assurance of safety and effectiveness for BECS and BECS accessories. Here we ask, if you disagree, please discuss how general controls alone are sufficient to provide reasonable assurance of safety and effectiveness for a BECS type of device.

CHAIRMAN JACKSON: So comments on this? Dr. Simon.

DR. SIMON: Again, I'll give you the industry position, as we discussed and looked at this, and we agree with the FDA. Obviously, there is some special characteristics of donor management systems, and I think they did a good job of pointing out the evolution, wherein early in the days, FDA found some significant problems, and then, over time, industry has corrected them. So I think that in the interest of protecting the patient and the donor, it's a reasonable position to have both the general controls and the special controls. So I think industry agrees on this position.

CHAIRMAN JACKSON: Okay, thank you. Others? Okay, go ahead.

MS. MORRIS: Okay. So to be under the statute -- again, you'll hear this again -- a device is potentially Class III if it's life supporting or life sustaining. FDA believes that BECS and BECS accessories are not life supporting or life sustaining. Do you agree with this assessment? If not, please explain why.

CHAIRMAN JACKSON: Dr. Leitman.

DR. LEITMAN: It would help to put the word "direct" there. They're not directly life supporting or life sustaining in the manner that an intra-arterial, intracoronary artery stint or a left ventricular assist device, something that’s in the body that’s allowing the circulation to occur. So I think it would help me to put the word "direct" there for clarification.

MS. MORRIS: Again, we're taking the words directly from the statute, and that’s what we have to present for the panel.

CHAIRMAN JACKSON: Well, I would agree in the sense that it's not ongoing life sustaining, life support sort of thing. Dr. Simon?

DR. SIMON: I think we all probably have a little problem with the words because, of course, we believe that blood transfusion is life supporting, life sustaining. But I think, in the sense of the statute and the sense in which we understand devices and their use, industry would and I would personally agree with this assessment. Again, I think the analogy Dr. Leitman gave was a good one. I think, you know, like ventilators, things like that if they malfunction, someone's going to die right then.

CHAIRMAN JACKSON: Right.

DR. SIMON: I think this is a different situation, so I would urge that we agree with the assessment.

CHAIRMAN JACKSON: Right, because we are not transfusing the BECS or the BECS accessories, right?

[laughter]

Okay. Other comments? Okay, go ahead.

MS. MORRIS: Okay, thank you. 2(c) under the statute: "A device is potentially Class III if the device is for a use which is of substantial importance in preventing impairment of human health or if the device presents potential unreasonable risk of illness or injury. Note that such a device may still be classified as Class II if application of special controls would provide reasonable assurance of its safety and effectiveness. Considering the risks and the benefits of these devices, FDA believes that BECS and BECS accessories are for a use which is of substantial importance in preventing impairment of human health and presents a potential unreasonable risk of illness or injury." Do you agree with this assessment? If not, please explain why.

CHAIRMAN JACKSON: Dr. Stowell.

DR. STOWELL: Yes, I would agree. I think the devices are put to a use which prevents potential impairment, mis-transfusion, and so on. And they do present the potential unreasonable risk; if they fail, you could transfuse an infectious unit or ABO-incompatible unit or something.

CHAIRMAN JACKSON: Dr. Simon.

DR. SIMON: Yes, I would also agree, I think, for the reasons Dr. Stowell indicated.

CHAIRMAN JACKSON: Dr. Leitman.

DR. LEITMAN: Just want to thank the FDA for actually making it easy for the committee. The definitions are really very clear and very well-stated. I know they're in the statute, but explaining it to us helps us, so thank you.

CHAIRMAN JACKSON: Yeah, yeah.

MS. MORRIS: Okay.

CHAIRMAN JACKSON: [unintelligible]

MS. MORRIS: Okay. 2(d): "FDA believes sufficient information exists to establish special controls for BECS and BECS accessories to provide that reasonable assurance of safety and safety effectiveness." Based on the information that’s been presented today, do you agree that sufficient information exists to establish special controls for BECS and BECS accessories to provide a reasonable assurance of safety and effectiveness? If not, please explain why.

CHAIRMAN JACKSON: Perhaps if you went through the special controls right underneath before we answer that that would be helpful, I think.

MS. MORRIS: So FDA proposes the following special controls that would provide a reasonable assurance of safety and effectiveness: The first one -- you've heard this from Darcel --

"Software performance and functional requirements are provided in a premarket submission, including detailed design specifications -- for example, algorithms or control characteristics, alarms, device limitations, and safety requirements. In addition, verification and validation testing and hazard analysis are performed and provided in a premarket submission, continuing labeling specific with labeling requirements, such as software limitations, unresolved anomalies annotated with an explanation of the impact on safety and effectiveness, revision history, and hardware and peripheral specifications. And four, the traceability matrix performed and provided in a premarket submission. And the last, performance tests are performed and provided in a premarket submission, as necessary, to ensure the safety and effectiveness of the system when adding new functional requirements, such as electromagnetic compatibility or wireless coexistence."

So please comment. You can combine this with the earlier question about whether information exists to establish special controls and then please comment on whether this is a complete and accurate list of special controls needed to provide reasonable assurance of safety and effectiveness for BECS and BECS accessories. If you disagree, please comment on what additional special controls are needed or explain which, if any, of the proposed special controls are not needed.

CHAIRMAN JACKSON: Yes, Dr. Knight.

DR. KNIGHT: I wonder if I could get a little clarification of item two in the list. It says, "Verification and validation testing and hazard analysis are performed and provided." I'm not familiar in the way these controls or mechanisms work, but I wonder whether the control mechanism would imply or would, in fact, result in testing results which were generally considered to be adequate to make the necessary statements. Mainly, submitting testing results without defining what that testing needs to be could lead to a situation, perhaps, in which inadequate testing was conducted, and that would be, I think, an unfortunate result.

CHAIRMAN JACKSON: Dr. Schexneider.

