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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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BLOOD PRODUCTS

ADVISORY COMMITTEE

86th Meeting

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P R O C E E D I N G S (8:03 a.m.)

Agenda Item: Welcome, Opening Remarks, Announcements.

MR. JEHN: Committee members, invited guests, consultants, public participants, I would like to welcome you to the 86th meeting of the Blood Products Advisory Committee.

I am Donald Jehn, the executive secretary for this meeting. The entire meeting today is open to the public.

We actually have six new members of the Blood Products Advisory Committee here today, and they are all sitting on my left here. If they would like to get up and introduce themselves briefly, that would be great.

DR. BALLOW: Mark Ballow. I am from SUNY Buffalo, New York, Women's and Children's Hospital, chief of the allergy program there.

DR. CRYER: Gil Cryer, and I am from Los Angeles. I run the trauma program at UCLA Medical Center.

DR. FINNEGAN: Maureen Finnegan. I am an orthopedic surgeon who is involved in trauma at Parkland Hospital in Dallas.

DR. KULKARNI: Rashni Kulkarni, pediatric hematologist, oncologist, at the Michigan State University.

Years ago I used to work at the American Red Cross.

MS. SZYMANSKI: My name is Irma Szymanski, I am from the University of Massachusetts Medical School. I am professor of pathology, and I used to run a blood bank for 27 years.

MR. JEHN: And Dr. Quinn will join us. He is local here at Johns Hopkins. We have three members not in attendance this time, Dr. Schreiber, Dr. Segal and Dr. DiBisceglia. Existing members, if we could just go around here.

DR. KUEHNERT: I am Matt Kuehnert, assistant director for blood safety at CDC.

DR. MANNO: I am Catherine Manno. I am a pediatric hematologist at the Children's Hospital of Philadelphia.

DR. QUIROLO: Keith Quirolo. I am a pediatrician in the sickle cell program in Oakland, California.

DR. WHITTAKER: I am Donna Whittaker. I am the director of the Robinson Blood Center at Fort Hood, Texas.

MS. BAKER: I am Judith Baker. My background is public health. I direct the federal hemophilia treatment center program in Region IX, based at Children's Hospital, Los Angeles.

MR. JEHN: Dr. Davis is coming back. He is a former member, but he is a temporary voting member today.

DR. DAVIS: Kenneth Davis. I am a trauma surgeon at the University of Pennsylvania.

DR. KLEIN: I am also a visitor today, since I have my plaque from the last meeting. I am Harvey Klein. I direct the department of transfusion medicine at the National Institutes of Health.

DR. KATZ: Dr. Louis Katz. I am the executive vice president and medical director at Mississippi Valley Regional Blood Center in Davenport, Iowa.

DR. MC GEE: I am Dan McGee. I also have a plaque. I am from Florida State University. I am professor and chair of the department of statistics.

MR. JEHN: And of course our chair, Dr. Allen. Let me begin with the conflict of interest disclosure statement. It gets a little lengthy. So, bear with me.

The Food and Drug Administration, FDA, is convening today's meeting of the Blood Products Advisory Committee under the authority of the federal advisory committee act, FACA, 1972.

With the exception of the industry representative, all members and consultants of the committee are special government employees or regular federal employees from other agencies, and are subject to the federal conflict of interest laws and regulations.

The following information on the status of this

advisory committee's compliance with federal ethics and conflict of interest laws, including but not limited to, 18 US Code Section 208, and 21 US Code 355(n)(4), is being provided for participants in today's meeting and to the public.

The FDA has determined that members of this advisory committee and consultants to the committee are in compliance with the federal ethics and conflict of interest laws including, but not limited to, 18 US Code Section 208, and 21 US Code 355(n)(4).

Under 18 US Code 208, applicable to all government agencies, and 21 US Code 355(n)(4), applicable to certain FDA committees, congress has authorized the FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweigh his or her potential financial conflict of interest, section 208, and where participation is necessary to afford essential expertise, section 355.

Members and consultants of the committee who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential financial conflicts of interest or their own, as well as those imputed to them, including those of their employer, spouse

or minor child related to the discussions of rapid tests for detection of bacterial contamination of platelets, public comments on the draft guidance for industry and FDA review staff, collection of platelets by automated methods, and proposed studies to support the approval of over-the-counter home use human immunodeficiency virus, HIV, test kits.

The committee will also hear an overview and discuss the research programs of the Office of Blood and Research Review.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda includes updates on the summary of the Department of Health and Human Services Advisory Committee on Blood Safety and Availability, current considerations for blood donor screening for west nile virus, classification of transfusion recipient identification systems, and a summary of the workshop on behavior based donor deferrals and nucleic acid testing.

Also, today's agenda for topic one includes the review and discussion of rapid tests for detection of bacterial contamination of platelets.

For topic two, the committee will review and

discus the public comments on draft guidance for industry and FDA review staff, collection of platelets by automated methods.

In accordance with 18 US Code Section 308(b)(3), waivers have been granted to the following special government employees: Dr. James Allen for topics one and two; Dr. Catherine Manno topic two; Dr. Irma Szymanski, topics one and two.

A copy of the waiver statement may be obtained by submitting a written request to the agency's freedom of information office, Room 12-A-30, of the Parklawn Building.

In addition, there may be regulated industry 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 they may wish to comment upon. These individuals were not screened by FDA for conflicts of interest.

Dr. Louis Katz is serving as the industry representative, acting on behalf of all related industry, and is employed by the Mississippi Valley Regional Blood Center..

His employer collects and distributes aphoresis

platelets. Industry representatives are not special government employees and do not vote.

This conflict of interest statement will be available for review at the registration table. We would like to remind members and consultants 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.

The FDA encourages all other participants to advise the committee of any financial relationships that you have with any sponsor, products, direct competitors and firms that could be affected by the discussions. Thank you. Dr. Allen, I turn it over to you.

DR. ALLEN: Thank you, Don. We are going to start with our committee updates. We are going to change the order slightly, however. The first speaker will be Linda Weir from the FDA, classification of transfusion recipient identification systems.

Agenda Item: Classification of Transfusion Recipient ID Systems.

MS. WEIR: Good morning. The purpose of this presentation is to provide FDA's current considerations on the regulation of electronic systems for matching blood

components to the intended recipients.

We have had a little difficulty naming these things. You will notice in your agenda they are called one thing, and they are called another thing in here.

What are transfusion safety management systems? They are an electronic system consisting of a bar code scanning device, specialized software, sometimes a portable printer, and possibly other accessories.

They are intended specifically for use in matching blood components to the intended recipient by scanning the bar code on the blood products with the bar code on the patient arm band at the time of transfusion.

They may be stand alone systems, they may be interfaced with hospital or laboratory information systems, or interfaced to blood establishment computer software BECs -- aka, a blood bank system.

They are used for positive patient ID at the bedside, may be used when the specimen is collected from the patient for compatibility testing, at which point usually a printer is used to print a label for the specimen container.

They aid in the decision to transfuse or not. They may be wired or wireless. They may be used to record vital signs pre and post-transfusion. They may be used to record post-transfusion events.

They may be used to track the blood product from the point of issue from the transfusion service or pick up, picking up the blood, through any subsequent refrigeration through transfusion.

They may record the time out of refrigeration and warn the user is time is outside the acceptable limits. All of these activities are tracked, the date and time of the transaction, and the user ID of the person performing the transaction.

Transfusion safety management systems have been determined to be medical devices within the meaning of section 201(h) of the Federal Food, Drug and Cosmetic Act, 21 USC, 321(h).

This is because they are intended to prevent transfusion of blood to the wrong recipient, thus preventing incompatible transfusion and associated hemolytic transfusion reactions. In other words, they are used for the prevention of disease.

Transfusion safety management systems are devices, then, that further meet the definition of blood establishment computer software, or BECs, the definition of which is software designed to receive and store data used by blood establishments, which includes transfusion services for 21 CFR 607.3(c), during the manufacturing process, which includes compatibility testing, per 21 CFR

607.3(d), from determining donor suitability through component processing, testing and labeling to product release.

The information on this slide is from a March 31, 1994 letter to manufacturers of blood establishments, and you can locate that document on the link provided.

Because the FDA regulates compatibility testing under 21 CFR 606.151, software products used in transfusion services for compatibility testing are also considered to be BECs.

Transfusion service software products often contain other functionalities consistent with those of BECs, such as inventory control, label printing, et cetera.

These software products also usually store recipient data such as blood types, known antibodies, and other functionalities.

So, our message to manufacturers of transfusion safety management systems, if you are manufacturing an electronic system intended for use in transfusion management, you should submit a 510(k) if you have not already done so.

Keeping in mind the meaning of intended uses under 21 CFR 801.4, which is the objective intent of the persons legally responsible for the labeling of devices, the intent is determined by such persons' expressions, or

may be shown by the circumstances surrounding the distribution of the article.

This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives.

These devices often use wireless technology in the form of a handheld device, and manufacturers of medical devices using wireless technology must consider electromagnetic interference, and electromagnetic compatibility caused by the device in the environment in which it will be used.

We request you provide the requirements as set forth in the recognized consensus standard -- and I apologize for this title -- AAMI/ANSI/IEC 60601-1-2: 2001, Medical Electrical Equipment Part 1-2; General Requirements for Safety - Collateral Standard; Electromagnetic Compatibility Requirements and Tests.

The manufacturer of the equipment or system should provide a declaration of conformity to this standard, or provide testing results as outlined in the standards in the 510(k) submission.

I need to expand on this slide a little. The submitter of the 510(k), which is usually the manufacturer of the system, can either obtain from the OEM manufacturer of the typically handheld wireless device a declaration of

conformity to the standard, and submit that declaration to us at the FDA.

If you cannot obtain that from the OEM manufacturer, you have to either do the testing yourself, hire a third party to do it -- and in that case we want to see the actual testing and results and not just the declaration of conformity.

Our message to users of these devices, know if the transfusion safety management system you are considering is intended for use in transfusion management.

If it is, you should know if the manufacturer has obtained clearance from FDA via 510(k). If it has not, note that your validation burden may be higher.

This is a list of our cleared systems, and I have to apologize for a typo. The word Korchek should be spelled K-o-r-c-h-e-k.

All of our cleared blood establishment computer software can be found at that link provided at the bottom. If you have any questions, this is my name, e mail address and phone number.

Please call me with any questions, even pre-submittal support. We would rather do the work up front than at the end, and I thank you very much.

DR. ALLEN: Thank you. We will open the floor for committee questions or comments.

DR. KUEHNERT: I just had a quick question. Is there a parallel process for tissues, to track tissues in hospitals, since hospital blood banks are increasingly given that responsibility in that setting?

MS. WEIR: I wouldn't have any knowledge of anything we are doing in tissues. I specialize in blood software. Would anyone else care to answer that question?

DR. KLEIN: It is my understanding that hospital information systems aren't regulated as medical devices. Hospital pharmacy systems that look at safe administration of medications aren't either. When blood systems are integrated into those, how are they regulated?

MS. WEIR: If they are only used at the front end to draw the -- in the process of drawing other samples, they draw the tests for compatibility testing -- we don't require 510(k) for that.

If they are used as the back end of the process to make a go-no-go decision on the transfusion, we do require 510(k).

DR. DOPPELT: In regard to using tissue, the tissues aren't typed. So, the donor receives tissue that isn't matched, obviously. So, the operating rooms have logs and the recipient's record has a log of the ID number for the tissue.

The operating rooms and the storage facilities in

the hospitals -- maybe the pathology department -- keep logs of which patient received what tissue in case there is a recall. It isn't quite as automated as this.

DR. ALLEN: That would be my sense based on everything else that I know about the way in which tissues are handled, but it is not nearly as closely regulated as are the blood and components.

DR. KATZ: Can you clarify for me, if a hospital has developed its own system, that is a front end and back end system, and has no intention to market it, do they still require 510(k) clearance?

MS. WEIR: If I understand your question, that would not meet the definition of interstate commerce. However, obviously, you would need to validate that pretty heavily.

DR. ALLEN: Dr. Holmberg, would you please identify yourself and all speakers from the floor microphones, please identify yourself for the recorder.

DR. HOLMBERG: Jerry Holmberg, Department of Health and Human Services. Your comment there about wireless technology, I assume -- and it is wrong to maybe assume -- that you are talking maybe about infrared for printing and for communication.

MS. WEIR: It is usually the radio frequency.

DR. HOLMBERG: Does this also include the RFID,

radio frequency identification?

MS. WEIR: We haven't had that occur yet, but I would assume that would be the same situation.

DR. HOLMBERG: My next question is, as far as integrating RFID into the collection process all the way through to transfusion of blood to the patients, would the organs -- because RFID could be applicable to bone marrow, any cellular products, tissues and organs -- would there be any requirement for testing to make sure that there is no adverse effect on the product?

Although most of the RFID that is being developed is a passive, which is only a loop and not an active RFID, is there a difference between the active and the passive, and would there be additional testing requirements put on the manufacturers?

MS. WEIR: I can speak only for the 510(k) for these devices. However, if the submitter tells us, we do not advertise using RFID. Sometimes the hospital chooses to use it.

We ask them to put in the labeling a statement that the hospital is then required to consider any interference from the device, and I believe HCFA would probably be the person who would look at that, but we do recommend that they put that in their labeling. Did that answer the question?

We are aware that there are other devices out there, and have been for years, used to collect phlebotomy specimens and other things in the lab that we do not regulate, and that use RFID. We can only speak for what we are requiring or asking for, for blood products used to collect or administer a cross match, because of the severity of what could happen if the cross match was issued to the wrong patient.

DR. HOLMBERG: So, you are part of CBER and not CDER?

MS. WEIR: I am CBER.

DR. HOLMBERG: I guess my question goes a little farther in the 510(k). If you add something to a blood bag or attachment to the packaging of a tissue, what does the agency, or how does the agency view that, and would there be additional requirements testing. Have you thought that far through the process?

MS. WEIR: To my knowledge, there is no decision that has been made, but we are aware that that is probably down the pike but, to my knowledge, no decision has been made on that yet.

DR. HOLMBERG: So, companies that are developing this, they would have to ask the question to get a decision?

MS. WEIR: I would say they definitely have to

ask the question.

DR. BIANCO: Thank you, Selso Bianco, America's Blood Centers. I just want to make a plea for simplicity in this regulatory process.

Transfusion of a unit of blood into an unintended recipient is one of the major issues that we still contend with in hospitals.

We are very afraid that sometimes complexity might inhibit manufacturers' software development from implementing something that we would like today to see every hospital, every transfusion service using. Thank you.

DR. ALLEN: Any other comments or questions on this issue? Okay, thank you very much, Ms. Weir. We will move on to the next update presentation by Dr. Jerry Holmberg, executive secretary for the department's Advisory Committee on Blood Safety and Availability. This will be a meeting summary of the committee.

Agenda Item: Committee Updates. DHHS Advisory Committee on Blood Safety and Availability Meeting Summary.

DR. HOLMBERG: Good morning. Thank you for that excellent update on closing the loop to the patient. The Advisory Committee on Blood Safety and Availability has been extremely concerned about the safety, and we echo Dr. Bianco's comments from the floor.

This is one of the major issues that the advisory

committee has been looking at over the years, to try to close that gap and to increase the safety to the intended recipient.

What I would like to do today is to give you an update on our January meeting, January 5-6 of this year. Unfortunately, I don't have handouts for you today, but everything that was part of this meeting on January 5-6 is actually on our web site, and you can see the recommendations that the committee put forward.

Of course, when I go through the recommendations today, they will be a summary of the recommendations, and the complete recommendations can be found there. Also, all the presentations are on the web site, and I will make these slides available to the Blood Products Advisory Committee, and they can post these if they wish.

The first thing that I want to -- the first person I want to introduce to you is our new assistant secretary for health, Dr. John Aguinobi.

Dr. Aguinobi has a remarkable background, with an MBA, and I didn't put there, but he has a masters in public health. He is a pediatrician and I am pleased to hear so many pediatricians being represented at the table today.

In 2001, he was chosen to be the secretary for health in the state of Florida, and then he was nominated by the President and cleared to be the assistant secretary

for health.

During the period of our not having an assistant secretary for health, Dr. Christina Iato was the acting assistant secretary. He is a commissioned core officer. He is a four star admiral in the Public Health Service Corps.

The issue that we discussed in January was the avian flu virus, H5N1. As you can see, the geographic location where this started, the picture there is really not of the Vietnamese Thailand area.

Actually, if we have people who are astute to ethnic regions, this is actually a picture from the Philippines, the only picture I had available, but I thought with the child in the back and the chicken, it got the message across, that we want to make sure that the blood community is really thinking about the impact of the avian flu.

I also have in this picture a clock flying. What I would like to say is that I think all of us realize that the clock is ticking. We just don't know what time it is.