DR. SCHEXNEIDER: I agree with both the questions 2(d) and 2(e). I was just noticing that these special controls are mostly technical in nature. They're about software and hardware, whereas the general controls are, I think, what we would think of as more traditional -- the good manufacturing practices, what devices we have, how we would use them. I wonder if we're at a point in our evolution of technology that some of these things that fall under special controls might move into the general control category. I don’t think it's particularly special that we're talking about software when we're talking about a BEC system, so that’s just sort of a global observation. Another one

would be, we might be thinking about how -- if we're making a new device, how we would use new data and big data to inform upgrades or revisions to the software. If we find something, as we're better able to analyze data, you know, in this age that would inform how we might use a device, you know, how are we on the lookout for new information that may inform how we use a device? So, you know, bottom line from my standpoint is that I agree with everything so far but wonder if we're at a time to change what we call a general control and a special control. Thank you.

CHAIRMAN JACKSON: Dr. Sandberg.

DR. SANDBERG: I'm wondering if we'd like to include something about post-marketing on surveillance.

CHAIRMAN JACKSON: Other comments? Yeah, Dr. Simon.

DR. SIMON: Well, I was going to make a [unintelligible] in general. I don’t know that it comes up elsewhere in the questions, but I wanted to make sure I got the concern of industry on the definition of the BECS accessories be acknowledged and worked on in terms of bringing up the final rules. So I assume that’s been heard and would be included. I think from the point of view of the regulated industry, and I speak mostly from the blood bank plasma donor centers that would be using the devices, but I think this would also support the position of the people who manufacture them. I think that the

FDA has found the, sort of the sweet spot, the right niche in which to put this. I think if we did move to a Class III, there could be issues in terms of restricting innovation and making it too burdensome and not being able to have the availability of the systems. And obviously, I think it's too important and there's too many critical functions to be Class I, so I think we're in the right spot here. And I think the general controls, like the good manufacturing practice and so forth, obviously serve us quite well. And I think the FDA has selected special controls which are appropriate, so I would agree with them. Whether they should be moved into the general controls as had been suggested, you know, I certainly don't have any objection to doing that at some point, but I suspect maybe can't be done for this rule. But in the future, perhaps it should be done. We haven’t found any additional -- or I haven't and those that advise me in industry have not found any additional special controls to recommend at this point.

And other than the concern about the BECS accessories definition, I think that this is -- and working through those problems and the problems that Allene brought up at the AABB statement, I think we're probably at the right spot to ensure that we have validated, appropriate software available and that it continues to improve. I think for those who haven’t been in the field, certainly, as we've seen the generations of

equipment, there has been significant improvement, and I think it served the patient and the donor both very well and has helped us really achieve better performance as an industry than we otherwise would have. So I think this is definitely a step in the right direction.

CHAIRMAN JACKSON: Dr. Lerner.

DR. LERNER: Not being a computer expert, I would wonder if, again, we could address Dr. Knight's questions regarding assurances, with regard to exactly what he was asking [laughs]. Because I didn't see that that was addressed in any way. Can you perhaps repeat? I just worry that many of us don't have that kind of competency. I know I would appreciate having it clarified.

DR. KNIGHT: What I'm concerned about is what would be considered acceptable in terms of the verification and validation? Validation is a process of determining whether the requirements stated are, in fact, the correct requirements. And those are in direct response to what the medical community considers to be what they want done with these types of things. Verification is the process of determining whether a particular implementation does what the specification requires. So, you're answering two separate questions here with this particular control. Validation is one question, verification is another. And I'm interested in knowing what exactly is expected in terms

of either of those, but my greatest concern is with verification; what is, in fact, going to be considered an acceptable level of verification? Now the field of testing is extremely broad. We have decades of experience with it and we have a very wide variety of results in that field. We have a wide variety of experience in other types of verification and so, the question of whether an implementation does what its specification says has been addressed by the community for many decades and it's an extremely difficult question to answer. So, I'm just anxious to know what exactly would be considered acceptable in terms of verification for this kind of software.

CHAIRMAN JACKSON: Would you like to --

MS. MORRIS: So during this period of the panel deliberation, it's usually not FDA's role to provide input and answer questions. That is during the presentation period, so this is your opportunity to make comments and provide us suggestions. If, for instance, there is a certain level of acceptability you want to recommend the agency to consider, we would take that under advisement. And this is all being recorded, in which we would go back and evaluate and see how to apply your comments to the decision that we make.

CHAIRMAN JACKSON: Well, if I could follow up on that, you do ask whether these special controls would provide reasonable assurance of safety and effectiveness. And just on this

verification, validation, or performance test are performed, just to clarify, does that mean--what is that exactly? Performance test, does that actually mean it's being used in a blood bank just to verify that its doing what it's supposed to be doing or is it just you're, sort of, pushing buttons to see if the code comes out and if the screen says what it's supposed to say sort of thing? Just, does performance tests actually --

MS. MORRIS: Performance testing can be any of what you've talked about and what I think that you should be doing in your deliberation is talking about what you think is adequate or suitable for BECS and BECS accessories. What is your set of expectations? And we can take that under advisement. But for us to tell you what we do, is crossing the line.

CHAIRMAN JACKSON: Okay, so along those same lines, it sounds like for Class II classifications that manufacturers are basically, not just these things, but are showing equivalence to what's already out there. Is that correct?

MS. MORRIS: Correct. I can speak to classification and what a 510(k) is and a Class II is. You're comparing to a legally marketed device, so we might ask for performance testing and we can ask for very detailed accounting of that performance testing, with respect to the legally marketed device, and determine if its substantially equivalent, not identical --

CHAIRMAN JACKSON: Right

MS. MORRIS: -- substantially equivalent.

CHAIRMAN JACKSON: So, basically, these special controls would, presumably, be already in place for what is already legally out there and you're just applying these same special controls to show equivalence when you're evaluating a new BECS or BECS accessory, correct --

MS. MORRIS: That’s the intent.