So, we need to be prepared within the blood community, within the entire public health community as far as the avian flu.

Some of the things that we did talk about at the meeting were potential human to human transmission of H5N1,

the global surveillance, vaccines, preparations, antiviral priority, local planning, communication, and also we had input from the AABB task force on pandemic preparedness.

Let me just say a little bit about this. Back in November, the President, at NIH, revealed his plan, his overall structure, for addressing the potential pandemic influenza preparedness.

There are different columns of strength that he has built upon, and then the agency has really developed a guideline, and then we are working right now on our concept of operation.

The one thing that you may have heard over the last couple of months is that the secretary, Secretary Leavitt, has actually been going around to all of the states and really emphasizing this to all of the states.

This is a state and local issue. The states and local governments, tribal governments, territories, need to be prepared for pandemic influenza.

The government, federal government, can do what it can as far as vaccine, making sure vaccine is available, and also in establishing priorities.

As we found out in this meeting, 90 percent of the vaccines will be allocated to the states, and the states will have the responsibility of determining the distribution of the vaccines.

As I said, their local planning is critical. One of the messages that we are trying to get out through the AABB task force is that the local blood banks need to be working with their planners, both at the local level and at the state level.

As I mentioned here, the AABB task force has been very proactive in doing this. The government has taken a position of being a liaison on that committee, and working with that committee to make sure that the blood community is prepared.

I must say that, when I say blood community, I think that we need to think a little bit broader, and it is not just the blood community, but it is the plasma community. It is also the organs and tissues.

We have to think about organ tissues, bone marrow progenitor cells, and what is the impact on the avian flu, on the availability of those products.

What we looked at is primarily that there would be a 30 percent reduction in work force. You have to remember, with a 30 percent reduction in work force, this is not only of the donor population, but it is also going to be the work force.

That includes not only the technical people, but it is also going to include the transportation people. It will include all of those supportive services. There will

be a 30 percent total reduction in work force.

As I mentioned, there will be a decrease in donor pool. The demand, we don't know. Right now we are working at the advisory committee. We did have three different models presented.

The purpose of seeing three different models was basically to see how the models were different, how we could validate some of the information and how we could come up with a common model to predict what would be the demand, what would be the effect on availability.

We know that there will probably be a decrease in elective surgeries. What we don't know is what effect the pandemic will have on the requirement for blood.

We do know that a lot of patients will be on ventilators. We do not know what will be the blood support for those patients on ventilators.

We don't know about deferrals. Generally speaking we say somebody has to be well, in good health, but we also know that there is going to be viral shedding during the second or third day of the infection, when the person is asymptomatic.

This may require that the blood centers have a donor call back. One thing that really came out over and over again was having a clear communication plan, a risk communication plan, not to scare people, but to make sure

that the facts get out there and that we are transparent in the information that the public has.

These were some of the recommendations that went forward to establish a national recognition of the blood and plasma system as a key element of the critical infrastructure under the HHS plan.

Now, one of the things -- I will re-emphasize this again -- it is not within our charter of the advisory committee on blood safety and availability to really go into the tissue and organ and progenitor cell aspect of this.

I think we still need to be thinking about those different products, and how they are part of the health infrastructure.

The committee also recommended to the secretary regarding funding of research to resolve critical scientific questions that impact blood, organ and tissue safety and availability.

The research to resolve clinical scientific questions would be to foster collaboration with other countries, to promote studies of possible viremia in asymptomatic persons, to support studies of H5N1 and other potential pandemic strains in suitable animal models, including non-human primates to try to determine viremia, organ localization, transfusion, transmissibility and the

impact of the infection or drug treatment on the accuracy of donor screening tests.

We have seen this in the past with different vaccinations that could potentially interfere with some of our established testing.

Research also to resolve critical scientific questions, to support sites of influenza viremia, to do studies where there is potentially outbreak of both non-pandemic and seasonal type of influenza, what is the effect on the blood and plasma system.

Support the development and validation of quarantine models, or quantitative models of blood availability and utilization of potential value of candidate intervention to prevent shortages.

Also provide target federal support to enhance global and domestic surveillance for seasonal and pandemic influenza, to recognize the central role of the AABB task force on domestic disasters and acts of terrorism, and the development and implementation of a national strategy to address potential massive blood and blood product shortages during a pandemic, by assuring that blood and plasma systems input into key federal policy making and communication, and promoting communication and cooperation among states and local public health authorities, and appropriate blood collection organizations, hospitals,

medical professionals, organizations and patient advocacy organizations.

Also, develop a national principle under which state and local public health authorities and health care providers can prioritize allocation of, and minimize disparities, in blood and blood product availability and use during critical shortages.

Those were the recommendations that were brought before the Secretary. The Secretary is now considering those, and hopefully there will be a response back to those.

We are already moving forward in many aspects of this, not only within the department, but also working with the AABB task force. Thank you. Any questions?

DR. ALLEN: Any questions or comments?

DR. FINNEGAN: A question. Recognizing that China doesn't give us much information, do we know what the hematological consequences of avian flu are? In other words, is there hemolysis, do bleeding times go up, or is the blood relatively protected in this infection?

DR. HOLMBERG: I am not real sure on that. I know that there is a hemorrhagic aspect of it. I don't know what it would do with the coagulation profile. Maybe Dr. Hewitt can respond.

DR. HEWITT: There are many reports in the

literature that seem to suggest that hemophagocytic syndrome is a common complication of avian flu infections. So, it has been reported.

DR. FINNEGAN: Has the demand for blood for the infected gone up or do you know?

DR. HEWITT: We don't know that at this point, but you would expect the demand to go up if that was a common complication.

DR. HOLMBERG: You have to understand that, in the places where this has really been the outbreak at the present time, again, we don't have human to human transmission documented, and a lot of these countries don't have a well established blood infrastructure. So, we have really not been able to get a lot of feedback as far as the blood needs.

DR. QUINN: Similar with other exercises we have done in biopreparedness, has there been a tabletop exercise of what the impact would actually be with an epidemic of avian flu in the United States, Europe and so far, in terms of the impact on blood safety, transfusion practices, the work force, as you mentioned, 30 percent loss in the work force and so forth.

We have done this with the smallpox preparedness. The question is, has that been done and is it going to be done.

DR. HOLMBERG: I can say that, within the department, we have had tabletop exercises. There has been a lot of planning on pandemic for a couple of years now. We are working within the various agencies to bring together the plans.

As far as a tabletop exercise within the blood community, no, there has not been. That is one thing that we are lacking right now, is a good model to be able to predict what some of those requirements are.

The chairman of the AABB task force, however, is the consumer representative at the table here, Dr. Katz, and definitely we are working with him on some of these issues, and that may be a very good suggestion -- I think it is a very good suggestion -- for the committee. Dr. Katz, did you want to respond?

DR. KATZ: Yes, this was the biggest mistake in my life. We are in the process now of identifying -- understand, the blood community in this country is so diverse that obviously the group that I am involved with, and Jerry is helping and others in the room, we can't write a plan because there are 76 independent community blood centers, and the Red Cross, a number of hospital blood collection facilities, all the hospital transfusion services, each with a different set of needs.

So, writing a plan is probably not feasible. What

we are doing is identifying the issues that each local plan or each blood region plan needs to be addressed, and that issues outline is now 14 pages long.

We suffer severely from a lack of any way to model the impact of pandemic on blood utilization. Obviously, the last serious pandemic was 1918, and there was no real transfusion medicine at that point. ICUs didn't exist. We really don't have a clue.

The conventional wisdom has been that there is some kind of balance that will occur as elective surgery disappears, hospitals shut down to use any surge capacity they have for influenza.

Then, a 1918 scenario, HHS estimates, will put 800,000 people on ventilators, two million people in the hospital, 800,000 people on ventilators.

We all know, those of us who have done critical care, people on ventilators have a tendency, the way we practice medicine in the United States, to use blood. So, we don't know.

Worse is the supply chain. For example, the people who supply bags to my center maintain a three week inventory in their warehouses. Just in time delivery is the way that we have moved the entire economy in the United States.

A pandemic wave like that in the summer and fall

of 1918 was, in fact, about 16 weeks. You can imagine, when I talk to the CEO of a company that has a three week inventory and say, what do you think about having a 16-week inventory, they say, Dr. Katz, this event has occurred once in recorded history and you want us to change our business plan. So, we are not ready for a tabletop.

DR. HOLMBERG: Dr. Quinn, if I can just add a comment to what Dr. Katz has mentioned, when I did brief the assistant secretary on this issue, his comments were exactly what Dr. Katz has said as far as developing a plan and developing a checklist for the local blood banks, the local blood community to be able to check off. As Dr. Katz said, we are a very pluralistic society as far as the way that our blood is supplied.

DR. SZYMANSKI: I would like to ask whether this plan would include the use of frozen blood.

DR. HOLMBERG: That is a very good question. When we were addressing the west Nile virus, there was a recommendation that plasma products be collected and frozen during the off seasons to be utilized during the summer seasons.

So, as far as plasma products, that may be another recommendation that may come down. Frozen red cells is always an option.

People tend to stay away from that, primarily

because of the intensity, the cost and the intensity ofthe work force, to be able to de-glyceralize that blood and to be able to get that on the shelf.

DR. ALLEN: Other questions or comments? Certainly, I am delighted to see this planning going on, although I think Dr. Katz' comment in terms of the frustration -- I don't want to say the futility, but the frustration of doing it is very understandable.

I am sure you have included in your discussions the duration of such a crisis and the fact that it might roll out over a three month period or longer across the United States, and what that might mean in terms of some areas being severely affected at one point in time, others later.

DR. HOLMBERG: Dr. Allen, that is a very good point. I know my time is up, but it is a very good point because what we think will happen is that it will not be like the seasonal flu and move across the country, but it will move across very fast.

One of the things that the blood community has to be aware of is how will the blood be tested. Many of our blood centers send the specimens out to other locations.

That is one reason why I really emphasize that 30 percent of our work force is going to be down. What happens with the transportation of those products from one to

another, or the samples from one to another location to be tested.

In the past, especially in seasonal shortages, with the seasonal influenza, you can move product from one part of the country to another.

Blood banks have to look at different options, and that is one of the reasons why the recommendation that the committee put forward about working at the local level to prioritize in a shortage, but there are other options such as what we recommended during west Nile, freezing the plasma product and, as Dr. Szymanski mentioned, frozen blood may be an option, too, for some people. Definitely, it needs to be well thought out and these are things -- the duration is something that needs to be put into the model to be able to predict what impact will this have.

DR. ALLEN: Thank you.

DR. KUEHNERT: Just a quick comment about the utility of this. I would think that almost all of the aspects of this would be relevant to disaster preparedness.

For those who say this influenza pandemic may not happen soon, I mean I would say this really is relevant to any disaster, and so is really essential, no matter if the pandemic happens now or later or not at all.

DR. HOLMBERG: Let me just follow up on that because I can't resist it. Yesterday, at the workshop on

behavioral deferrals, a comment was made about a book that was written about, I think, the swine flu virus, the pandemic that never occurred, never happened.

I fully agree with this. Whether the pandemic happens or not -- as I mentioned before, I think it will, it is just that the clock is ticking.

I think that what this is really doing, I think it is really helping the blood community to coalesce and really come together on our disaster planning. So, the planning that we are doing for this is going to have ripple effects.

DR. ALLEN: Thank you very much. I think that is a good comment to end on. We will move on to our third update, Dr. Pradip Akolkar, current considerations for blood donor screening for west Nile virus.

Agenda Item: Current Considerations for Blood Donor Screening for West Nile Virus.

DR. AKOLKAR: Good morning. This presentation is going to be to inform you about current consideration of blood screening for west Nile virus.

As you all know, the first outbreak of west Nile occurred in the summer of 1999 in New York. Although the main mode of transmission of west Nile infection is known to be through mosquito, in August 2002, CDC proposed that there may be a theoretical potential for transmission of

west Nile virus by blood transfusion.

In September 2002, this was confirmed in a transplantation recipient as well as a transfusion by a blood transfusion.

In the same month, we develop the strategies for preventing the west Nile virus transfusion through blood transfusion, the AABB sponsored a meeting of decision makers, experts in the field from various local and state and federal government, as well as the blood and device industry.

This was followed by an FDA sponsored workshop in November 2002 to support the test development, and facilitate the communications between the test manufacturers and the users.

As a result of cooperation between the various parties, in July of 2003, nationwide screening of volunteer blood donations for west Nile using NAT was implemented and approved. R&D was performed on minipools of six or 16 donations, depending on the assay that was used.

In November 2003, the sensitivity of minipool NAT was to detect the low levels of viremia was evaluated by the prospective studies using ID NAT.

These studies identified ID NAT positive units that were negative by minipool NAT. This study also confirmed six cases of west Nile transmission by

transfusion from mini-pool negative units.

As a result of these studies, in the summer of 2004 and 2005, ID NAT replaced MP NAT in the areas of high west nile activity during a limited period of time.

Now, you see the benefits of this screening under IND. About 1,500 infected units were removed from the nation's blood supply, at the same time reducing the incidence of transmission of west Nile through transfusion.

As you can see in 2002, there were 23 transfusion transmitted cases because there was no testing. In 2005, there was none.

One of the interesting things is, in the one case that was reported in 2004, was during the transition time from minipool testing to ID NAT testing.

So, as the status of west Nile assays, FDA licensed the first west Nile NAT for volunteer blood donor screenings.

The Procleix west Nile assay on eSAS Donor screening for west Nile virus as in December of 2005. Donor screening for west Nile virus RNA in that IND protocol is still continuing.

You can see that this will allow us to get additional data about the west Nile infection in transfusion cases.

The current consideration on the assay

implementations are, we considered, recognized, that west Nile RNA NAT for testing samples from volunteer blood donors for transfusion may involve the use of complex cooling systems, as well as a testing system.

We are considering recommending that you implement the licensed NAT for west Nile RNA within six months from the date of the publication of the notice in the Federal Register announcing the availability of the final guidance.

The next couple of slides present the current testing consideration. We think that the implementation of licensed NAT for west Nile RNA for screening volunteer donors of whole blood and blood components for transfusion will improve the safety of the nation's blood supply.

West Nile screening by minipool NAT to be performed year round, with the implementation of ID NAT in the specific geographical area where west Nile activity is high.

Switching from MP NAT to ID NAT to be defined by triggers based on the incidence rate. This would increase the sensitivity of west Nile testing within the constraints of available technology and personnel.

Now, we need a dialogue with the blood establishment regarding the criteria to define the triggers to switch from MP NAT to ID NAT in geographical areas with

high west Nile activity, and the appropriate parameters to switch back from ID NAT to MP NAT.

Now, the next few slides describes the consideration on donor deferral and donor management, as well as recipient notification.

This has been published as a final guidance in assessing the donor suitable and blood and blood product safety in case of known or suspected west Nile virus in June 2005.

Defer the donor who is diagnosed or suspected of acute west Nile infection for 120 days following the onset of illness.

Defer presumptive viremia which has been west Nile NAT reactive for 120 days following NAT reactive donations.

Defer a donor who is suspected of west Nile illness within two weeks of donation, for 120 days following onset of illness.

Defer a donor who may have transmitted west Nile infection for 120 days from the date of donation.

A deferred donor may be reentered after 120 days of the last testing.

Now, for the donor management, reasonable attempts should be made to notify the deferred donors of the rest results.

Alternate NAT and antibody testing may provide information for donor counseling purposes. Follow up testing may provide further information on the course and outcome of infection.

As you know, this has been done under IND protocols, that is, the alternate NAT antibody testing and follow up testing. We considered that this should be continued on the IND protocols.

As far as the unit management issue, we recommend to discard the unit that is NAT reactive. This was not part of the June 2005 guidance.

The quarantine in-date blood and blood components, including unpooled recovered plasma and source leukocytes from a donor who is diagnosed with west Nile infection, that the donor who is presumptively viremic -- that means west Nile NAT reactive -- and a donor who may have transmitted west Nile infection or has an undiagnosed illness that presents like the infection with west Nile.

The recipient notification considerations are: The blood establishment that receives information regarding the diagnosis of west Nile infection or illness may consider tracing the record and notifying the transfusion services regarding the relevant unit. The transfusion service may then consider notifying the testing physician of prior recipients.

As far as the labeling is concerned, we are considering recommending that the container label and the instruction circular that reflects the results of west Nile nat be consistent with labeling for other infectious disease markers, upon the implementation of licensed NAT.

West nile reactive units should not be shipped or used except as provided in an FDA approved program and/or research or autologous use only, and such units should be labeled with appropriate warnings. Thank you.

DR. ALLEN: Thank you for the update. Committee comments or questions?

DR. BALLOW: Could you explain a little bit more the difference between the ID NAT and the MP NAT? It looked like from your table that there were contaminated blood products that sneak through the NP nucleic acid testing procedures. That is correct; right?

MR. AKOLKAR: Yes.

DR. BALLOW: So, you are switching back and forth between the two assays. What is the utility of even using the MP NAT if contaminated products sneak through that assay?

DR. NAKASHI: I don't think the word contamination is the right word. I think the minipool NAT sensitivity, which has a certain level of sensitivity, and in the beginning, the technology and the logistic nature of

the testing was such that we had to go with the minipool NAT testing.

Soon after, when we started testing with minipool NAT, we realized, and the blood community realized, as Dr. Akolkar mentioned, that there were some blood samples which were below the detection level, had the viremia below the detection level of minipool NAT. Therefore it was switched to the individual NAT testing format. Did I answer your question?

DR. BALLOW: Yes. So, what are the recommendations now, just to do the individual test?

DR. NAKASHI: No, the recommendation at this time is to continue testing minipool NAT. .Usually, what we found out is that, in the last couple of years, that where the west Nile incidence is higher, switch to ID NAT during that time.

The question was, what would be the trigger to move from minipool NAT to an ID NAT, and there were several proposals.

One of the proposals that we have been following the last few years is that, if the incidence rate is you find one in 100,000 samples that you are picking up in your blood banking in a particular one week period, and you switch to minipool NAT, that is suggesting there may be more samples coming up.

MS. RIOS: I just would like to clarify here that ID NAT is not feasible at this time. It is a logistical problem in blood bank settings.

The issue about going from minipool NAT was the approach taken to screen blood donors for HIV and HCV. The problem with west Nile is that, in the early stage of infection, as well as in the late stage of infection, the viral load declines.

The minipool is no longer sensitivity enough to pick up the infected unit. The logistics of going to the minipool from ID is that the test is performed all year round, even when west Nile activity is not obviously occurring, or this surveillance is not finding any west Nile viral activity.

So, when human cases start appearing, that is when the blood center considered to then go back to individual testing and identify low viremia units.

This has occurred in 2003, but in 2004, by implementing these measures, these problems apparently disappeared. Does that clarify to you?

DR. BALLOW: That clarifies it, but is it worthwhile doing the minipool during the seasonality when there isn't any west Nile virus?

MS. RIOS: Well, this is a decision for the blood centers to be taking. To our best knowledge, it is easier

to keep the minipool on and then go back to ID NAT than to shut it off completely and reinstate the procedure when the season comes.

We also didn't expect to have a continuous outbreak of west Nile as there has been for seven years in the United States. This is unheard of in the world.

So, CDC has considered west Nile now endemic in the United States. That means apparently it is here to stay. Last year outbreaks were higher than the year before, and we don't know what will come next.

DR. ALLEN: Please understand, as background, all of the testing to date, or at least through the end of 2005, was done under IND. There was no licensed test.

There is now a licensed test. They are still working through the guidance in terms of exactly how it will be implemented at a point in which we may be moving from epidemic levels of disease, at least in different geographic areas of the country, to an endemic level of disease at an unknown level.

So, there are a lot of questions here that need to be worked through in terms of the protocol. We really need to move on. We will take just a couple more comments.

DR. .NAKASHI: One more correction here. I think there is now a licensed test. You mentioned there was no licensed test.

DR. ALLEN: I said through December 2005. The testing done during west Nile epidemics to date, through 2005, there was no licensed test. There is now.

DR. NAKASHI: In December 2005.

DR. ALLEN: Very quick questions?

DR. BUSH: Just a statement, that we developed this targeted ID NAT strategy where we convert from minipool to ID NAT based on an observed yield of minipool NAT based on the data from 2003, and we turned it on at the beginning of 2004.

Since we turned that on, there has not been a single transmission of west Nile virus documented by blood transfusion. The one case that happened in 2004 came in June, and it beat the implementation of the targeted ID NAT strategy.

So, we are pretty confident that this approach of tracking minipool yield and converting to ID NAT is extremely effective at interdicting the low viremic infectious units.

MS. HEWLETT: I just have a comment that when west Nile first showed up, that we had to work with what we had in place, and that this minipool NAT testing for HIV and NCV.

So, there was a rapid response put together to develop the existing platforms to put NAT testing in place.

Obviously, there is an interest and intention to move toward ID NAT. So, that point needs to be noted.

DR. QUINN: A very quick question. What is being done in terms of organ transplantation, since there have been known cases transmitted of west Nile through organ transplant.

DR. NAKASHI: Last year there was one transmission through organ transplantation. This west Nile test which was approved is also now being used, is being approved for detection in organ donors.

DR. QUINN: It is now mandatory of all organ transplants that their blood be screened? That is what I was getting at.

DR. NAKASHI: No, it is not yet mandatory.

PARTICIPANT: There is a licensed test.

DR. QUINN: There is a licensed test available, should you wish to do it.

DR. NAKASHI: We in our office do not regulate organs.

MS. RIOS: There have been three cases of organ transplantation confirmed as of 2005. In 2005, there have been seven confirmed cases to date.

DR. KUEHNERT: Just a comment on the organ transplant issue, that there is information on the United Network for Organ Sharing web site on the use of organ

donors who are suspected of having encephalitis and may have west nile, the use of those organs. There is a working group discussing screening, but there are no recommendations at this time.

The question I had regarding blood screening was just about the end of the IND and what happens after that concerning confirmatory testing.

I am just concerned, we have wonderful data now on evaluation of the tests and, as we talk about switching from minipool to ID NAT et cetera, are we going to lose that opportunity to evaluate once the IND ends? I just wondered if there were plans in the guidance about confirmatory testing after the IND ends.

DR. NAKASHI: That is a very good question. I think we are thinking about it because everything is under IND. So, we are taking up considerations for that, and we will take that into consideration, because I think it is an opportunity to really find out what is happening with this thing.

DR. ALLEN: Thank you very much. We will move on to our last update presentation, workshop summary from yesterday on behavior based donor deferrals in the nucleic acid testing era.

Agenda Item: Workshop Summary: Behavior-Based Donor Deferrals in the NAT ERA.

DR. DAYTON: Yesterday we held a workshop which reexamined the issue of behavior based donor deferrals, now that we are in the era of NAT testing.

We had representatives from industry and academia and also from the FDA, and this was a chance to bring to bear the most recent data and thinking in the field.

We started off with a presentation from the FDA, from Dr. Goodman, Dr. Epstein and Allan Williams, summarizing current blood donor deferral policies, and giving an overview of our approach to deferral, and I am not going to summarize their talks for this body, because I know it is well known here.

Ruth Solomon gave an interesting talk comparing and contrasting some of the blood donor deferral policies to deferrals for human cell, tissue and tissue products.

The basic take home there is that the behavioral deferrals for HCTPs are often less stringent than for blood, and she provided an overview of the rationale for that.

Basically, more reliable answers to the donor history questionnaire can be obtained if questions pertain to the recent past -- for instance, the past five years -- rather than since 1977. As many of you know, these are numbers that come into play when we are considering a deferral for MSM behavior.

This was also considered to address the problem when you are getting a history, not from the donor himself, but from the next of kin.

There is also limited availability of certain cells and tissues, and there is a particular need for HLA matched cells, for instance, the hematopoietic progenitor cells, and there is limited availability. There is a problem with size restriction for pediatric tissues, for instance, heart valves.

The differences in risk of viral transmission are due to more extensive processing of certain types of tissues that came into play, for instance, removal of blood and viable cells by extensive washing, use of isopropanol, hydrogen peroxide, radiation, and proprietary methods for viral clearance.

So, there are differences between the tissue arena and the blood arena, and they have different -- they play out difference.

Klas VanderPaul(?) from The Netherlands gave an update on current European policies for blood donor deferral.

To summarize what he presented, the European Blood Alliance decided not to change the present policy of permanent deferral of potential donors who had a history of MSM.

There were reasons for this deferral, which are summarized in their report. It should be publicly communicated, preferably in collaboration with MSM representative groups.

Fifteen out of 15 countries had permanent deferral of donors with sexual behavior which puts them at a high risk of acquiring severe infectious diseases, and also there is a need for further studies to assess the safety of low risk cohorts and presently excepted donors.

There were ethical issues involved in these considerations. In the case of four MSMs, I believe, brought suit against four blood banks.

The decisions were based on an equal treatment act which forbids discrimination offering goods or services, and the key is, the verdict is, there was no direct discrimination. The purpose of selection was to prevent virus infection, including HIV.

Homosexual men are disproportionately affected by the selection. So, there is indirect discrimination going on. However, it was objectively justified.

It was not disproportional given the interests of the recipients of blood. So, that gave an international comparison for our own policies.

Matthew McKenna from CDC then updated us on current prevalence and incidence of HIV. There are about

half a million MSM infected with HIV in the United States. There are about 250,000 to 300,000 injection drug users infected with HIV in the United States.

About three quarters are diagnosed in both groups. The incidence in MSM is approximately two to three percent per year in high risk and about one percent per year in the lower risk MSM groups.

The incidence in injection drug users is about half a person to a person per year, but it is declining. Also, you made a point that the overall population prevalence and incidence does impact the risk to the blood supply.

Ian Williams gave a summary on HBV and HCV and this is a slide he had on infection in selected U.S. populations. I lifted it from a talk.

These here are the various categories, and these color bar graphs here are for infection with HBV. Here you see, these are the prevalence in blood donors in general population.

HBV Is significantly much more highly prevalent in young injection drug users, older injection drug users, young MSM, older MSM, STD patients, and in prisoners.

Then, the HCV story, the colors didn't translate so well onto this computer, again, the general population and blood donors are fairly low, but the injection drug

users are really quite high, whereas MSM are fairly low, STD patients are still pretty low, and then prisoners are pretty high.

Ian Williams from the CDC gave a summary of the -- sorry, this is a continuation of Ian Williams' talk. He pointed out the incidence of acute HBV and HCV infection has declined in the past two decades, and the primary risk factors remain unchanged.

Transfusion, historically, was an important risk factor for infection, especially for HCV infection, but currently is extremely rare. When transmission has been observed, it has been due to window period donations and not testing errors.

Ed Murphy from UCSF gave a very nice summary talk on HTLV, and I think one of the things that really stands about HTLV compared to the other major viruses that we are worried about in transfusion is that there is considerable controversy over the sensitivity of the ELISA test for HTLV.

There is only one test for HTLV, and that is an ELISA. There is no NAT out there, for instance. Even a test that is similar to current licensed tests, with only getting about 99.5 percent sensitivity, we usually look for 99.9 percent sensitivity. That is what we are used to for HIV.

Bernie Poy(?), he cited some literature from a paper -- a paper from Bernie Poy suggested that for HTLV-2, which is similar in prevalence to HTLV-1, that a lot of the tests that are kicking around really have very poor sensitivity.

So, this is very relevant when we make models of changes in policy and how they might change the number of infectious HTLV units which get through.

If we compare HTLV-1, it is about .01 prevalence in current U.S. blood donors, but in certain groups, such as Japanese Americans, Caribbean, Central African ethnicity, it is about 10 or 100-fold more prevalent, and in commercial sex workers it is extremely high in comparison to the current U.S. blood donors, and also you see the same thing in STD clinics.

HTLV-2, which is about .02 percent in current U.S. blood donors in infectious drug users, it is .5 percent to 17 percent, according to the locale you do the test in. It is really quite disturbing. These are really very big numbers. Sexual partners of IDU is also an increased risk, and in certain Native American groups.

Finally, he summarized that HTLV-1 and 2 residual risk has not been estimated since 1996. It is probably still about one to two per million units, and he also pointed out that cold storage and leukoreduction probably

reduces risk, but the data is inferential.

We then had an update on HHV-8 from Sheila Dollard. To summarize what she said, about 2.3 percent -- this is in a prospective study in Uganda of HHV-8 seropositive blood units -- led to infection of the transfused patient.

However, the criteria for HHV-8 seropositive and seroconverted were very stringent. So, she believed that this estimate was probably low.

If you look at HIV positive MSM prospectively, they followed 50 MSM for two years, and patients had an average of six follow up patients, three to six months apart.

About 32 percent of patients, HIV positive MSMs, had detectable HHV-8 DNA in the blood for two or more visits, although the average viral load was fairly low.

The seroprevalence of HHV-8 in U.S. populations is listed in this table. The U.S. screened blood donors were about two to four percent.

In the general population you get a range of estimates varying from two to 10 percent, and it usually depends on what control population that study selects.

Injection drug users, heterosexual HIV, -6 to 11 percent, injection drug users, heterosexual HIV positive, 13 to 18 percent.

In men who have sex with men but who are not infected with HIV, the prevalence is estimated at about 12 to 16 percent. So, it becomes very important which of these numbers here you select to compare it to.

Now, MSM who are infected with HIV, the numbers are very high, 40 to 50 percent, and patients with CAPA C, it is greater than 95 percent.

Some of you will remember that in 2000 and previously in 1998 we brought quantitative models into this field trying to estimate the changes in infectious units that would be introduced into the blood supply as a function of changes in policy, particularly focusing on the deferral of MSM.

There were several factors that go into these models. One of them is testing error. If you change the policy, you get more MSM donors, you get more infected units in quarantine released.

How do they get out? Well, one of the ways they can get out is by testing error. Mike Bush has actually gone back with a re-testing strategy, identifying units to be re-tested by discordance. He identified candidate specimens to go back and re-test to see if a negative test now converts to a positive test, to summarize basically what he is doing.

Basically, he can determine a primary false

negative test error rate for the tests for -- let's see, this one here was, I think -- Mike is in the audience, and he doesn't want me to make a mistake -- the false negative error rate in serology is about .028 percent, and the NAT error is about .037 percent.

What happens is that, in all of these viruses where you have two of these tests, the probability of both of them failing at the same time for a virus for which you haver an ELISA and a NAT, the probability of having a test error on both of these is the product of these, and it turns out to be an extremely low number.

So, the test errors essentially drop out of the equation for HIV, HBV and HCV, because they each have two tests to pick them up.

HTLV, as I mentioned, only has the one ELISA test, and that has a rather poor sensitivity. So, there is no redundance protection for HTLV.

Mike also presented data showing that the odds ratio of having a positive screening test in the blood environment for MSM behavior within 12 months or 12 months to five years is either 2.9 or 4.3, suggesting that there is still risk in these behavior categories.

For MSMs who had abstained for more than five years, they basically had an odds ratio of one, suggesting that there may be something identifiable about a five-year

abstention that identifies a safe subset.

Now, there are caveats to that, and there are also possible biases in studies like that. It is definitely something that is on our radar screen.

One of the things we did to reevaluate the models was to address the issue that came up in 2000 and also before, that we identified as quarantine release errors were a very big worry for us.

Again, if you change a deferral policy of the increased number of a high risk subgroup presenting to the blood bank and donating blood, you get increased amounts of infectious blood in quarantine.

How does it get out? It can also get out, not by test error, which we have now seen are mostly small, but by quarantine release errors.

We actually measured them. Sharon Callahan pulled out information from the biological products deviation reports on the erroneous release in the whole blood industry of either confirmed positive units, of which there were only two in three years, and repeat reactive units, of which there are a couple of dozen over three years.

The Red Cross provided us with prevalence information in their quarantine during that time period, saying how many repeat reactives they actually had in quarantine.

We were able to actually put those two numbers together to estimate a quarantine release error rate. Using confirmed positives and repeat reactives, we get these results, .4 to .5 per 10,000 from blood centers.

Hospitals are about 17 times higher than that in their error release, and we had seen this before in previous data, with about seven out of 10,000.

We put this together with expected changes in infectious units entering with the changes in policy, and compared it to concurrent residual risk using two types of data.

One was the biological product deviation report data which I just described. The other was using some older New York State data, which we had relied on when we last examined this in 2000.

These numbers are in percentages of current residual risk, and these are the policies. So, if we switched to a one-year deferral policy, we would predict, with the biological products deviation report, that we would have an additional 1.7 percent of current residual risk from HIV and a very small number for HBV.

If we looked at the New York data, it would be rather significant, 25 percent. So, basically, for both of the MSM deferral policies, we had fairly small increases in residual risk, which were not that different predictive

changes in risk, which were not that different from changes in the population, the blood donor population, you would get.

For IDU, for injection drug use, when we modeled it, the numbers, even with the biological product deviation report numbers, are fairly problematic, particularly for HCV, which could add an additional 40 percent to the current residual risk. HTLV, of course, this is a percentage. So, it is off the map.

One of the other things that this committee had asked us to do was to come back with uncertainty limits on these calculations, and Steve Anderson did that.

I have just given you an indication of some of his data. These are not in percentages. These are the actual -- the current residual risk is here, and you see you basically get the same answer. This is with the New York State data.

So, you have a couple of percent for HIV with a five year policy, and the error bars are reasonable. It may be up to five out of 12 residual risk.