CHAIRMAN JACKSON: -- unlike the Class III, where you would be potentially asking them to provide clinical data and various things?

MS. MORRIS: Correct. A Class III device is where it's quite novel, the technology is not quite well understood, and you have to evaluate them individually. Every manufacturer, it has to stand on its own in terms of establishing safety and effectiveness. A Class II is for a type of device, so you can generalize. You can say that they all have these characteristics, they have these specifications, and this general battery of tests will ensure a reasonable assurance of safety and effectiveness.

CHAIRMAN JACKSON: Simon.

DR. SIMON: My understanding -- and I don’t recall exactly, of course. IT isn't my field. But I think there's been a lot of information on validation of these systems, and they've had -- I know there have been conferences. Doesn't a specific FDA

guidance on validation exist or papers or whatever?

MS. MORRIS: Yes.

DR. SIMON: It does?

MS. MORRIS: Yes.

DR. SIMON: Okay, so I think, generally, we know what to follow based on many years of discussion of this topic.

CHAIRMAN JACKSON: Okay, I think the question, again, is do we agree that sufficient information exists to establish special controls to provide reasonable assurance of safety and effectiveness for BECS and BECS accessories? If not, explain why. So does anyone on the committee feel that they don’t agree with this, that it doesn’t provide reasonable assurance? And if not, explain why. Yes, Dr. Knight?

DR. KNIGHT: I still find myself concerned because there is a question up on the screen -- I was asking for clarification, essentially, in my previous comment, and the question says if you disagree, please comment on what additional special controls are needed. And my concern is that there is nothing stated here about what exactly is meant by verification and validation. There was a comment from another committee member about validation guidance, and that's fine, but nothing about verification guidance. And I feel that I have to prepare the point that this statement, as it is a control right now, is insufficiently specific to allow one to draw conclusions about

safety of the implementation of a software system.

CHAIRMAN JACKSON: Okay and my understanding is we are not voting on these issues, you are just asking for--

MS. MORRIS: Correct--

CHAIRMAN JACKSON: --comments on this.

MS. MORRIS: So we are asking for comments, suggestions, so that’s a very valuable comment that perhaps we need more specificity. There are guidance documents on both verification and validation. Every medical device is different, so if would be very device specific what that would entail. But, certainly, we hear the comment that more specificity in what is required under verification and validation, is what I heard.

CHAIRMAN JACKSON: Yep. And I think, in general because it does ask about the safety and effectiveness for BECS and BECS accessories, about clarification about what exactly is a BECS accessory. I think you've heard that.

MS. MORRIS: Right. We also heard that comment as well, that that needs to be better specified.

CHAIRMAN JACKSON: Okay. Other comments? Yes, Jay, Dr. Epstein.

MS. MORRIS: It was working before. And Jay, if you could introduce yourself, please, for the record.

CHAIRMAN JACKSON: It works.

DR. EPSTEIN: Yes. Where you went back to the actual list of

proposed special controls, maybe it was subsequent. See, I think, first of all, we hear loudly and clearly the suggestion that additional specification may be needed for what we mean by verification and validation. I think that's your core point. But I think the question that's being asked of the committee is whether the regulation itself, which states verification and validation testing and hazard analysis and provided in the premarket submission, itself needs to be changed. Is that sufficient at the regulation level above and beyond the question of whether we may or may not need additional guidance to explain what we need? Are you, in fact, saying you think that that specification needs to be in the classification regulation itself? And I -- and I frame it that way for you because, generally speaking, the regulation does not always have to have all the details in it. It simply lays out what the requirement is, and we often explain in guidance how we think industry should comply with the requirement. So are you objecting to the statement of the requirement, or are you just calling attention that we need to provide guidance?

DR. KNIGHT: That is an excellent point, and I thank you for pointing that out. I'm very serious now. The idea that verification and validation materials, let's say, provided is really the critical issue. And, indeed, associated guidance which indicates what that should be would certainly -- would

certainly cope. I'm not sufficiently familiar with the way that the details work at the FDA, but that seems like an excellent suggestion, that the issue really lies in guidance, which is behind this. The key observation from that point that I take is that the special conditions ask for these things to be provided, which is excellent, and exactly what gets provided can be specified separately. I'm very happy to hear that. I would very much like to hear what the guidance end up being, but that’s not the point for today. Thank you very much, indeed, for that comment.

CHAIRMAN JACKSON: Other comments on this? All right. Ms. Morris, do you want to go to the next question?

MS. MORRIS: Oops, I went the wrong way. So we're finished with 2(d) and (e), correct?

CHAIRMAN JACKSON: I believe so.

MS. MORRIS: Okay. The final part of 2 is 2(f), and this is where we would like everyone to go around the table and answer. Do you agree that the agency's proposed classification for BECS and BECS accessories as Class II with special controls provide reasonable assurance of safety and effectiveness?

CHAIRMAN JACKSON: Okay, we want to start with Mr. Dubin. Do you agree with that? We are going to go around the table, she asked that we go around the table and whether that provides -- or does anybody want to -- I don't want to start with --

MS. MORRIS: You can abstain.

CHAIRMAN JACKSON: -- ask Mr. Dubin if he wants to defer for a minute.

MR. DUBIN: Yes, I would appreciate that.

CHAIRMAN JACKSON: Okay.

DR. SCHEXNEIDER: I agree.

DR. SIMON: I also agree.

Dr. DR. RHEE: Yes.

CHAIRMAN JACKSON: Dr. Rhee.

DR. LERNER: Yes.

CHAIRMAN JACKSON: Dr. Lerner, yes.