So, again, the New York State data is still worrisome, even when you put error bars on it, and this is the one year, and you get similar results for HBV.

Roger Dodd made a commentary that emerging infectious diseases do not appear to have overall common

characteristics with the suspected class of organism route or pathogenesis.

So, consequently, they cannot be considered as a homogeneous group. All transfusion transmitted infections must necessarily have a blood borne phase. This doesn't mean that they are going to be transmissible by sexual or low volume non-parenteral routes.

Consequently, risk behaviors associated with such transmission routes are not common to all transfusion transmitted infections.

Selso Bianco addressed some alternative testing strategies that might be included, including pre-testing. He pointed out that additional measures, if implemented, must apply to all donors, not just testing high risk donors, for instance, that are identified on the questionnaire.

Measures restricted to at risk donors would not resolve issues of discrimination. Rapid HIV tests used for pre-testing are not compatible with current good manufacturing requirements for collection facilities licensed by FDA.

Pre-testing of first time donors would have a severe impact on blood availability.

Substantial operational improvements in the past few years have reduced risk of inappropriate release of

marker positive components, and that would be consistent with our quantitative parameters.

Based on parameters used in a model that is somewhat different from ours, he suggested a change in referral criteria for MSM from indefinite to one year could increase the risk of HIV by one in 46 million, or one case each 32.8 years.

Finally, we had a presentation on the difficulties of designing a questionnaire and making questionnaires work from Kristin Miller.

Basically, the key points, the factors impacting response accuracy or stigmatizing behaviors, that is the motivation of the donor, the literacy of the donor, how difficult the questionnaire and how long, there are time frame and memory problems, and donor knowledge and understanding of risk. I will stop there. Thank you.

DR. ALLEN: Thank you, Dr. Dayton. Could you give a brief 30 second summary of what the FDA intends to do with this information and what the next steps are.

DR. DAYTON: I think there was a consensus that we want to get all the modelers together and hammer out the last of the differences.

I think we want to vette the models that way, and then I think obviously we would consider bringing it back before this committee to decide what to do.

DR.ALLEN: Thank you. I am going to call on Dr. Steve Kleinman to make a very brief perspective statement on behalf of the American Association of Blood Banks. Steve, are you representing other organizations also?

DR. KLEINMAN: It is a joint statement with the Red Cross.

DR. ALLEN: Would you just introduce all of that, introduce yourself and any conflict of interest?

DR. KLEINMAN: Good morning, everyone. I am Dr. Steve Kleinman. I am senior medical advisor to AABB. I have a statement today that represents the views of AABB, America's Blood Centers, and American Red Cross on one of the issues addressed in the workshop.

I just wanted to make two introductory comments. The first was to compliment FDA on I think what was a very informative and well constructed workshop. We got a lot of data out, and I think that was the intent.

The second comment is that the statement which was prepared prior to the workshop -- I talked to several people afterwards and it hasn't changed the mind of the blood banking organizations. We still have the same position that we had before the workshop.

So, with those caveats, or those additional clarifications, let me read the statement.

AABB, America's Blood Centers and American Red Cross thank the FDA for the opportunity to speak at today's meeting.

AABB, ABC and ARC commend the FDA for holding a workshop to review the issues associated with the deferral of prospective blood donors on the basis of an elicited history of behavioral risk.

In the context of that workshop, we would like to comment on the deferral criteria for men who have previously had sex with men.

On September 14, 2000, the AABB spoke before the Blood Products Advisory Committee, making the following recommendation:

Since 1997, the AABB has advocated that the deferral period for male to male sex be changed to 12 months.

Modifying the deferral time period for MSM contact to 12 months will make that deferral period consistent with the deferral period for other potentially high risk sexual exposures, and will improve the clarity and consistency of donor screening questions.

The potential donor will be directed to focus on recent, rather that remote, risk behaviors, and should have better recall for answers to the screening questions.

This recommendation was not accepted, largely on

the grounds that any relaxation in the criteria would increase the number of HIV seropositive individuals presenting to give blood, and thereby increase risk to recipients because of false negative laboratory screening or inadvertent release of infectious units.

We now have evidence to show that the vast majority of donors with prevalent infections will be positive by both antibody tests and NAT, thus assuring redundancy in laboratory testing.

AABB, ABC and ARC believe that the current life time deferral for MSM is medically and scientifically unwarranted, and recommend that deferral criteria be modified and made comparable with criteria for other groups at increased risk for sexual transmission of transfusion transmitted infections.

Presenting blood donors judged to be at risk of exposure via heterosexual routes are deferred for one year, while men who have had sex with another man even once since 1977 are currently permanently deferred.

Currently duplicate testing using NAT and serological methods allow detection of HIV infected donors between 10 and 21 days after exposure.

Beyond this window period, there is no valid scientific reason to differentiate between individuals infected a few months or many years previously.

The FDA sanctioned uniform donor history questionnaire was developed, recognizing the importance of stimulating the recall of recent events to maximize the identification of donors at risk for incident, that is, recent infections.

From the perspective of eliciting an appropriate risk history for exposure to HIV and other sexually transmitted infections, the critical period is three weeks immediately preceding donation, since false negative NAT and serology reflect these window period infections.

The length of these window periods provide the scientific basis for the deferral periods imposed for at risk sexual behaviors.

It does not appear rational to broadly differentiate sexual transmission via male to male sexual activity from that via heterosexual activity on scientific grounds. Neither does it seem reasonable to extend this reasoning to other infectious agents.

To many, this differentiation is unfair and discriminatory, resulting in negative attitudes to blood donor eligibility criteria, blood collection facilities and, in some cases, to cancellation of blood drives.

We think the FDA should consider that the continued requirement for a deferral standard seen as scientifically marginal and unfair or discriminatory by

individuals with the identified characteristic may motivate them to actively ignore the prohibition and provide blood collection facilities with less accurate information.

AABB, ABC and ARC acknowledge the concern that relaxation of deferral criteria may increase the number of presenting donors who are marker positive.

However, this impact has not been measured directly. It has only been modeled using what may be incomplete or at least invalidated assumptions.

The blood collectors are willing to assist in collecting data regarding the actual impact of changes in the deferral in order to allow for informed decision making and/or for the development of additional appropriate interventions to ameliorate the impact.

In summary, AABB, ABC and ARC believe that the deferral period for men who have had sex with other men should be modified to be consistent with deferrals for those judged to be at risk of infection via heterosexual routes.

We believe that this consideration should also be extended to donors of human cells, tissues and cellular and tissue based products. Thank you for the opportunity to comment.

DR. ALLEN: Thank you. I will just comment briefly that this two-day workshop was shoe horned into

about nine hours yesterday. It could have gone much longer.

There are a lot of important issues here that the FDA and the blood collection agencies now need to wrestle with and I think we will be hearing a lot more about this.

I would like to ask the committee just to limit their comments and questions to clarifying points, and other very important statements.

DR.KLEIN: I would like to clarify one point for the record, because either I heard wrong or you heard wrong, and that is that the quarantine will release errors.

First, the New York State data are very old, and the difference between those data and the deviation reports probably refer to the fact that information systems that now are in every blood center in the country were not in place when the New York State data were collected.

The second point is that the errors, there were two errors from the blood product deviation reports that were called quarantine release errors.

One of those was, in fact, a testing error, as I understand it, not a quarantine release error, and the second one was a recovered plasma for fractionation that was released, not a blood component that was released into the transfusion service. I think that is correct. If not, please clarify it.

PARTICIPANT: That is correct, but for the confirmed positive analysis, we only had those two specimens, but we looked at the repeat reactives in a separate analysis, which numbered about two dozen releases, and got almost identical results. So, we have confidence in those results.

In fact, it was suggested that we should enlarge what we are looking at, and we made some quick calculations yesterday afternoon looking at the total number of erroneous releases reported in that three-year period and dividing it by the number of donations. If you do that, the numbers might go down even more.

We agree that the New York State data is kind of old and it probably is. That is why we kept the two analyses separate. It probably does reflect a change, an improvement in inventory management since then.

DR. ALLEN: Other comments or questions?

DR. FINNEGAN: What is the deferral for the intravenous drug users? Certainly the HCV causing requirement for increased liver transplants would certainly be a significant health burden on the community. What is the deferral for those people?

PARTICIPANT: Injection drug use is forever, lifetime deferral.

DR. ALLEN: Okay, thank you all very much. We

will hear much more of this, and I think pulling together other strains from the past, such as the uniform donor history, data from the uniform donor history questionnaire and so on will fit into this.

We will now move into topic I, which is rapid test for detection of bacterial contamination of platelets. Introduction and background of this topic will be by Dr. Vostal.

Agenda Item: Rapid Test for Detection of Bacterial Contamination of Platelets. Introduction and Background.

DR. VOSTAL: Good morning. Today we are going to talk about bacterial detection in platelets. What we are going to outline for you is our plan to move from the first generation of bacterial detection devices to the second generation.

So, I would like to start off by discussing how we regulate bacterial detection devices. We do this by basing this on the intended use of the device.

We recognize two uses. The first one would be quality control indications, and this is for sampling a small number of collected products to ensure that the collection process is in control. This can be as few as four per month, or it can be actually 100 percent quality control.

The key issue for this indication is that you don't have to wait for the results of the test to transfuse the product.

The second indication is a product release indication, and this includes screening of all products prior to release for transfusion.

Here, the decision to transfuse depends on the results. Once tested, the products can be labeled as tested negative for bacteria by the specific method.

For these two indications, we have different criteria in terms of how we evaluate these. For quality control, our clearance is based on in vitro testing.

The device is tested on platelet products that are intentionally contaminated with variable levels of bacteria, which is commonly referred to as a spiking study.

These types of studies identify the analytical sensitivity for particular bacterial species, the adequate sampling times, the sample volumes and the hold period for that device.

There are, however, limitations to this approach. We don't have the clinical sensitivity, specificity and predictive value, and these types of parameters will need to be defined by a field trial.

The criteria for release of platelet products is more stringent. The intended use is to assure, with a

defined confidence, that the release products are not contaminated.

That is, if bacteria are present, they would be below a certain level defined by the sensitivity of the device, and then the frequency of contamination is predictably low. That means that we will know the frequency of false negatives for this particular device.

These types of studies will require field or clinical trials to establish the false negative and the false positive rate under actual clinical use.

So, those are our criteria. Let me just take you through how we have regulated this in the past. We started back in 2001, when we approved two culture based bacterial detection devices, and these were cleared for quality control indication.

They were the Pall EBDS and the bioMerieux bacti-alert. Three years later, in 2004, we cleared a third system for quality control, and this was the scan system by Hemasystems.

All during this time we were encouraging these companies to go ahead and apply for a release indication. However, this did not come about, and we had a number of discussions, even including a BPAC presentation in 2003, how the validation for release test should be conducted.

What we presented in 2003 was a field trial to

validate the performance of a bacterial detection device on clinical products.

Unfortunately, due to the low contamination rate in these products, the study would have required 50,000 products.

The large size of the study was a major hurdle for the companies, and this study was never conducted. Therefore, the progress toward the release test, the way we envisioned it, stalled, and the future didn't look so bright.

However, there were a lot of people still interested in a release test for bacterial contamination. A major breakthrough happened in 2004, when the AABB bacterial detection standard went into effect, and the quality control data was being collected across the country.

We worked together with the AABB and the CDC in the bacterial contamination working group, and we finally, in 2004, outlined a new pathway to obtain a release test indication that utilized the available QC data collected under the AABB standard.

After we outlined this pathway, Gambro followed the pathway to obtain clearance for seven day platelets when their system was used with the Bacti-alert by bioMerieux. Soon after, Baxter followed the same pathway

and they also obtained clearance for seven-day platelets.

In 2005, we were finally capable of obtaining a released test indication. However, this indication does not attach the device that is attached to these blood collection systems.

In 2005, we also cleared a pre-storage cooling bag to pool and store platelets up to five days and, when these are tested with a culture based bacterial detection device -- this is for a QC indication -- and the device is the PALL EBDS.

Also, in 2005, we cleared a culture based device for QC of pooled platelets, and this was the bacti-alert by bioMerieux.

So, the current approach to validation of our release test for a bacterial detection device is to obtain data on performance of an FDA cleared device when it is used to meet the AABB bacterial detection standard.

The standard has been in existence since 2004. The initial application by Gambro included over 400,000 samples tested with the bacti-alert device.

We would accept this data as the basis for approval of seven-day platelets, provided there is a commitment by the company to perform a post-marketing study.

The post-marketing study would consist of an

additional culture on outdated products, on day seven, to confirm the day one negative culture readings.

The goal of this study would be to demonstrate a point estimate of risk at day seven to be one per 10,000, with a 95 percent upper confidence limit that the risk is lower than one per 5,000. Again, because of the low contamination rate, the study size still has to be 50,000 products.

Here is a graphic representation of what this study looks like. So, a unit would be tested with a bacterial detection device.

If it is a positive result, the test would be repeated then to determine if it is a true positive or a false positive, and this is the data that makes up the QC data set that we would be looking for.

If the initial test is negative, those platelet products are put into clinical use, and they can be used up to seven days.

Those that out date are again tested with the device to determine if it was a true negative or a false negative, and this is the post-market data that we were looking for.

I am pleased to say that this study is actually on its way already, and we are starting to collect this kind of data.

So, that is where we are. Now I am going to start outlining what we think would be appropriate for the rapid bacterial detection devices, for them to get cleared for a specific indication of bacterial detection.

This slide compares or outlines the advantages or disadvantages of culture based bacterial detection devices. These are the ones that are used for units shortly after collection.

The advantage that they have is, they have high sensitivity, and the current range is one to 10 CFUs per ml. Another advantage is that we have an extensive data base, based on their performance, in the QC applications.

However, they do have some disadvantages. They have a long turn around time, up to 24 hours after being inoculated. They take a large volume of samples, four to 16 ml, they have a high up front cost due to the hardware, to the incubators and detectors, and there is only one major manufacturer that is out there, which could lead to a problem if there is an issue that develops with that particular manufacturer.

Now, these are the characteristics of a rapid bacterial device. This would be a test for contaminated platelet units at the time of issue.

The potential advantages are rapid turn around time, which would be somewhere on the order of minutes to

hours, small sample volumes of less than one to two ml, and we anticipate that these would be a lot less expensive.

There are, however, potential disadvantages. They have lower sensitivity when compared to culture based systems, due to the lower volume sampling, and alternate technologies.

For example, a single determination per sample of these rapid bacterial detection devices goes up against continuous reading of culture bottles for length of the product storage, which is true for the bacti-alert by bioMerieux.

So, we propose that these rapid bacterial detection devices would come to us as 510(k) application, with the currently marketed culture based devices as predicate devices.

We anticipate that they would come in for the same types of indications as for quality control. Again, this determines whether the collection process is not introducing bacteria to the products. It would also be a release test which would determine that the platelet product is not contaminated.

However, for rapid bacterial detection devices, we also envision an additional indication, and this would be an adjunct to a bacterial release test.

This would be a test performed at point of issue

in addition to a release test performed early in the platelet storage.

So, the platelet product would be tested with a culture based device early in the storage, maybe even in the first 24 hours, and then tested again with one of these rapid detection devices, either at the time of release or at the point of transfusion.

The current predicates for this would be the Gambro or the Baxter seven day aphoresis platelet collection systems.

So, the big problem we have is how to determine whether the new or rapid bacterial detection devices are going to be substantially equivalent to the currently marketed devices.

The major problem that we are dealing with is the sensitivity of the devices. Now, this slide sort of summarizes some of the issues that go on in determining or in designing bacterial detection devices for platelet products.

This is a platelet product bad that contaminated at the time of collection. Usually at the time of collection, the contaminations can be very low, maybe a few bacteria for the whole bag.

These bacteria then proliferate during the storage of the product, and it can reach very high levels

by day three, four or even day seven.

Now, the issue for detecting is sampling as early as possible as is done with the culture based devices. Here the issue is sample error.

If you sample the wrong two or three ml of the product that don't have any bacteria, you may not collect any bacteria in your device.

If you are lucky enough and you get one of the bacteria in the device, this can then proliferate and amplify the signal. So, the unit can be detected as contaminated.

So, the big difference between the culture based device and current rapid bacterial detection devices is the amount of volume that they take.

These take up to four to 20 ml, if you use one than one bottle. These use one to two ml. So, already you have a 10-fold decrease in sensitivity.

In order to compensate for this, we think it would be possible if you could test at different points, hoping that you would be able to capture more of the bacteria at the time that you test.

So, we are referring to this as a kinetic analytical testing, or we would like to see the time when the sampling of this bag produces a signal that could be compared to a signal generated by a culture based device.

There are additional issues to consider when you are looking for bacteria and platelet products. There are fast growing bacteria and slow growing bacteria that could be present at contamination.

The fast growing bacteria, usually represented by the gram negatives, are capable of growing up within the first 24 to 48 hours to very high levels.

There are, however, slow growing bacteria, like staph epidermidis, which make take three or four days to generate significant levels.

So, if you are trying to detect bacteria with the culture based device, you have to consider the appropriate timing.

If you sample too early, you may be able to detect rapid growing bacteria, but you will probably miss the slow growers.

So, you have to optimize your sampling times somewhere in between these two points to be able to have a good chance of capturing the slow growing bacteria.

Now, this problem is also amplified when you talk about the rapid test device. Again, you might have to delay your testing for the rapid test device by a day or so to be able to capture the fast growing bacteria, but this might have to be delayed even further to be able to deal with the slow growers.

So, we gave it a lot of thought and we were trying to figure out how to decide what would be an appropriate clinical trial or field trial to evaluate the performance of a culture based device versus a rapid test device.

We went back to a similar design that we used for the field trial for the seven-day platelets. What we think would be appropriate is if the units that are currently tested with culture based devices on day one, if this unit is termed to be positive, this unit could then be repeat tested, again with a culture based device, to determine if it is a true positive.

Then we think it could be tested again with a rapid device, either at this point right here or on subsequent days, to find out at what point in time the rapid test device would be able to determine that unit as positive.

That way we would be able to find out the appropriate testing strategy that would make this device equivalent to the culture based device.

If that unit test is declared negative, then it could then be put into clinical use, and then tested again by both devices at the point of release or at out date.

So, here is a summary of the proposed regulatory pathway for rapid bacterial detection devices. So, we

envision these devices coming in as a 510(k) application based on the intended use of the device.

For a quality control indication, we would look for definition of analytical sensitivity by spiking studies, and this would be the same list of bacteria as is used to validate the predicate devices.

We would also try to establish equivalence to marketed culture based devices by a time sampling study on spiked platelet units. Again, the same list of bacteria species would be used in this type of kinetic study.

For an adjunct to a release test, we would encourage the companies to obtain clearance for a QC indication, with a commitment to do a post-market field trial with a time sampling study.

Here we would be looking for a repeat sampling of clinical units declared positive by a culture based device to determine when the rapid detection device also identifies the unit as positive.

We would be looking for a test of at least 60 units to provide 95 percent confidence, that the device can detect 95 percent of the contaminated units.

Finally, for release test indication, we would encourage the companies to get a QC indication as before, develop a standard operating procedure that defined an appropriate sampling strategy which assures substantial

equivalence to a marketed bacterial detection device, and then establish an extensive data set for QC performance, as was done for the culture based devices, and this would most likely involve hundreds of thousands of samples.

Then, commit to a postmarket study on 50,000 units that will be re-tested at our date to determine whether there were any false negatives during testing.

So, that is our current plan. What we would like to do is get the committee's input on three questions. The first question would be, is the proposed three-tier regulatory scheme for clearance of rapid bacterial detection tests acceptable.

The tiers, as I was just describing, are clearance for quality control, adjunct release test indication, and a release test indication.

The second question would be, what would be the minimum sensitivity in CFUs per ml for detection of a contamination platelet unit.

Finally, the third question would be, is the kinetic comparison -- that is, the time sampling and spiking study -- an appropriate design of an equivalency demonstration between a culture based and rapid test devices. Thank you.

DR. ALLEN: Thank you for the summary. I have got a couple of questions, just to start things off, and this

relates to the question about sensitivity.

Is there clinical information, if a patient receives a platelet product that has 10^3 or 1,000 bacteria per ml, 10,000, 100,000, what are the clinical implications of that?

I know that that depends on the patient's underlying condition as well as the type of bacteria. Certainly there is no question, when you get to the higher levels, there is a very significant and immediate impact.

At least a healthy person, who is not likely to receive platelets, can handle a fair number of bacteria fairly easily. What are the clinical implications, and how does that relate then to the sensitivity?

DR. VOSTAL: We are actually very fortunate to have Dr. Yamtovian here today, and she is going to present her data on particularly that question. So, she has levels of CFUs compared to outcomes of transfusion reactions.

DR. ALLEN: Okay. Using a culture based system, if you look at all of the units that are tested on a culture based system, they are negative on a 24-hour sample.

If there is a subsequent sample taken at, say, three to five days, what percentage of the subsequent samples are positive that were negative when tested at 24 hours.

DR. VOSTAL: So, you would be looking for the false negative rate.

DR. ALLEN: Right.

DR. VOSTAL: We don't know that data yet. That is why we have this ongoing postmarket study that was initiated by Gambro, and now also Baxter is going to join into that.

They are conducting a study where they test the platelets at out date, at day seven, to see if that initial negative reading was correct or not. That data will be coming in the next couple of years.

DR. ALLEN: I have got just one other follow up question. Of the percent that are -- when you take that 24-hour sample and you read it at 24 hours and it is negative, what percentage of those, if you read it out at 48 hours, would have turned positive because of the slow growing organisms that didn't give a positive test at 24 hours.

DR. VOSTAL: You mean if you delayed testing --

DR. ALLEN: No, you do your sample, but you read it at 24 hours and it is negative, but you go ahead and hold the test for another 24 hours.

Maybe that is not appropriate using these culture systems. I don't know. In other words, if there is a slow growing organism that doesn't show up as being positive at 24 hours, but it would if you held it for longer, do you

have any -- does the FDA have information on that.

DR. VOSTAL: So, you mean if you hold the bottle for the duration of the product storage, like you hold the bottle in the incubator seven days?

DR. ALLEN: Even if you took it out in two or three days.

DR. VOSTAL: I am not aware of data like that, but I suspect, because the slow growers take a long time to proliferate, that you are going to run into a sampling error up front, where you don't get enough into your device and you won't be able to detect them. So, we will miss some of the slow growers.

DR. KLEIN: Again, just as a point of clarification, I know that we struggled with the culture system, and many people on this committee are not familiar with it.

That is, rapid tests are a fundamentally different technology. The two problems with the culture system are as you stated, if you wanted to put up that testing slide again, that you might miss the bacteria when you first culture it.

Second, when it turns positive, even though you are continually monitoring the culture system, the platelets may already have been released and transfused before you get the result back.

The fundamental difference in the rapid test is that it is done at the time of release. Now, this is an important point because there are two times of release.

One might be when it is released from the blood center. The other, and the one that I am most concerned about, being a hospital based physician, is the time that it is released to the patient.

At that point in time, you would expect as many bacteria as possible to be there, and that is the time when we would like to see a release test, especially a rapid one, go into effect.

It is certainly possible, in fact it is probable, that the one mistake you miss with the culture system stochastically, at 18 or 24 hours, which will never culture positive because you never got a bug in there, would in fact be positive with a rapid test if you issue them at five days or seven days and test at that point in time. I think that is correct, is it not?

DR. VOSTAL: That is correct.

DR. KUEHNERT: Could you go back to your slide with your bugs in the bag? Great. What I am wondering, and if it is not clear we can go back during the discussion on this, but where you are comparing your test -- this follows Dr. Klein's comments about wouldn't you get the test results -- so, are you comparing our rapid test result at

the time of inoculation of the bottle, or are you comparing it at the time the test actually turns positive?

It would seem that, when you would want to compare, like you inoculate, say, at day one, and then the test turns positive at day five, it would seem appropriate to then compare the rapid detection device performance at day five. Do you see what I am saying?

DR. VOSTAL: Yes, I understand what you are saying, but what may happen is, you sample here with a culture based device and it is growing and it is taking its time to grow into a positive signal, but all this time bacteria are also growing in the bag.

So, if you have to wait until day three, you could have transfused this product over here that had a certain level of contamination.

I think it is open to discussion, but right now we are looking at comparison, when did you detect this unit as positive with this device, and the unit came positive at day three with this device. What we are looking for is if those devices can actually detect a positive unit.

DR. KUEHNERT: You are thinking of it from, I guess, a technical performance perspective. I am thinking of it from a practical use perspective.

It doesn't matter that the culture based device is going to pick it up some day. It matters what the result

is right then and there, and that is the benefit of the rapid test. Maybe we can discuss it in more detail later, but it is a point I wanted to bring up now.

DR. EPSTEIN: One clarification on the slide. For the approved systems, we don't actually sample the platelet bag on what is called day zero.

Jaro is calling it day zero because it is day zero of sampling, but that is actually after at least 24 hours of incubation of the platelet at room temperature.

That is precisely to mitigate the problem of sampling, the theory being that organisms will be growing in the platelet container during the first day of storage. So, it is really day zero of sampling is day one of storage.

Secondly, I agree with you completely. The comparison that we are interested in is the rate of detection at each possible day of release.

So, what we are really asking is, how often will the rapid test be positive on day two of storage -- here it is called day one of sampling -- compared to whether the culture on day one has already turned positive, and then likewise for each day.

That is why the kinetics matter. The understanding here is that the more sensitive test is likely to come up sooner than the less sensitive test.

Where is the cut point?

Sort of fast forwarding the whole discussion, it might be in the end, when we have the data, that we would say you can use the rapid test, but only after day three or after day four. It actually depends what the kinetics actually are.

DR. KUEHNERT: You are comparing when the culture based device turns positive with when the rapid test device turns positive.

DR. EPSTEIN: That is correct. That is what counts on day of issue. What we want to know on day of issue is, has the culture turned positive or, alternatively, would the rapid test be positive. So, each comparison is referable to a day of issue.

DR. ALLEN: For clarification, I am going to call on the committee members first. Dr. Katz?

DR. KATZ: Every center that is collecting platelets probably has a slightly different number, but we culture 24 hours after collection, and now we are almost two years into our experience.

About 20 percent of our positive cultures occur after we sent the unit out, and about half of those have been transfused by the time we have a positive result, and everybody is going to have slightly different numbers, but it is in that ball park in terms of a continuously

monitoring device.

Now, I understand that the EBDA is a one-time read. So, you don't have that problem or advantage. I guess it depends on how you look at it.

Of the late ones that have already been transfused, we have not seen a clinical transfusion reaction. So, there are relatively low numbers of bugs at low virulence in most of these circumstances, but not all.

I want to just reiterate what Harvey says. I am not too smart. I want to prevent bad outcomes. I am not so interested in kinetics as whether or not we can prevent bad outcomes with a rapid test.

I am going to plead for a regulatory approach that will allow us to use a system at point of release, at the transfusion service, that will prevent bad outcomes.

DR. ALLEN: That certainly has its own implications because that is not in the blood collection centers. It is in the hospitals where the blood is being used.

DR. CRYER: To help me figure out how to think about this, I have a couple of questions. What percentage of the platelets are not transfused by seven days? How big is that pool?

DR. VOSTAL: I don't have data on that. I think maybe some of the blood centers might be able to comment.

DR. CRYER: Then the other one is, what is the incidence of contaminated units out there? How big a problem is it?

DR. VOSTAL: So, the contamination rate is thought to be somewhere between one per 2,000 to one per 5,000.

DR. KATZ: We out date five percent of our aphoresis platelets in our system.

DR. QUINN: This has to get back to what tests you are comparing. While we might be looking at some tests, or you may be looking at the results of some tests that have lower sensitivity, there is the alternative that you will have tests with higher sensitivity than culture based systems, and I am referring to the generic 16S ribosomal RNA bacterial genes that could be detected by PCR.

This can be done, we have screened endocarditis patients by this method, picking them up in emergency rooms and getting them on antibiotics immediately before culture results come back.

We screen viruses in blood transfusion products, as the previous speaker had just gone on, the HIV, hepatitis B, C, and so forth.

You know, in your studies, as you design these for evaluation of assays, are you thinking as well that down the line manufacturers will be coming to you with

rapid based NAT tests, nucleic amplified tests, for bacteria in these products, in which case, is this design going to be appropriate for them as well? You always set up the predicate, is this going to fit as well, does the shoe fit all sizes.

DR. VOSTAL: We would not have a problem if the devices were more sensitive than the current devices. So, we have a standard of safety that is established by the culture based devices, and we have a sensitivity in the one to 10 CFUs per ml.

If there is an equivalent sensitivity device, you know, we would be able to just compare them head to head, same level of sampling, same timing of sampling, and see if they are equivalent.

The problem we have with these devices is they have a lot lower sensitivity. We are trying to figure out a way to compensate for that by waiting a little bit longer, until the bacteria in the bag proliferate to high enough levels, so these devices have a chance of detecting them.

DR. SZYMANSKI: I agree very much with Dr. Quinn. I hope that those types of tests would be coming. My question was to the different sensitivity of the culture based tests and rapid tests. Are there any rapid tests that have a higher sensitivity on the market or in use?

DR. VOSTAL: A higher sensitivity than we currently have?

DR. SZYMANSKI: Yes, is somebody doing that.

DR. VOSTAL: We are going to hear from the manufacturers today about their specific devices, and they will tell us what the sensitivity is.

DR. ALLEN: Yes, that comes in the open hearing right after this session.

DR. KUEHNERT: When you are comparing to the culture based device, are you comparing it to manufacturer's instructions for use or the prevalent current use by blood centers?

DR. VOSTAL: We are comparing it by manufacturer's use, what they were approved for.

DR. KUEHNERT: So, it would be an aerobic and anaerobic bottle that you would be comparing it to?

DR. VOSTAL: Right, that would be for a seven day platelet product, a seven day release test. That would be comparison to aerobic and anaerobic. For QC, aerobic is sufficient.

DR. CRYER: One last question. Is there a clinical difference in the effect of a platelet contaminated with the fast growing bacteria compared to the slow growing bacteria?

DR. VOSTAL: A clinical difference?

DR. CRYER: The effect on a patient.

DR. VOSTAL: I think Dr. Kuehnert can comment on it, from his Bacon study. He demonstrated that the gram negative is a lot more likely to kill patients than gram positive.

DR. CRYER: There are two issues to consider here. One is, what is the effect of the bacteria itself. The other is, what is the effect of dead bacterial cellular products, endotoxin and so on. Both of them can have a clinical effect and may be quite different.

DR. BALLOW: That just triggered another question in my mind, not only the effect on the patient, but what about the effect on the platelets. Those studies must have been done.

If you get a certain amount of contamination of bacteria in the platelet bag, what effect that has to do on the platelet function, has that been looked at?

DR. VOSTAL; What happens is, if you have very high bacterial proliferation in the bag, if you utilize available glucose, the pH tends to go down in the platelet products.

When pH goes down, the platelets don't perform very well. You can start to see changes in the platelet morphology. They go from the discoid to the round stage, and they can start to lose their shimmering capacity.

DR. BALLOW: That must occur with very high bacterial contamination. Is there a certain threshold?

DR. VOSTAL: I am not aware of a threshold.

DR. BALLOW: In other words, is it 100 colony forming units, 10 colony forming units, 1,000?

DR. VOSTAL: One way of looking at that would be, people have used pH levels as a measure of contamination. I think their sensitivity is 10^6, 10^7. So, when the pH starts to drop, that is probably with that level of bacteria.

DR. FINNEGAN: I am going to ask a funky question. Has the FDA ever thought of looking at this from the 30,000 foot level in view of disaster preparedness?

That is, that in fact healthy people do need platelets when they manage to drive their Suburban off a cliff or something, but they can tolerate a reasonable dose of a contaminant.

So, have you thought of coding these as level one for the cancer patient who can't tolerate any infection, and level two for, if we have a disaster, where you could in fact tolerate a low level of contaminant?

DR. VOSTAL: Right now the FDA does not have a requirement for bacterial testing. All this testing that is being done is under the AABB standards requirements.

DR. KLEINMAN: I just wanted to make a comment about the clinical studies that might need to be done. I

know this is going to be talked about further in the program.

It seems to me, for analytic spiking studies, the comparisons can be laid out quite nicely. For clinical studies, I think the problem may be that right now we get a certain set of results from cultures that are confirmed positive, and that is because, how do we make the definition confirm positive.

The product is still available and we are able to culture it again. Then we get a certain set of results that are called indeterminant, and that definition is, we got an initial positive culture. The product is no longer available, it has been transfused. That is why we can't confirm it.

Then we get a set of results that we term false positive, product that we get an initial positive, the product is still available, we culture it, we can't repeat the culture.

So, I think there may be problems in your design because the indeterminant products are gone. They are transfused into patients.

So, you don't know how to evaluate a finding on that kind of a product. If the culture comes up and if the product is gone, you can't do a rapid test on it, because it has already been transfused.

I think by definition you are really needing to evaluate products, and that is proportionate to time. So, in general, if the cultures come up after 24 hours, in general that product has been transfused. In many cases it has been transfused.

So, I think you have to factor that in some way as you think about the clinical studies. I am not sure how you do it.