DR. KNIGHT: If I could take a little more of the committee's time and just ask about addressing the questions that have been posed about exactly what an accessory is because I think that is a very important clarification perhaps and a very simple thing to do would be to consider the entire set of components as being a BECS system and eliminate the notion of accessories. I don’t know how to deal with that, but it does seem like there were several comments made, and having that clarified seems to be a good idea. The proposed classification, I think, is very tied in with that because several of the points, at least the way I heard them, were concerned with whether a particular accessory was going to be within this framework. So I think maybe that would be a helpful thing to

clarify.

CHAIRMAN JACKSON: Anyone else? Dr. Bonilla?

DR. BONILLA: I agree with the proposed classification.

CHAIRMAN JACKSON: Valerie?

DR. DURKALSKI-MAULDIN: I agree.

CHAIRMAN JACKSON: Dr. Leitman?

DR. LEITMAN: I agree with the categorization as Class II with the caveat that we need more definition of what a BECS accessory is. That’s important.

DR. STOWELL: Yeah, I would agree that comment as well.

MALE SPEAKER: I second what Dr. Leitman said.

CHAIRMAN JACKSON: Dr. Ward?

DR. WARD: I agree with the classification as Class II.

DR. SANDBERG: I agree.

CHAIRMAN JACKSON: Okay, Dr. Sandberg. Okay, anything else, Ms. -- oh, Mr. Dubin.

MR. DUBIN: [inaudible]

CHAIRMAN JACKSON: Do you mind saying it into the microphone, Mr. Dubin? I appreciate it. Thank you.

MR. DUBIN: I guess in this meeting, I'm the consumer rep, non-voting, so I would've voted yes if I were voting. The arguments are compelling, and some good comments have come up around the table.

CHAIRMAN JACKSON: Actually aren't taking a vote, we're just

getting people's --

MS. MORRIS: No vote today.

CHAIRMAN JACKSON: -- comments. So --

MR. DUBIN: No, I'm saying, but if there had been a vote--

CHAIRMAN JACKSON: If there -- okay.

MR. DUBIN: -- which is how, I understand, when I change hats this way, I'm supposed to --

CHAIRMAN JACKSON: Okay.

MR. DUBIN: -- look at it. So I would've said yes.

CHAIRMAN JACKSON: Okay, thank you.

MR. DUBIN: [affirmative]

MS. MORRIS: Okay, thank you very much, and we'll take all of your comments under advisement.

CHAIRMAN JACKSON: Okay, thank you. At this point, we're quite early, and I suggest, if we can -- I don't know if the speakers are here for the updates. Mr. Emery, if it's okay with the committee --

MR. DUBIN: Yeah, let's do this.

CHAIRMAN JACKSON: -- we can get done quicker.

MR. DUBIN: So we skip lunch and the break. Can we take a short kind of restroom break, Dr. Jackson?

CHAIRMAN JACKSON: Right now, you mean?

MR. DUBIN: Yeah, before we do the updates --

CHAIRMAN JACKSON: Okay, why don't we --

MR. DUBIN: -- if that’s all right with people.

CHAIRMAN JACKSON: -- take a 10-minute break?

MR. DUBIN: Okay, thank you.

EMERGENCE OF CHIKUNGUNYA VIRUS INFECTIONS
IN THE WESTERN HEMISPHERE AND POTENTIAL IMPLICATIONS
FOR BLOOD TRANSFUSION SAFETY

CHAIRMAN JACKSON: Okay. We have two committee updates, and on these updates, the FDA is not seeking advice for recommendations from the committee on this topic. It's an update only. And our first speaker is Dr. Maria Rios, who will be giving us an update on the emergence of chikungunya virus infections in the western hemisphere and potential implications for blood transfusion safety. Thank you, Dr. Rios.

DR. RIOS: Good morning. And we will, as he said, talk to you today about the update on chikungunya virus in the Americas and the considerations for blood safety strategies. Initially, I will give an update about what -- background on what the chikungunya, it's an arbovirus virus of the genus alphavirus family Togaviridae, closely related to byetta, o'nyong-nyong, and Ross River virus. The genome of the virus is 11.8, approximately 11.8 kb single-stranded positive polarity RNA. That means when it gets into the cell, it's immediately translated. The coding of the virus has two open reading frames and one encode for the nondestructive regions. There are four proteins in the -- oh, non-destructive proteins. And the second portion that it's near to the three to the [unintelligible] of the virus code for five destructive proteins that makes the virus itself.

Based on the genetic -- on the genetic sequences of the E-1 gene of the chikungunya, the virus has been divided in three phylogenetic groups. One, it’s the West Africa. That was the first one. Actually, chikungunya was first isolated in the '52-'53 outbreak in Tanzania. It’s enveloped virus. The second one was -- and this spread to Africa and a new phylogroup appeared, and then the third phylogroup was emerged around the time of 2004, when the outbreaks in the Pacific Islands were intense, and it’s call the East Central South African phylogroup. The virus is transmitted by the vectors Aedes aegyptis Aedes albopictus. Both vectors has recently been demonstrated to be capable of transmitting all viral genotype in the same intensity and degree. There is some discussion about the Aedes aegypti to be more transmitting, more fit transmitting, but it’s due to the pattern of biting. The hosts are human and nonhuman primates, and the outbreaks of chikungunya are often explosive with high morbidity and low mortality.

Regarding transmission between humans, the human-to-human transmission is commonly done by a vector, a vector by that infected person, amply the virus and transmit to several others, but there have been rare documented cases of transmission in utero, intrapartum from viremic mother to the -- to the child, percutaneous by needle stick, and laboratory exposure. There is no evidence of virus in the breast milk, and there is a

theoretical concern of transmission by blood transfusion organs in tissue transplantation.

The infection of chikungunya -- the clinical manifestation of chikungunya infection is very similar to that of dengue, and it’s often misdiagnosed by dengue because these virus [unintelligible] not infrequently because the same mosquitos transmitters. And it’s also reported that the same mosquito in the same human can have dual infection of dengue and chikungunya simultaneously.

The symptoms are high fever, nausea, rash, polyarthralgia, sever and debilitating muscle and joint pain that can last for days or weeks and in several cases may persist for months and years. Other clinical manifestation are neurological -- myocarditis, hepatitis, gastrointestinal and ocular manifestation, and can cause hemorrhage, so very similar to dengue. There is no specific treatment or vaccine available. Although intense trials and develop a vaccine, it’s not ready to be used. There is a rare fatality that occur primarily [unintelligible] or very young individual with immature immune system, immune compromise, or debilitated patients. And actually the most recent fatalities in Puerto Rico, diabetes is one of the causes that can culminate with infection for chikungunya and fatality. There is also symptomatic infection, and that has been reported, that between 15 and 28 percent of the infected people

may never develop symptoms. There is a preclinical incubation period while there is no symptoms and this is between three and 12 days, and the infection causes high viremia, ranging from 10 to the 4 to 10 to the 8 [unintelligible], and can last for up to 18 days. And this study was performed recently and the latest outbreak showing that the asymptomatic individual could have viremia lasting for up to this time.

Although there is no chikungunya transmission by transfusion documented yet, there is a potential risk for transmission by transfusion due to high viremia, as I've been mentioning, lasts for up to 18 days, an incubation, asymptomatic period, asymptomatic infection with the high viremia. In the proportion of the cases, if the later symptom occur, it may be just mild, like a headache or that we will never be thought as chikungunya. In addition, blood components that have been tested by -- in the latest outbreak have shown that CHIKV RNA-positive components were present in both La Reunion and Thailand.

Between the 50s and the 80s, the chikungunya outbreaks were sporadic, and outbreaks have occurred in Africa, Asia, Europe, Indian and Pacific Ocean country, but since 2004, the intensity and frequency of these outbreaks have increased, and at least 15-16 outbreaks between 2010 and 2013 were documented. And finally, the virus reached the Americas in December this year in the Caribbean, and that's ongoing, and it's estimated now that

approximately 950,000 cases have occurred.

The first case of chikungunya in the Americas actually was reported on December 13, 2013, in the Island of Saint Martin and was one case confirmed in -- by February. There were 10 localities with transmissions and over 2,500 cases confirmed by laboratorial tests. The virus then reached Puerto Rico in March and, since then, has spread to the south and north of the Americas and Central America. And right now, there have been reported chikungunya cases, including imported and locally transmitted in about -- in 101 countries and territory. And what you see in this map here is that the dark area, the dark green, are current or previous location where local transmission has occurred. So it’s really spreading throughout the world. This slideshow posted in the PAHO website, distribution found in the Americas now, and in purple are the countries where local transmission has occurred. And these stars indicate where important cases are, and you can see that it can go from -- goes from Canada to deep down into Argentina. And around this area, a lot of the mosquito -- transmitting mosquito exists.

Regarding to blood safety measures in the Caribbean, the French territories have taken measures. The whole blood collection were placed in quarantine while the testing by [unintelligible] was performed Marseille. There is a publication in "Blood" reporting that among the 2,149 donations tested, four

were identified as reactive, or .19 percent of the donors. Of these four individuals that were reactive, two remain asymptomatic throughout follow-up and two report symptoms 12 to 24 hours post-donation. In the French territory also, the platelets were treated by amotosalen and UV, and Puerto Rico has recently some measures to mitigate risk, and I will talk about that a little bit further down with other slides. And there is no other parts of the Caribbean or the Americas that I'm aware of that have taken measures regarding blood safety so far.

What this slide shows you is the status of the chikungunya imported cases locally transmitted in the U.S. until 30th of November. There is a total within including Puerto Rico and the Virgin Island and the U.S. itself of 26,675 cases reported in the U.S. and territory, and that includes imported tested and suspected cases. In the U.S. mainland, 46 of the states have chikungunya -- imported chikungunya, including Washington, D.C. and 11 cases of locally transmitted chikungunya has occurred in Florida. In Puerto Rico, there is about over 24,000 case -- oh, 23,000 cases of chikungunya. Thirty-five hundred and fifty-three have been tested, but the agencies don't have enough reagent to test to perform in all of the suspected cases. And there is close to 20,000 suspected cases. And there is also five fatalities, most of them the patient had diabetes. So the number of cases are increasing in the U.S., and the risk that we have

to consider for an outbreak in the U.S. is really maximized by the observation of the distribution of the both transmitting mosquitoes, the Aedes aegypti and albopictus. In blue, it’s the overlap of the two agents, or two vectors, and the Aedes albopictus is shown in the left-hand side map. And in red is what was already reported. And all the dark areas are a status in several period of the showing presence of the mosquito and the same in Aedes aegypti on the right. And the data in red is from 2010. The data in blue for the aegypti is 2013. So there is a concern that an outbreak could occur here during the summertime.

As for blood safety measures in the Continental U.S., the AABB issued a bulletin in June 6, 2014, in response to the ongoing outbreak of chikungunya in the Caribbean to provide information about the potential transmission by transfusion and the educational post-donation information material to be used by blood collection organization in consideration for collecting facilities to act in response to post-donation information reports. For donors travelling to the Caribbean 14 days before donation, if post-donation information they indicate unexplained illness, including of -- two or more of the symptoms listed in the material, they suggest that the collection center consider to recall non-transfused products from such donors. In this specific donor referral, by just unexplained illness was not

recommended; however, if the PDI, or the post-donation information, reports a confirmed case of chikungunya or dengue to consider recalling the products collected 14 days before the onset of -- the onset of symptoms, and defer the donors for 28 days following resolution of symptoms, and you can find the extent of this bulletin on the AABB website.