DR. VOSTAL: I think that is a very good point. This is a design that we came up with to try to demonstrate clinical products, but we are open to suggestions if the company or the committee can come up with an alternate design.

MR. BRECKER: Mark Brecker, University of North Carolina. Just a point of clarification to your question, Dr. Allen, about preliminary data on the predictive value of the culture tests, there are some data.

A study from Gail Rock in Canada, looking at random platelets from whole blood, 12,000 random platelets tested with the original configuration of the Pall BDS, picked up three after at least a 24 hour hold. Then they were sampled.

Then they were recultured at the time when they were pooled into pools for transfusion and tested on an agar plate.

They found one that they had missed with the initial configuration of the Pall BDS, which only had a sensitivity of about 100 to 500 CFUs per ml. So, that was relatively poor. So, one in 12,000 using that system.

In this country, in my lab at the University of North Carolina, we screened 2,400 aphoresis platelets, interdicted three that were contaminated, and recultured them at the time when they were issued or when they out dated, and found that none were missed, with a preliminary bacti-alert culture. We did use two bottles, aerobic and anaerobic.

DR. ALLEN: Than you very much. That is helpful information to have. Other questions or comments for Dr. Vostal at this point?

PARTICIPANT: I would just focus the committee, because it is of great interest. Virtually everything we have been talking about is single donor aphoresis platelets, that virtually 100 percent being produced in this country now are being screened with one of the three licensed system, and actually with one of the two culture based systems primarily.

Probably 25 percent, 30 percent, of the platelet doses or platelets from whole blood -- Roz or Mark, is that right? There is still substantial use of platelets from whole blood in pools that are being tested with things like

dip sticks and pH meters.

I personally look at one of these rapid tests available, particularly at point of pooling and release, as an opportunity to prevent what is happening from those pools, and it is not really addressed, I don't think, in the questions and we need to think about it.

DR. ALLEN: Good point. It is almost 10:30.We are running behind. We move now to the open public hearing. I have got five speakers from industry.

I will just run through the names quickly: Dan Erickson from SUBC Inc, Nancy Hornbaker from Verex, Boris Rotman from BCR Biotech, Jim Fleming from Genprime, Andrew Levin from Immunetics. If that is not correct, please see Don Jehn at the break.

We then have three speakers also from organizations or universities, and we will take them after the industry presentations.

I am going to go ahead and have the coffee break at this point. Please be back in 15 minutes, and we will get underway with the open public hearing.

[Brief recess.]

I will call the meeting back to order.

Agenda Item: Open Public Hearing.

DR. ALLEN: I need to read an open public hearing announcement, particular matters meeting, e.g., product

specific.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the 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.

Our first speaker in this session is Dan Erickson from SUBC Inc.

Agenda Item: Presentation by Dan Erickson, SUBC Inc.

MR. ERICKSON: I thank you. I am Dan Erickson, and I am actually directly with SUBC Inc. Additional funding that we have here is the project in the rapid bacterial detection system that we have. We have been fortunate enough to receive NIH funding as a small business entity.

What I am going to describe very briefly and rapidly to you is, we have a -- we work on a system that is both a device with a disposable.

It is a rapid diagnostic test, and what our goals were and what our target was, and what we hear from this audience, is rapid, reliable and affordable, and affordable keeps coming back over and over again. So, we try to target that here as well.

Basically, what our system is, when we have a system where platelets and cellular debris are removed by a filter system here.

The bacteria, we have a bead binding event. We bind the bacteria onto basically a ligand coated bead microsphere bead population chamber.

Basically, our attempt is to receive isolation and concentration and culture-like status by a bead binding event in a rapid single pass manner here from two to three mls of platelets.

Then we lyse the solution with a combination of lyse solution and with the heat in our microfluidic engine. Then we measure, in very rapid -- this is all done within two minute time here -- ATP content, and we get a burst of light, and that is a generation.

Our signal that we have here, there are two ends to our device here. One is a very inexpensive -- as you see here, what is labeled there is our bacterial binding chamber.

Remember, that is our microsphere ligand coated beads, which bind actually in excess of the 15 organisms that we took or directed from the 15 organism paper a few years back.

Basically, what we do is, we pull two to three mls at time of sampling, single pass, push it over our chamber here just in a matter of 10, 15 seconds, and then load it into our instrumentation here, and it is all microprocessed, or microfluidic engine driven, and we hit the start command.

So, basically, I won't go into it too much, but basically what we have is two systems. We have a disposable and we have a fluidic engine.

The fluidic engine does the sample, the sample processing, which takes care of dilution, mixing the chemistry, and obviously the heart and soul of our machine

is our photon counter. We have to be able to have single photon sensitivity here.

We achieve this by using basically a pump valve and detector system here, once again, just for the mechanism here, after we had a bead binding event. We have to have a way to treat the bacteria here, so we can get basically an optical measurement, and we have a high end photon counter here to achieve that.

So, just the cartoon of it here. From the platelets, the first thing, as you saw in that bead binding chamber and the syringe here, for the low end cost portion of this, we just run it over the beads in a single few seconds here, and then it goes over the bead binding chamber here.

Our fluidic engine has the rinse, our luminescent reagent, our waste, the reactor, and then the detector there as well.

I won't go into the chemistry of it too much, but basically what we are trying to achieve, we came back here and we actually had some different membrane markers, but we have always tried to come back. We want to get the sensitivity of 10^2 to 10^3 but, at the same time, to retain cost, so at the end of it the cost is both rapid within a few minutes time, and try to have 10^2, 10^3 sensitivity here.

Earlier we made our first prototype device here,

basically just a bench top model run off of a computer or a laptop here, and you can actually see it is very crude in its earliest form here.

We had HPLC valves and pumps and heaters and reactors and detectors. It was not really a fully automated system, but it was our way to first check our beads, our system, and try to get it to rapid testing.

From the testing that we did, then, we took our December 2002 BPAC, 15 organisms here, that were basically our first hurdle that we had to catch.

First of all, we had to trap all 15 organisms, and then we had to be able to do the detection in that. So, the ones we can detect are obviously the 15 here, and we have also done verification and validation above and beyond that 15 here. It is a cocktail of ligands, and captured microsphere beads that we have used here.

So, the system that we have here I just simply call roll back from our earliest conception here, from our drawings.

We went to literally what was a black box prototype here to a fully automated system here, with a fully embedded fluidic engine where we saw the valves and pumps that were now internalized, a touch screen monitor -- obviously it is not down to a chip yet, but it has basically got an Intel processor on it -- a microprocessor

driven reagent cartridge, loading sample.

Basically, what you do is after you run the sample over the bead binding cartridge, you hit the start button on the panel, and then within an additional 90 seconds we should get a bacterial load here.

We are fortunate. As we mentioned, we have had funding here from the NIH here as well, and what we are trying to do here is, obviously our goal here is the 15 organism protocol that we have to do to get our equivalency, that is our -- what we look at as kind of our lower hurdle, basically trying to take a look at what we capture and measure.

Our true goal here is to do a point of release testing here. What we are working with is Dr. McCollough at the University of Minnesota and the Mayo Clinic down in Rochester, where our company is based here.

We have a project basically here, once again, through the funding here, the grant, we are looking at a 21,000 study here at the University of Minnesota.

There they do glucose meter testing. They did some pH testings, predominantly glucose meter testing right now. Then basically what we are going to do, the positives will go to the microlabs, the negatives to the platelet pools.

So, then we will reconfirm by culture here, and

then also trying to take a look at pools here, along the bottom half of that protocol.

The main thing -- remember, once again -- what we found here is that the 15 organism study is a good place for us to start, basically, and that is our first obstacle, and we have met with the FDA here previously, and that 15 organisms is our step one, as outlined by Dr. Vostal today.

Obviously, the bigger picture, as we look at it, is our point of release testing. What we are looking at here, as was mentioned before, is 50,000 unit, 100,000 unit.

A look at what both Gambro and Baxter have done at 400,000. That exceeds what we can do here as a small company.

So, what we are looking at doing, we are doing a study in India. The percent positive in India -- we have done Bangalor, Hidruvad and New Delhi here -- it is a remarkably high number compared to what were here.

They do very diligent efforts here, and the do the best they can with what they are given, but positives are greater than six percent positive for bacterial contamination.

So, what we have done here is say, okay, first of all, a spike and grow experiment is a criteria that we can reach in a laboratory, but what we really need is the

validation and verification in a field study, and yet we need some type of economical hurdle here to try to access that without doing 400,000.

So, we are doing a 2,000 patient study here in India, trying to do that same spiking and growing, and we are also very fortunate as well to have government funding for that as well.

Basically, we have some documentation and literature and peer reviews in New Delhi, where they have the greater than six percent positive.

So, I just wanted to give a real quick overview. I know we are going to hear about different technologies that industry is doing, and this is one of the applications that we are trying to pursue and our goal is rapid, reliable, affordable, and at the end of the day we want to get to point of release testing. Thank you.

DR. ALLEN: Would you stay for just a second. Let's see if there are any questions.

DR. KLEIN: It wasn't clear to me, do you have any data on the spiking studies yet?

MR. ERICKSON: Yes, we have done the 15 organisms for spike and grow. Our sensitivity here is 10^3 in all organisms. I am sorry, it is 10^2 for all the organisms except for two where we are stuck at 10^3. Staph EP and one of the bacillus are more difficult for us to lyse here.

Obviously, I would like to be able to tell you we are 10^1 or 10^2 across the board, but our statistical analysis is going to fall in the 10^2 to 10^3.

DR. KLEIN: And false positives?

MR. ERICKSON: The false positives, what we are doing here is, in spike and grow experiments here, you get spike and die sometimes, but you don't get false positives. So, that is a little bit misleading.

That is why the study that we are doing with Dr. McCullough with the University of Minnesota in India will hopefully address that.

DR. KUEHNERT: Just a quick word of caution about this study in India with a contamination rate of over six percent, that just seems awfully high, and there are a lot of gram negatives from your last slide.

So, I would just urge caution about trying to figure out the quality control or what is happening there if they are having contamination during their cultures or if there is contaminated saline that is being piggy backed onto the blood or what is happening, but it just seems very unusual.

MR. ERICKSON: I appreciate that, thank you.

DR. ALLEN: In order to get the sample from the collection bags, is that an individual technician that has to go one to one?

MR. ERICKSON: As it is right now. What we have done and what we have actually discussed with the FDA and had the list from them, is using a sterile docking port here to get it from the bay, at this point in time. We do not have our own.

DR. ALLEN: Other questions? Okay, thank you very much. The second industry speaker is Nancy Hornbaker from Verex.

Agenda Item: Presentation by Nancy Hornbaker. Verex.

MS. HORNBAKER: Hi, good morning. My name is Nancy Hornbaker. I am a paid consultant to Verex, but I am here today to represent them, to make this presentation to the committee.

We are here today to talk about something a little different than what the last presenter showed. The Verex test, the Verex platelet PGD test, is a simple, qualitative, rapid immunoassay based test for the detection of bacteria in platelets.

It has been designed to detect bacteria in random donor platelets, pooled random donor platelets, and single donor platelets, regardless of whether or not they have been leukoreduced.

It is a simple test requiring very minimal training and very little labor to run the test. While the

analytical sensitivity is likely between 10^3 and 10^4, we think that, because of the use of the test near transfusion, that that will more than maximize the clinical performance of this test method.

The test was developed with consultation from a number of leading experts in the field of transfusion medicine. I am sure you recognize a few faces up there.

The test is based on a patented technology, PGD, or pangenera detection. In that technology, it is looking at the detection of LTA and LPS, which are conserved antigens found on cell surfaces of all bacteria pathogenic to humans.

The test device itself, that cartridge that we saw earlier, actually contains two immunoassays that are performance simultaneously.

One side is the gram negative assay. One side of the cartridge is the gram positive assay. So, from the depiction up here, it is a pretty traditional looking antibody sandwich assay.

You can see that, on one side, you are going to look for LTA for the gram positive bacteria, on the other side looking for LPS, for gram negative.

This depicts the basic steps of performing this assay. Essentially, there are three. In the first step, the technologist would spin the sample down for about five

minutes and decant.

In the second step, they would re-suspend the resulting pellet, and then in the third step deliver that sample to the test cartridge, thus initiating the device, the test, the assay, wait a brief period of time from a room temperature incubation, and then read results.

The next slides will be some actual pictures of some test cartridges, to give you an idea of what this may look like.

In the center of the device, you will see a sample well. In that sample well, about 300 microliters will be presented to the test to initiate the start of the assay.

On either side of that sample well, you see two read windows, one labeled GP for gram positive, and then GN for gram negative.

If gram positive bacteria are presented in the sample, during the assay a line will form in that reading window.

Conversely, if gram negative bacteria are detected, a line will form in the gram negative window. Further out toward the ends of the cartridge, you see two additional windows labeled C.

Those are procedural control windows. Those windows right now, it may be slightly difficult to see, but

they are bright yellow.

Before a test cartridge is used, those procedural controls are a very bright yellow. When a test is completed properly, those procedural controls will turn a violet-ish purple, telling you that the assay is valid and it is now time to read the result.

This cartridge shows you what a non-reactive test result would look like if you were testing an uncontaminated platelet unit.

You can see that both the gram positive and the gram negative windows are empty. They are completely white, no lines are formed.

You can see that the two procedural controls have triggered and have turned a purplish color, telling you that this is an assay that was valid, and you can report a non-reactive result.

This one represents what a positive result would look like, or a reactive result. In this case, a gram negative bacteria would be detected, the line forming in the gram negative window.

Again, it is important to note that the two procedural controls have turned purple or violet, depending on your eyesight there, indicating that enough sample was added, the sample ran to completion, and the result is valid and is ready to be interpreted.

This last slide shows what might happen if there was an operator error during the running of this assay, for example, insufficient sample volume or reagent was omitted.

You can see that, while no lines have formed in the read windows for the GN and the GP, one of the procedural controls is purple, but the other one has not turned color from yellow. This would indicate an invalid assay, and the sample would need to be tested again on a fresh cartridge.

We have already heard some presentations today that talk about this, so I won't spend much time on it. This is just our picture of issues of challenge of sometimes early sampling for methods such as culture, where not all bacteria will be blooming early on enough, and you may not be lucky enough to actually pick up bacteria in your sample and deliver it to a culture device.

This can actually result in false negatives, as we heard earlier, and they could be at fairly high levels of contamination before those units are transfused.

Again, just passing through this briefly, three of these kinds of incidences were reported over a year ago of CDC of breakthrough cases, where early testing or other testing showed false negative results, platelets were transfused, and patients died.

We think that testing just prior to transfusion

offers an opportunity to prevent some of those false negatives.

It would avoid call backs and you would end up looking at a result that is representative of the sample just prior to its use, rather than one taken early on during its storage, right after collection.

I will sort of diverged a little bit from talking about the assay to talking about some of the issues that FDA has raised, and ask you to consider today.

We agree with FDA that, for rapid tests, it makes sense to look at a kinetic approach to compare a culture based method versus some of these rapid tests.

That way you can actually sort of normalize the results you would get based on the time of sampling versus the analytical sensitivity of the method.

We are concerned about setting an a priori cut off or acceptable limits of detection at this point in time, when we believe that proximity of testing to the point of use may be even more important than the actual analytical sensitivity of the method.

Until we have enough information and clinical data to tell us that, we would just warn against, caution against, setting a number that we may not be able to support one way or another as far as its relevance.

This next slide may be kind of scary looking.

There is a lot of print on it. This was an attempt to take a stab at looking at a rough calculation of what the risk would be after testing, if you were testing platelets within four hours of transfusion on a rapid test.

What we did is looked at literature and picked up the contaminants that were implicated in most fatal transfusion reactions and their frequency, looked at the time required to grow one log once they have entered into log phase growth, again from the literature, and then through surveys the distribution of when platelets are typically, at least today, transfused. How old are they when they are transfused.

Throwing all of those together into an equation, we come up with residual risks that can be parsed out into what if the analytical sensitivity were A, B, C or D, what kind of residual risk do you get.

That last column is then placed on this slide with some important thresholds, we think. The one in 10,000 hurdle has been mentioned earlier today and in prior meetings as being a hurdle for residual risk for culture based methods, and probably the standard for anything else going forward.

As you can see from the earlier calculation we did, using our assumptions and our models -- and I didn't mention it but the slide showed it. Our assumption was that

there would be a true incidence of one in 2,000. So, that was the foundation for coming up with our numbers.

That is equivalent to a sensitivity that is actually quite high, 10^7 to 10^8 to get to this one in 10,000 hurdle.

If the Verex analytical sensitivity is, indeed, determined to be 10^3 to 10^4, then you can see that it should be pretty easy for a tough device such as this to meet FDA's one in 10,000 hurdle for residual risk.