As I mentioned, Florida had 11 cases. And one blood in Florida adopt a stipend strategy with measures to prevent both chikungunya and dengue transmission by transfusion upon recognition of local transmission, following a model that was applied by the AABB issue on virus -- emergent virus. And the area would be represented by zipcode. So they would call the code green no arbovirus threat, continue to monitor and follow AABB bulletin recommendation. Code yellow: travel-acquired cases are present in that area, in that zipcode, so add an additional donor question and defer donors travelling to the Caribbean Suriname for 21 days. Orange code: one to five locally acquired cases in the zipcode area within a rolling 30 days' period, activate a scripted proactive callback system. The center would call the donors and ask questions directly to the donors. The red alert would be six or more locally acquired cases within that area within a rolling period of 30 days, seize platelet collections in the affected areas, place a seven-day hold on red cells prior to the release, and combine with proactive script,

and contact all the donors before releasing and making sure that there was no report of symptoms.

But blood safety measures were also taken in Puerto Rico. American Red Cross seized blood collection in Puerto Rico, and it's currently importing blood components from the mainland U.S. to prevent both dengue and chikungunya. And Puerto Rico Department of Health placed an order saying they're currently recommending pre-donation screening questions regarding symptoms or contact with symptomatic individuals in the last seven days. In the case of affirmative answers, donors are to be referred by 28 days. They also recommend the collection of post-donation information of symptoms; discarding dated products beginning seven days before onset of symptoms; and defer donors for 28 days if they report any symptom; quarantine products, every product, for 72 hours to allow the donor to report the information after collection; and increase vigilance for chikungunya and dengue in [unintelligible] plaza unit, discard units if donor cannot be contacted in 72 hours post-donation to confirm absence of symptoms. And I have to call your attention that Puerto Rico has a massive outbreak. It's over 23,000 cases now, and it was in a short period.

The other ongoing activities to address CHIKV, CBER is monitoring all of the activities in close collaboration with national, local, and public health systems in considering

development of a guidance document. CBER is developing a CHIKV reference reagent for using validation of [unintelligible] as a -- trusting future donor screening as a development in the case of need, and there's [unintelligible] release when DSAs are licensed. That's what I had to tell you today. Thank you.

CHAIRMAN JACKSON: Thank you very much, Dr. Rios. The committee can ask questions at this point. Just we're not asking for -- the FDA's not asking for advice or recommendations, but if you have questions, that's fine.

MR. DUBIN: I appreciate your presentation. As a journalist in the 80s, we saw a lot of hemorrhagic dengue throughout the isthmus and in Managua and Nicaragua and around the blood center -- Nicaragua blood center. I'm curious about, though, the distribution in the United States because we had raised issues at the committee about blood collection along the Southern Tier and our concern about dengue. So any thoughts you have on that distribution map you showed, I'd be very interested to hear.

DR. RIOS: Distribution map of chikungunya in that area, meaning this?

MR. DUBIN: Yeah.

DR. RIOS: In the -- in the lighter blue, they are imported cases, and as you can see in the side, the numbers, New York has 525 imported cases now. Florida comes second with 383. And there is a discrepancy between what the State Department reported,

mainly for Florida and CDC. So you have to be looking at every single State Department. There is no monitoring for mosquito infection during the time that mosquito were active and that there is no surveillance in the country right now. So it’s very hard to tell you what's, in fact, going on.

MR. DUBIN: Thank you.

DR. RIOS: Sure.

CHAIRMAN JACKSON: I had a question. In Minnesota, the mosquito is the state bird, and they are actually 51 --

[laughter]

-- different species of mosquitoes, but I don’t know if those two, the Aedes aegypti and the other one -- I know vexans is the mosquito in Minnesota. Is it -- that map you showed there, is it because the virus only infects those two types of mosquitoes? Or is it…

DR. RIOS: Yes, so far, that’s what has been -- we have been seeing, and those are the mosquitoes. But remember that when West Nile came to the country, it was only Culex pipiens that was infected. And now we have 58 species of mosquito being infected; although, there is a big difference because chikungunya is like dengue. It goes from human to mosquito to human, and we don’t know if a reservoir or of they nonhuman primates. It’s not to say that there is any, but the likelihood that other species of mosquito get infected, we don’t know, and

there is no studies in laboratory to prove that.

CHAIRMAN JACKSON: I see. Okay. So, in fact, the rest of the country may be at risk from these other mosquitoes as well.

DR. RIOS: Yes.

CHAIRMAN JACKSON: Okay. Other questions about this topic? Okay, thank you very much, Dr. Rios.

FIRST SURVEY OF THE RAPID DONOR SURVEILLANCE (RapidDOS) PROJECT ON MIDDLE EASTERN RESPIRATORY SYNDROME (MERS-CoV)

CHAIRMAN JACKSON: Our next presenter will be Dr. Mark Walderhaug, who will give us a presentation on the first survey of the Rapid Donor Surveillance, RapidDOS, project on Middle Eastern Respiratory Syndrome, or MERS. Go ahead.

DR. WALDERHAUG: Thank you. And I compliment the committee on its patience. The -- I also want to say I'd like to think that they saved the best for last.

[laughter]

But I have to say Maria's -- or Dr. Rios is better than I am. So you have to be a little disappointed, I suppose. What I'm going to talk about is actually a donor surveillance project that's been undertaken both with the FDA and blood-collecting organizations and -- to do surveys of donors on their possible exposures. And this is going to be a report on that first survey, which concerned possible exposures to Middle Eastern Respiratory Syndrome, or MERS-CoV.

So the origin of this problem was a task that the Office of Blood Research and Review gave us many years ago, to characterize the risk of transfusion transmitted malaria for travel to Mexico, and we didn't have good data on how many donors travelled to Mexico and where in Mexico they went. So we

were looking at travel data and trying to figure out the number of people who could drive to Mexico, the number of people who could fly to Mexico -- there is some data on that -- the number of people who go on cruise ships, and then take a 5 percent estimate of blood donors relative to general travelers. In other words, there was a lot of uncertainty associated with that estimate, and it wasn't until the blood-collecting organizations provided us with very good information about where donors had travelled in the past year to Mexico that we were able to get a much more -- I would consider less uncertain and more invaluable risk assessment to provide to the Office of Blood Research and Review. So we've engaged in developing an infrastructure to working with the blood-collecting organizations, to help us characterize possible exposures by blood donors, and the other interesting aspect about this is that we wanted to use electronic surveys because of the fact that that's the upcoming media, and it's something that was not able to be done in the past. And we wanted to try and help move things along to the future. And the blood-collecting organizations were very helpful in agreeing with us on that. So basically, we developed the survey.