We are also concerned about the kinds of data and the amounts of data that might be required to get some of these release indications for a rapid test, and would urge that some of these postmarket -- I guess I shouldn't call them post-approval -- postmarketing studies are of significant size, and in fact, look like they might be collecting overlapping data with time.

We might want to consider doing something else other than these postmarket studies. We, in fact, believe that it might be more cost effective and quicker to look at structured, well controlled and designed studies prospectively, going out to collect the kind of data that would be required to get a release claim.

We are also worried that -- and I think this also came up in an earlier talk today. Some of the data that it looks like we are interested in collecting in these

postmarket studies might not really be available.

Given that a rapid test is going to be used within four hours, say, of transfusion, you are not going to have outdated units that you can later go back and culture to see if, in fact, originally rapid test negative results are still negative at the time that the platelets would outdate.

Again, we think it is one more reason that it might be worth looking at a prospective, well designed trial before getting a release time, and then doing an additional follow up post-market study, if necessary, to just collect some observations on performance in the field.

We would urge FDA to consider, perhaps, fewer than the three step approach that they have so far recommended today. Thank you. Do you have any questions?

DR. ALLEN: Thank you. Questions for Ms. Hornbaker? You, in fact, have tested this device against all of the bacteria that you listed in the table?

MS. HORNBAKER: We have looked at all of those bacteria at least at one time or another. Right now we have gone to production scale and manufacturing.

We are right now making the multiple lots of product that will be formally tested for the 510(k) studies for a QC release claim.

DR. KLEIN: You may have said this, but how long

does it take to perform the assay?

MS. HORNBAKER: It would be roughly a half an hour plus maybe five minutes up front for the original sample processing. It is about a half hour incubation to make sure your procedural controls trigger.

DR. ALLEN: But the technician time to set it up and all would be much less than that.

MS. HORNBAKER: Right. After you deliver the sample, the device will run on its own, and it is a matter of monitoring to see when you can actually read the result and interpret it.

DR. ALLEN: Other questions or comments? Again, that slide indicated that where you are right now in terms of detection sensitivity, it is at the 10^3 to 10^4.

MS. HORNBAKER: Yes, that is correct.

DR. ALLEN: Thank you. Our next speaker will be Boris Rotman from BCR Biotech.

Agenda Item: Presentation by Boris Rotman, BCR Biotech.

DR. ROTMAN: I have no conflict. We are NIH funded. We are a small company, a spin out from Brown University.

We also aim at the rapid screening shortly before injecting the product. Our approach is entirely different from those available or even in the literature.

Our technology uses engineered spores that act as nanodetectors, producing fluorescent light when a bacterium is nearby.

Therefore, it does not depend on antigens or culturing, and it can detect pathogenic, nonpathogenic, even non-viable bacteria.

The only requirement is for the bacteria to have an enzyme which so far has been shown to exist in every micro organism, and that is an amino peptidase.

The second novel feature of the technology is the use of a device that we call 80K biochip. The reason for this is because the biosensor is, in fact, a massive array of 80,000 microscopic independent biosensors. I am going to explain that later.

The third technology is a state of the art image analysis. The LEXSAS is our system, and it can detect and quantify low bacteria levels.

The results are available in about 20 minutes, cost effective, linear detection, low instrumentation costs, and it can be automated.

Now, the question is, why are you using these engineered spores. Very simply, because the spores are unique organisms, very, very stable, resistant to heat, to chemical injuries.

At the same time, they are always alert to

glutiants in the environment, and they respond, as I will show you later, within minutes.

In the LEXSAS, we have engineered the spores so that they are not fluorescent before they encounter bacteria nearby.

This cartoon explains how the LEXSAS works, the bacteria with the amino peptidase in the presence of a compound that we call germinogenic substrate.

It triggers the receptors of the spores, and the spore produces very strong fluorescent signals that are then captured by standard technologies.

This illustrates the response of the spores after a lag of about 30 minutes. The fluorescence increases autocatalytically within five minutes or less.

This shows the 80K biochip, and what is unique in this technology is the use of a very small reaction volume. We call the chamber microcollander, because it has holes underneath.

So, when bacteria on the spore detectors are filtered, they are retained in the microcollander, but the small molecules that may interfere with the assay are washed away.

This is an actual electron micrograph of the biochip, illustrating the microcollander, and here is a microcollander with about 200 spores.

That is where the bacterium will land. Each colander will have either no bacteria or one bacterium, except for those bacteria that aggregate.

This shows the device that we use to hold the 80K biochip. This is a filtration device, and you see it is a small device.

The biochip in the cartridge goes in this holder, in this instrument. This instrument is a laboratory prototype, and it is introduced in the instrument.

This instrument operates with an ordinary digital camera. So, it is a very inexpensive instrument. It is not a photon counter.

So, this shows the operation. We process the platelet samples very much like in the Vertex system. It takes about five minutes to separate the bacteria. We use the fact that the bacteria is resistant to detergents and osmotic shock.

Then we mix the sample with a germinogenic substrate and we filter it through the 80K biochip, and we take readings at intervals to obtain the data.

This is -- the last time I presented this to the committee, it was before we had the engineered spores. There was a confusion as to how this thing operates, how the biochip operates.

This illustrates, in this field we have roughly

800 microcolanders, and then we have here only a few of them fluorescent.

This corresponds to those microcolanders with one bacterium. So, what this illustrates is that you can capture this without using a high resolution optics. This can be seen on a $100 digital camera.

This is an actual picture from our scanner. I don't think you can see that 10, but I can see from here maybe four. There are 10 significantly.

This is a close up where, on the left, you see the microcolanders under normal light and, on the right, under fluorescent light, and it is very clear that there are four microcolanders with florescent. Those dots, those are camera noise.

This is just brief company information. We have been funded mostly by NIH, and this is our list of publications.

I would like to close also expressing our concern about the FDA requirements, because we submitted to NIH for phase III what FDA recommended, and one of their reviewers said, you cannot compare oranges and apples. Thank you.

DR. ALLEN: Thank you, Dr. Rotman. You indicated early in your presentation that the amino peptidase enzyme was present universally almost in bacteria. Have you tested this device against a variety of different bacteria?

DR. ROTMAN: Yes, we have tested 23 species, including yeast also, because we are also interested in bacteremia. NIH is funding our biosensor for bacteremia.

Actually, it makes sense. This enzyme degrades only peptides. So, their bacteria needs an enzyme to digest amino acids in the polypeptides.

DR. ALLEN: If I heard you correctly, even non-viable bacterial cells would still have sufficient levels of enzyme to activate the spores?

DR. ROTMAN: That is correct. The bacteria retain their enzymes for quite a long time after losing their viability in a stationary phase. All the bacteria have enzymes, and we have maybe 10 percent viable.

DR. ALLEN: In terms of the sample size, it is a small volume. In terms of the number of colonies required for detection, how does that translate? Can you detect as low as 10^2 or 10^3 bacteria per ml, or how does that translate out, approximately?

DR. ROTMAN: The limiting number is the background. Pessimistically, I would say that we could detect 500. Optimistically four or five, because the biochip has this capacity to see individual cells.

So, the noise in the sample is what would limit that. We obviously would have to work more on getting better samples.

DR. SZYMANSKI: I understood that you concentrate the bacteria first. So, how big a sample do you use for that? Is that more than one milliliter of platelets?

DR. ROTMAN: No, our standard sample is half an ml. Also we are adding a carrier of dead bacteria in order to increase the pallet.

it is very difficult to pallet four or five bacteria. So, in the platelet sample, we add dead bacteria as carrier. So, we spin the carrier and then we suspend.

DR. SZYMANSKI: So, dead bacteria do not have the enzyme?

DR. ROTMAN: No, we autoclaved them.

DR. SZYMANSKI: You know, half a milliliter really must have lots of bacteria for something to be detected.

DR. ROTMAN: No, our samples, we are spiking to get about 500 to 1,000. This is for starting the optimal buffer solutions and so forth.

DR. SZYMANSKI: It sounds interesting. Thank you.

DR. QUINN: I don't now how far along you are in this testing, but I was just curious, that you were funded to go ahead and look at bacteremia.

A very simple thing is to take this assay into the laboratory, into the microlab, taking out positive culture sets, and that would be the comparable comparison

to what you are getting from the culture detection systems of the plasma cells.

They -- you know, it is the backpack system. Have you assayed your system against the standard culture system, just to look at sensitivity, specificity, how well it is picking up positives over sensitivity, false positives and so forth? Do you have that data yet?

DR.ROTMAN: No, we are at the stage where we are going to have to go back to FDA in order to conform our NIH application with FDA. We didn't get funded with the study that the FDA proposed to us.

So, we are not at a stage yet to obtain the data of false positives or negatives, because it is all on the spiking that we are doing.

DR. CRYER: One question. Since this amino peptidase seems to be rather ubiquitous, what are the chances that you will end up with a false positive, just that it comes up positive when there is no bacteria, but there is something else that has this amino peptidase?

DR. ROTMAN: That is a good point. It has to do with the sample. In our case, we are favored by the low sample.

If we could, for example, examine platelets three or four hours before transfusion, we could use as little as 100 microliters of sample, which would really eliminate all

the false positives.

DR. ALLEN: Other questions? Thank you very much. Our next speaker is Jim Fleming from Genprime.

Agenda Item: Presentation by GenPrime.

MR. FLEMING: My name is Jim Fleming. I am with the company Genprime. I would just really like to thank Dr. Vostal and Jim for assisting in putting this together.

Our company is involved in really the development of, as you can see, our global plan, technological innovations for a safe and healthy world.

They revolve around a concept we developed some years ago when this company was founded, which was to develop a suite of robust rapid microbe detection technologies based on some core technologies.

Basically, this just gives an idea of the kinds of different products that our company has gone into with these rapid microbe tests.

We had focused our attention on blood products, and especially the platelet contamination issue last year, primarily because our local blood bank, Inland Northwest Blood Center, came to us and pointed out the potential problem with platelet contamination, and of course the AABB mandate.

There is no sense repeating all of this. Everyone is familiar with this, that bacterial contamination of

platelets is certainly a concern to the medical community.

It seemed to us, after we looked into this, that blood banks and hospitals, any transfusion service, really are looking for a rapid robust bacteria assay that would be sensitive, cost effective, user friendly, with the potential for computer interface capability, so you don't have technicians writing down numbers like you do with these pH and glucose tests.

As you all know -- and this has been stated over and over again -- the current methods that are actually employed in the transfusion services or blood banks, the rapid assays aren't sensitive, and the sensitive assays aren't rapid.

If you look at some of the current techniques that are being utilized today, or have been in the past, you do have rapid tests, and it is very clear from this slide that the rapid tests are not particularly sensitive.

Dip sticks, for example, the pH and glucose monitoring, which seems to me to be still routinely carried out with whole blood platelets, is not a particular good assay.

The two culture methods, the BDS and the Bacti-alert, are actually quite sensitive and good technologies, but it takes 24 hours to obtain the answer under ideal conditions.

Of course, we have heard today there are other methods currently under development, including the one that we are working on that we are going to tell you very briefly about today,which is basically an antibody technology that, in many respects, is similar to the tests that we heard about by Verex.

It is a broad spectrum antibody based lateral flow device for the detection of bacteria, which will be capable of detecting bacteria in either aphoresis or whole blood derived platelets.

We have developed a lateral flow scanning system with a pass fail software system that sort of takes the subjectivity out of the analysis of lateral flow devices.

I don't know how many of you have run those, but we have run a lot of tests with lateral flow devices where we run around and ask somebody, is there a line on this one, are you pregnant or not.

There is some subjectivity to lateral flow devices when you get down into weak ranges, is there a line or isn't there a line.

So, the way our current test is designed -- and this is still in development and we are working very hard on it -- we initially started with developing a rapid bacterial test for platelets using a fluorescent technology that we had utilized for some of our other products, and

sort of pulled away from that in view of the fact that it looked to us like there were too many steps involved, and the potential for issues associated with that.

So, we developed this, which is basically a simple, straight ahead, capture antibody lateral flow device, that will come with a bar code on it, and it is designed to detect 14 contaminating organisms.

This is a list from Dr. Brecker's paper basically, and these are the organisms that we are currently developing antibodies against, using some unique method that we have worked with, with others, in consulting roles as well as some other universities that developed some very rapid, high affinity methods for developing antibody surface antigens, basically, that we are utilizing against these organisms.

With our target sensitivity of 10^3, which seems to be the sort of number that floats around -- because the reality is that when you are talking about antibody based tests, you are probably not going to get better than 10^3 under any situation, unless you could start with a large sample.

I mean, that is a question. If you could start with 100 milliliters of platelets, you could get any kind of sensitivity that you wanted.

Basically, right now, this is just some

preliminary data from the first series of antibodies that we had actually originally developed for a different product, but just showing that we had done some spiking studies in platelets with a particular e coli strain that we are making the antibody against. This is a strain that is based basically for water testing.

Currently we are at 10^4 CFU per ml, but our target is 10^3 and we know we can get 10^3 with other bugs. This is just an example of this.

If you notice, on that 10^4, some of you probably see a line and some of you don't, but there is really a line there.

We believe that this is why it is important to develop or provide the blood banks or the hospitals with an objective method for determining whether that line is there.

So, our assay is designed similar to the others that you have heard, that rely on antibody based technologies.

It is fairly simple. It is mail order list of platelets. it is designed right now for one milliliter. It is a three minute sample preparation.

It takes about 15 minutes to run that lateral flow strip, and a little bit less than a minute to scan the strip.

Of course, you can run multiple steps simultaneously with a test like this. Our scanning system for the whole sort of product would look like this, and our scanner will probably have enough room to run about 15 to 20 strips simultaneously. So, you could easily set up a system for running around 15 or 20 tests simultaneously if you needed that sort of throughput.

Then the software which we have developed, which has already been written for another application, is essentially going to be a pass fail threshold based on this 10^3 sensitivity cut off for what a line looks like on a lateral flow strip at that level of sensitivity.

So, we are in the process of developing this particular product. It should be finished by May or June, at which time we would come to the FDA to follow along with their QC testing protocol.

there are two main components here. One is sensitivity, which we believe it makes a lot of sense to do spiking studies in platelets to determine whether or not you can pick up these organisms in platelets, and with a statistical sample that makes sense in terms of this 10 out of 10 actually equals the detection limit.

Then the other issue that has come up that I think is an important one to discuss for this committee is this comparison to a predicate device, where one would

spike platelets at some level and collect samples at intervals to determine when it is that there are rapid tests.

In our case, our case would essentially correlate with what was happening with an already approved culture test.

I think there are some issues, some of which have already been pointed out. One is this low spiking level, one CFU per ml. That is not very many bugs. It strikes me as a difficult problem, putting one bug per ml in platelets, and then looking at this time frame.

In addition to that, some of these bacteria don't grow well in platelets, and we have had that experience as well.

So, that is something to consider. If you look at the situation that I think Dr. Vostal had, where you had platelet bags and you were taking samples out and running them in, let's say, the bacti-alert, and then taking samples out for your rapid test, you are actually looking at bacteria under completely different growth conditions.

So, you are looking at them growing in a media versus looking at them growing in platelets. I think that needs to be considered in terms of how that study is designed.

Anyway, our conclusion is that we are working on

a test that we think would be very useful for blood banks and transfusion services, a simple dip stick format, it is rapid, it is fairly sensitive, has automated data tracking capability and will be very cost effective, or certainly a cost competitive test to what is out there now. So, that is it. I am Jim Fleming, again, with GenPrime.

DR. ALLEN: Thank you. Questions for Mr. Fleming?

DR. FINNEGAN: Do you see your test ever being able to differentiate between bacteria, or is it always just going to be able to say that there is a load.

DR. FLEMING: I am sorry, I couldn't understand that.

DR. FINNEGAN: Do you see your test ever being able to differentiate which type of bacteria there is in there or is it just going to be able to say that there is a load.

DR. FLEMING: It is not currently designed to do that. It is currently designed as part of our philosophy of our company, is to develop broad spectrum bacterial assays. It is much like what Dr. Rotman was talking about where you are looking at are there any bacteria present. That could be done, though.

If that was of use to blood banks or hospitals to determine which organism was present, yes, that could be

done, but that could be much more expensive.

DR. ALLEN: Any questions or comments? Thank you very much. Our last industry presentation is by Dr. Andrew Levin, Immunetics.

Agenda Item: Presentation by Andrew Levin, Immunetics.

DR. LEVIN: Good morning. I am Andrew levin, CEO and scientific director of Immunetics, Inc. in Boston. First, I would like to thank you for the opportunity to come here and present some information on our BacTx test for detection of bacterial contamination of platelets.

Here is a picture of the BacTx test. It is configured as a kit for multiple sample testing. I should say also that our R&D work has been supported by grants from the National Heart, Lung and Blood Institute.