The survey in the past could be an email contact to go to a particular website, something like SurveyMonkey. Some blood organizations use SurveyMonkey. Some use SMS messages to blood

donors that directed them to URLs that got them to the survey. They would administer the survey. Well, I'm jumping ahead. We also worked with the blood-collecting organizations to develop a statistically representative sample so that rather than biasing our sample to a certain subset of donors, we tried to look at the demographics of the donors and get a sample frame that we could query. We had to get clearance from the Office of Management and Budget to undertake this survey, and of course, we had to get approval from the Institutional Review Boards, both of all the blood organizations as well as FDA's Institutional Review Board of the blood-collecting organizations administered the survey. The results were sent to the contractor, who is AABB, and the National Organization for Opinion Research, and they made certain that the data were de-identified. And then they were shared. We analyzed and we will be reporting on this in greater detail in the future.

So the participants were HHS, at the secretary's level was CDC, and the offices within CBER. AABB is one of the contractors that I mentioned, and the National Opinion Research Center pretty much provided a lot of the engineering for the questionnaires. The blood-collecting organizations who participated in the survey were American Red Cross, OneBlood, the New York Blood Center, Blood Center of Wisconsin, and Blood Systems on the Pacific.

So just to provide perspective on Middle Eastern Respiratory Syndrome, it’s highly contagious with a very high mortality rate. It’s a coronavirus similar to SARS. It’s been identified in multiple countries in the Arabian Peninsula, and in fact after the survey was developed, that Yemen and Oman were also -- should have been on the list as well, but weren’t on the survey. It’s very deadly in the sense that it’s killed over 364 people in Saudi Arabia, and there have been imported cases in Europe, Africa, and Asia, including the United States for which fortunately both patients were covered, and there were no secondary infections in the hospital environment, which apparently in Saudi Arabia has been a very, very important cause of the spreading apparently. A relatively few people get it primarily and most of the cases were form secondary transmission from those who had been infected.

So the survey was structured -- it's spread over two slides here -- basically, we asked if they’d travelled to Saudi Arabia, the United Arab Emirates, Qatar, or Jordan, and if they said no, we’ll pass on to the next slide. If they said yes, we have them check on whether or not they -- which ones they attended, and if there were more than one, they went to the more than one. And then we asked how long it’s been since they returned after that length of time that they spent. And then if you had said no or had travelled, we asked whether or not to your knowledge you’d

come in contact with someone who travelled in the three, four countries and then asked whether or not there'd been anyone had severe respiratory illness, and was it severe enough that you or your family members sought treatment. So it was a relatively short questionnaire, and if you had not travelled, it really was only, you know, four questions instead of more, and that's, I think, very important from our perspective, that we do not overburden the donors, but rather make this as easily completed as possible.

So here are some of the results. You'd be interested to know that of the 7,128 survey participants, we aimed for having 1,000 from each of the five blood-collecting organizations, but we collected more than that, partly because we did a trial survey ahead of time, but also, once you were invited, if you, you know, responded after we'd reached the number of total that we accepted your answers, only 10 visited one of those countries, and because this was an electronic survey, one donor was still in the Middle East and, you know, answered that questionnaire. Most were in Jordan only, but they were represented in the other countries, as you can see. One of the points that I unfortunately have to raise right now is the fact that the engineering for some of the donor surveys was not such that what we try and do is make certain that you can't skip questions but that in some cases, questions were skipped. So we

have missing answers. We're going to try and fix that for the next survey. So for the person who said he had been since in Saudi Arabia, we don't know how long they were in Saudi Arabia, because they did not complete that part of the questionnaire. But again, I hope to fix all the missing questions for the next round of the survey.

So this gives you a breakdown of some of the ages to look at in terms of where the respondents were in the first column. You can see these are the age breakdowns for all the respondents, the people who did travel to the Middle East, you can see are mostly very young or very old, and I think we can, you know, the very young people unless it's become the new spring break to go, we can make certain estimates about who they were. As far as the contacts and the illnesses were concerned, it's about the same number. Relatively, you can start making inferences about what's going on with this data, but I think they're not as informative I think as who has been travelling to the Arabian peninsula, and again, at the bottom, we have the total numbers, and the numbers in parenthesis represent the missing data. And again, we're going to try and make certain that we don't have missing data in the future by better engineering our questionnaires. This gives you an idea of how we frame -- what our representation is of our sampling of the five blood-collecting organizations represent around 2.5 million

people with the following breakdown according to ages provided there. I had to make a small correction to this slide for the population numbers. That's actually ages 16 to 20, but our survey only is of adults. So the way Excel made this, I could only have 18 to 20 to represent the fact that we don't survey people who are not adults and it's a part of our protocol. In any case, what you can get from just looking at the breakdown of the respondents versus the sample frame is that the younger people are relatively less represented than the older, and this was a little bit surprising because you would expect because this was electronic survey that young people would be more likely to complete it. But the older people, apparently, are holding their own with electronic devices. So there's some hope for us oldsters I suppose.

We divided the country up according to PHS region. The reason why some of the PH regions were combined here are is that we wanted to make certain that for each of the geographically reported information that there were at least two blood-collecting organizations being represented in all those locations, so that no blood collecting organization could be singled out based on the data. So PHS regions one through three were combined as were PH regions six and seven. Again, looking at the representation of the populations would show a good idea of what all donors are looking like. Our sample frame is

relatively close to what the population is, and of the respondents you can see PHS region four came through for us more than the other sections did.

So what did we learn? I think our main problem was, in spite of the fact that we had a trial survey ahead of time, we had missing data because the way the questionnaires were set up was not exactly implemented the way we had hoped, and resulted in missing data that in the future we were working on solutions to fix that. And our other problem was developing that sample frame is a challenge for the blood-collecting organizations, because of the fact that for some organizations their donor recruitment databases are separate from their donor databases, and so we've been stimulating them to try and combine some of these databases, so that they can be better integrated into the sampling process. And we think we're going to make progress on that. And it's going to result in a better sampling infrastructure that the blood-collecting organizations can use themselves. The next survey that we're planning to do is going to be on estimating very [unintelligible] residual risk in donors, and we are funded for a third survey which will probably be related to emerging infectious disease travel exposures. So those are our plans, and we'll take feedback on that.

I want to acknowledge Steve Anderson, who was able to assemble the funding for this project; Jay Epstein and my guru

Hira at OBRR; Jim Berger at HHS. Susan Hinkins is the person who provides the sampling expertise, along with Mike Stern, at the National Opinion Research Center. And Barbee Whitaker of AABB is the sparkplug who keeps us all tied together. Drs. Dodd and Stramer at ARC, American Red Cross, Brian Custer at Blood Systems, Jerome Gottschall at Blood Center of Wisconsin, as well as Debra Kessler and Beth Shaz at the New York Blood Center, and German LePrac all worked very hard to get this project going, and I think shows a lot of promise for making -- helping us provide the Office of Blood Research and Review with accurate assessments of risk and benefits for future risk assessments. Thank you.

CHAIRMAN JACKSON: Okay, thank you, Dr. Walderhaug. Is there any comments, questions for -- yes, Dr. Simon?

DR. SIMON: Yeah, I think this was very nice. So thank you very much, and certainly this will help inform us on these issues as we go forward. I did want to ask about vCJD, seeing that is your next project. And given the passage of time since we had the issue in the UK, at what point does this fall off the radar as being a significant transfusion risk?

MALE SPEAKER: Yeah, that’s a good question.

DR. WALDERHAUG: I think that’s a very excellent question that we’re going to try and address with the data that we will get, and of course, given the fact that there will be recall

data, we will, you know, have to deal with the fact that will probably be less accurate than this survey was in terms of people being able to recall how long they spent and where they travelled to. But as far as when we stop worrying about that, I think we'll probably have the TSEAC committee start providing us with input on that.

CHAIRMAN JACKSON: So to follow up on Dr. Simon's question, so on the survey for CJD residual risk, I don't understand. This is in donors, you had said, that you're going to do this. I mean, what's the likelihood that a donor who develops CJD is going to answer your questionnaire?

DR. WALDERHAUG: Well, it's not that we're asking donors about whether or not they've developed vCJD. Our question is going to be better characterizing the travel to not just the UK but to other areas in Europe where vCJD risk may have been underestimated over time, and so we're trying to provide that data foundation to assist in a better characterization of what that risk might be.

CHAIRMAN JACKSON: I'm sorry. So you're going to ask them their travel history?

DR. WALDERHAUG: Yes, their travel history, and so --

CHAIRMAN JACKSON: And so this is obviously they donated years and years ago, because they haven't been able to donate since.

DR. WALDERHAUG: And we will also have a sample frame representing donors that travelled, could have travelled at that time. So we will not be asking a questionnaire of donors who are too young to have been exposed to the vCJD risk, and that way we'll be able to engineer a more relevant survey to the people who would have most likely have been -- have that aspect of risk.

CHAIRMAN JACKSON: But I mean, just finding these people after 30 years is going to be tough.

DR. WALDERHAUG: Yes, yes, we acknowledge that, but at the same time, this is -- it's much better for us to have actual data on this question --

CHAIRMAN JACKSON: Yeah.

DR. WALDERHAUG: -- rather than intuiting, because as we did for the risk assessment for travel to Mexico and transfusion transmitted malaria, we had no detailed information and actually getting donors to respond was a -- it was actually blood-collecting organizations who assembled that information. It's having real data as opposed to intuitive data, is a big breakthrough for us.

CHAIRMAN JACKSON: Mr. Dubin.

MR. DUBIN: A compliment to FDA in general, in terms of the event horizon, what we like to call the event horizon, and emergent pathogens. This is a very different FDA than we saw in

the 80s, and even in the 90s. This is an FDA that really starts to get a hold of that horizon and take movements that are important, and we want to acknowledge that. We had a call last night, and that came up from Dr. Colvin [spelled phonetically], who sat on this committee, and some of our people. So I wanted to say I really appreciate both updates, especially the dengue and the chikungunya, because we saw a lot of that, as I said, as reporters in the region, and I was always a little nervous about getting hemorrhagic dengue, not that it would kill me, but that it's so painful. The other point is -- and I just want to throw this out, Dr. Jackson and Dr. Epstein, as maybe a future discussion. We still have concerns about the border and source plasma collection along that Southern Tier, and we don't want to do a political discussion. We want to do a scientific discussion of what the risk landscape is. We've been discussing this for a long time, and that was the number one concern from our, what we call the canary working group, canaries of the coal mine, our Blood Safety Committee. And so I'd just throw that out there as a potential area of discussion in the future, from a scientific standpoint, characterizing the risk of the border collection. Thank you.

ADJOURNMENT

CHAIRMAN JACKSON: All right, thank you for your comment. Any other questions on this issue and the presentation? All right, well, I think that wraps up this BPAC meeting, and I want to thank everyone for taking the time to come here. It’s very important. I know your time’s very valuable. And we’re finishing early. So maybe you’ll be able to get back a little earlier, too. So thank you again and see you -- our next meeting is -- when is that? Maybe in March. Okay, thank you.

(Whereupon, at 11:51 a.m., the meeting was adjourned.)