Some key features of the kit. The turn around time from start to finish is less than an hour. In practice it would be somewhere in the 40 to 50 minute range, depending on the sample throughput.

It requires a one ml sample volume of platelets, and the reagents are pre-measured in vials. So, there is no need for accurate pipepetting.

The test detects both gram positive and gram negative bacteria, and the analytical sensitivity is in the range of 10^3 to 10^4 CFU per ml.

If you look at a potential actual contamination event, where you might have less than 10 CFU per ml, that can be detected following a 24-hour incubation period.

Finally, the assay output is a measurable absorbance, which can be provided as either hard print out or uploaded to a computer.

Now, the key target is peptidoglycan, the major structural component of a bacterial cell wall, and peptidoglycan is a polymer composed of alternative sugar residues and acetyl glucosamine and acetyl muramic acid, cross linked by peptide bridges which seem invisible on this slide. I can see them on my monitor.

The monomer unit of peptidoglycan, again, the two sugar residues in acetyl glucosamine and acetyl muramic acid. The peptide side chain cross linked to other similar units.

This is the assay target. The BacTx assay relies upon a peptidoglycan binding protein which recognizes this structure which is common to both gram positive and gram negative species. It is not an immunologic assay.

Here is a diagram showing the assay principle. We have the peptidoglycan polymer here, recognized by the peptidoglycan binding protein.

That binding action triggers an enzyme activity which ultimately results in conversion of a chromogenic

substrate, a product which should be red, and that color product is what is measured.

The assay procedure is relatively simple and straightforward. A one ml sample of platelets is taken either by syringe or a docking mechanism.

After a brief centrifugation and extraction step, it is transferred to a reaction tube, where it is incubated for 30 minutes and, after 30 minutes, the reaction product is visible. Again, it should be red in the tube and can be red in the flotometer.

Here are some data on the sensitivity of the test, looking at two species. Here is serratia marcesis(?) and e. coli.

These species were spiked into platelet units and assayed. The test BacTx is able to detect bacteria in the range from 10^4 CFU per ml down to 10^3 CFU per ml, and in some cases even lower.

Visually, the assay result is again a red colored product which can be seen. In this case we had five species tested -- e. coli, pseudomonas, staph epidermidis, serratia.

In concentrations from 5,000 CFU per ml down into the hundreds of CFU per ml, the signal is clearly visible. Purified peptidoglycan yields a similar dose response curve.

Of some interest to our discussion this morning, if you look at a potential contamination event in which, say, 10 CFU per ml of staph. epidermidis is spiked into a platelet bag and incubated over time, in this case the platelet bag has been sampled at increasing time intervals and tested in the BacTx assay.

Within seven hours, we can pick up a clearly detectable signal at a concentration which is still fairly low. It appears to be in the hundreds of CFU per ml. As time passes, up to 48 hours, both the assay signal and the bacterial concentration continue to increase.

Looking at the potential concentration of bacteria in a platelet unit at the time of testing, if it were, say, 10^3 to 10^4 CFU per ml, this is what could be expected.

The BacTx assay, these four species of bacteria -- pseudomonas, staphoryous, staph. epidermidis, and serratia -- in this experiment have been spiked into platelet bags and tested right away.

The BacTx assay yields a positive result in less than one hour, basically, the assay turn around time. While our culture bottles spiked at the same time in running the Bacti-alert system it required a minimum of eight hours and in most cases over 10 hours to yield a positive result. So, in this case, the BacTx test would be significantly earlier

in detecting a positive result in culture. This was presented at the AABB meeting this last year.

We have gone a little further in looking at these four species -- serratia, pseudomonas, staphoryous and staph, epidermidis -- spiked into platelet bags at three levels, the lowest being a half to one CFU per ml, in this case five to 10 CFU per ml, and 50 to 100 CFU per ml.

After 24 hours of incubation, the five to 10 CFU per ml tubes and above were all clearly detectable, and the half to one CFU per ml tube, three out of four were detected as positive.

Again, it seems difficult to see the red positive markers here. There was one tube of staphoryous that was present at such a low concentration that it was negative at this time point.

At 48 hours, all tubes were detected as positive, and this was consistent with the bacti-alert results for culture bottles spiked at the same time with the same doses.

A look at the false positive rate of this test in a group of platelet bags which had been prescreened by automated culture with either the Pall BDS or bacti-alert systems, and including single donor units, random donor units and non-leukoreduced random donor units. All samples were negative by a BacTx method consistent with results

from bacterial culture.

Finally, the BacTx assay works equally on both single donor units and random donor units. It is a little hard to see the purple column there, but these columns represent three sets of platelet bags inoculated with pseudomonas, staphoryous or serratium marcessius.

They were incubated 48 hours and then assayed. The results, the signal from the random donor versus single donor units is fairly comparable, differences being related to the actual concentration of bacteria, which differed from one unit to another. So, it can be used on both aphoresis and random donor units.

That is the end. Thank you for letting me present some basic information on the assay and introducing it. I would be happy to answer any questions now or later.

DR. ALLEN: Thank you. With regard to some of the studies that you showed, for example, the table where you had the inoculum experiments, how many replicates did you have of those?

In other words, we are not looking at just one or two samples, or are we looking at 10 or 50 replicates for each one?

DR. LEVIN: These slides which I presented show several replicates. So, the number of replicates per experiment is low. In this case, we took one of many

experiments which had been similar, yielded similar results.

DR. ALLEN: And you have had fairly consistent results throughout those replications?

DR. LEVIN: Yes.

DR. KATZ: How long can you incubate this? It sounds like you can look at this repeatedly over time like you can a bacti-alert. Am I getting it right?

DR. LEVIN: This is an end point assay. You look at it after 30 minutes incubation.

DR. KATZ: So, those studies that were strung out were multiple assays.

DR. LEVIN: We had sampled the platelet bags after spiking at increasing periods of time.

DR. QUINN: This is probably an unfair question to you, especially in front of the FDA, but you have already started doing the spiking experiments. you have presented some data, which I am really quite pleased to see, and compliment you on that. So, we can start to get a sense for this.

In terms of what the FDA is having us review in terms of requirements for clearance, do you have any reactions to that?

You have already started the spiking experiments. I mean, there is the post-marketing experiments, but some

of the others? I am just curious to hear an industry reaction to that.

DR. LEVIN: I think the design of our spiking experiments followed along the pathways which were presented at the previous AABB meetings by the FDA.

DR. ALLEN: Other questions or comments from the committee? Okay, thank you very much. Do you have a comment or a question?

MS. GREENWALD: Yes, I am Melissa Greenwald in the office of cellular, tissue and gene therapies. I just have a general question for any of the manufacturers. Have you been considering use of your tests in any other types of products besides platelets, particularly in gene therapies or cellular products like peripheral blood stem cells.

DR. LEVIN: I couldn't actually hear your question. I wonder if you could maybe speak louder.

MS. GREENWALD: I am sorry. I was just curious whether any of the manufacturers are considering developing your product for use in things other than platelets, like peripheral blood stem cells, gene therapy products and that sort of thing.

DR. ALLEN: We are really short on time. I think that is a good question, but it is not germane to our discussion today. So, if you could ask people to talk with

you at the break, I would appreciate that.

We have got three other speakers in the open session, five minutes each. Dr. Selso Bianco, America's Blood Centers.

MR. BIANCO: We will pass, for the benefit of time.

DR. ALLEN: Thank you. There is a handout available. Dr. Jacobs or Dr. Yomtovian or both? I would ask you to be brief, please, five minutes between you. They are from Case Western Reserve University and University Hospitals of Cleveland.

Agenda Item: Presentation by Michael Jacobs and Roslyn Yomtovian.

DR. YOMTOVIAN: Thank you very much for inviting, or for allowing us to invite ourselves -- that would be more accurate -- to present our data to the committee.

We are going to do this in tandem. If I speak too fast, I apologize. I am trying to honor the chairman's request, but the data is very germane to the questions that the committee has been asked to consider. So, I hope you bear with us.

I am Roslyn Yomtovian. My colleague for many years, Michael Jacobs, and I have been working on the subject of bacterial contamination of platelets for 15 years or so.

Here are disclosures. We have received funding to investigate the subject from a variety of companies, Gambro, Hemasystems, Immunetics, Pall Corporation, Verex.

Our travel today has been paid by University Hospitals, and I am a medical advisor to both Verex and Immunetics.

We really became interested in this around 1991, actually somewhat before that, when a report appeared in the MMWR regarding four episodes of bacterial contamination of platelets which occurred in an Ohio hospital, namely our hospital, which we reported to the FDA and the CDC.

There was an extensive investigation, which resulted in an additional article by Dr. Zaza et al, which appeared in Infection Control and Hospital Epidemiology, for those of you who are interested.

In that sense, it was concluded that there was nothing that we were doing incorrectly, that this was a to be expected event. Why it happened to cluster in this period of time, no one knew, but clustering had been observed before. I won't say anything more about that at this point.

So, the Case definition and methods were utilized. Let me say that none of this is spiking studies that we are talking to you about today.

We are going to be talking to you about our

experience with actual cases of platelet transfusion and surveillance that we did, both active and passive surveillance, and Dr. Jacobs will tell you a little bit more about that.

Basically, we required the isolation of an organism from an aliquot of a platelet product obtained at the time of issue.

We used a plate culture. We realized this is less sensitive than the other culture systems. This was done intentionally to reduce the number of false positives, and also to provide more rapid identification of the organism.

We did aerobic cultures only on a blood agar plate, and five percent CO2 for up to 48 hours, plus we required repeat isolation of the same organism from the same source and, in the case of random donor platelets, from the remnants of one of the random donor platelet units which we kept at four degrees, used to make up the pool.

Then we did do quantitative plate cultures which, again, Dr. Jacobs will talk to you about, and I apologize that the colors aren't as nice on this cartoon as they are in the original. This is an epidemic curve of our findings, and we have had a total of 46 cases between 1991 and 2005.

I do want to point out, where the key is, there is a big empty place. That is the time period when we

stopped doing active surveillance and, lo and behold, we had no cases. Of course we had cases. They just didn't come to our attention.

As you will hear in a minute, there is a very poor correlation between reporting of cases by the clinical services and actual contamination. Now Dr. Jacobs will go through a lot of data with you, and then I will sum up for you.

DR. JACOBS: I want to start by acknowledging Dr. Yomtovian for bringing this problem from the blood bank to the microbiology lab.

As a clinical microbiologist, I was very interested in this topic and, as you will see, have got a lot of information from the cases that we have had over a 15-year time period.

Over this time period, we have had 46 cases that we have detected by both active and passive surveillance. The important point here is, we only picked up three of these cases by passive surveillance, 40 were picked up only by active surveillance.

Thirty five of these were from random units, 11 from single donor aphoresis units, six of them were less than or equal to three days of age and 40 of them, the vast majority, were four or five days of age.

This is a table from our publication which is

going to come out in the next few weeks documenting our 15-year experience.

Just to give you a couple of highlights, our bacterial contamination rates, rates of contaminated units transfused, transfusion reactions and bacteremia were not different based on units, but they were different based on using four units per pool for random donor units. So, you can see that all of those p values are significant but, on a unit basis, they are the same.

The total number of units that were used, both random and single donor units during this time period was approximately 220,000 units.

At one stage, we were prospectively doing gram stains and, on all of these positives, we retrospectively did gram stains.

This shows the 39 gram stains we reported in our paper. As you can see, we got very good sensitivity of 10^5 CFU per ml, which is the expected sensitivity of gram stain.

We then looked at 32 of the units which were transfused and which is in our paper. As you can see here, we classified them as to whether there was no clinical reaction, no clinical reaction but the patient had a positive blood culture or leukocytosis, the patient had fever, chills and rigors, accompanied by hypertension, or a

transfusion was stopped because of the reaction in the fourth column. The most serious column, patients developed fever, hypertension and, in some cases, died.

I have also updated this because I have added in the two index cases that were presented in the MMWR report, and also four cases that we had in 2005. So, you can see here we have now brought the number up to 38, with 18 no reaction, three leukocytosis or positive blood culture, and I have also circled the positive blood cultures.

Six patients had fever, rigors, seven with hypertension, and four with the most severe reactions, with three of these being fatal.

So, what we have here, we have quantitated and speciated the pathogens. As you can see here, the most significant pathogens were the enteric gram negatives, pseudomonas and serratia, but we did have one serratia in the second column, as you can see there. That was asymptomatic, leading only to leukocytosis.

On the whole, you can see there is a fairly good dose response curve, with most of the severe reactions and all the deaths occurring in the fourth or fifth column.

If you look at what I have illustrated here, it was looking at the sensitivity of a system that would pick up 10^5 CFU per ml at issue.

This would have detected 10 of our 11 serious

reactions, and 79 percent of all reactions and would have picked up all fatal reactions.

If we had a system that was 10-fold more sensitive, this would have detected all 11 serious reactions and 84 percent of all reactions, again, picking up all fatal reactions.

Even going down to a sensitivity of 10^3, which is very sensitive for an at issue test, this would be even better, picking up all 11 serious, 95 percent of all reactions, and 79 percent of all cases. I am going to hand the podium back to Dr. Yomtovian.

DR. YAMTOVIAN: This is an important slide because it illustrates some particularly recent data, and it shows three examples of what we will call breakthrough cases, one by the plate culture, which led to a death from serratia, one by the EBDS system, and one by the bacti-alert system for staphoryous and co-ag negative staph respectively.

With the co-ag negative staph case, the patient needed to be admitted to the hospital and was in the ICU with severe fever and some other accompanying symptoms.

We don't know about the staphoryous case in terms of symptoms. We have been unable to get the information because the platelets were sent to a different hospital although we cultured them.

So, these are important cases that culture missed and yet, in certainly two out of the three, there were clinical findings.

Validation studies of an at issue detection method, I am just going to pick and choose what I read here, and say that, as has been said before, it is difficult to work with some species at low inocula because there is self sterilization, particularly with pseudomonas and co-ag negative staph.

Certainly validation studies should concentrate on the most virulent pathogens. That would be particularly gram negative staphoryous, also, the single most common contaminant, co-ag negative staph, which comprised about two thirds of our cases.

Then a little editorial comment, we threw in species that have been reported only once, such as clostridium perfringens, or have never been reported, c. difficile, or are very rare and very low virulence p. acnes, we believe do not need to be studied, but obviously that is a matter of great controversy.

So, our conclusions. Bacterial contamination of platelets is a significant problem. Contamination rate of older, random and single donor units is around one in 2,000 units with the rate being five-fold higher for our pools, which are pools of five.

The rate of transfusion reactions associated with bacterial contamination based on all transfusions in our experience is at least one in 16,000 random platelet units, and STP units, again with the rate being five-fold higher in the RDP units.

Since the introduction of new rules for limiting contamination by AABB and slightly before that by CAP, we have had three of 10 instances which were breakthrough cases in aphoresis units, screened at 24 hours, which I have already mentioned.

Based on our experience of over 15 years an at issue detection system, with a sensitivity of 10^5 CFU per ml would have detected 10 of 11 serious reactions, and 15 of 19 with any reaction. A sensitivity of 10^4 would have detected all 11 serious reactions, and 16 of 19 with any reaction, and down to 10^3 would have detected 79 percent of cases including all serious reactions, and 95 percent of reactions of any kind.

So, the bottom line, an at issue detection system, with a sensitivity of 10^5 would have prevented all fatal reactions, 91 percent of serious reactions, 79 percent of all reactions. 10^3 would have prevented all serious reactions, 79 percent of all cases and 95 percent of all reactions. I thank you very much for your attention and we are available for questions or comments.

DR. ALLEN: Thank you, it is very useful information to have presented. Questions?

DR. QUINN: Just a point of clarification because it is so very important. The CFUs, that is at the time the sample was obtained from the platelet bag at the time of release and then cultured and quantified?

DR. YOMTOVIAN: Correct.

DR. KUEHNERT: I just had a question about your classifications of reactions. Do you have a breakdown of what patients were able to have reactions, were on antibiotics, were intubated, you know, conditions that would have presented a reaction?

DR. YOMTOVIAN: We have some of that data in the paper, particularly the antibiotics. Of course, many of these patients, of course, are on antibiotics. It is probably why there weren't more positive cultures.

Regarding things like intubation, we did not look at that uniformly. They virtually all had lines and indwelling catheters, which obviously is a risk factor.

So, yes, we have some of the clinical data spelled out in detailed tables in the paper. We probably could have more.

DR. KUEHNERT: Do you have a sense of like where it says no reaction, like how many of those had --

DR. YOMTOVIAN: Where it says no reaction,

thorough reviews -- once we knew the cultures were positive, I personally combed through every chart in detail if there was any question, which sometimes there was.

I mean, I included nurses notes, the vital sign sheets, everything, talking to the attendings, at times even talking to the patients. So, that is pretty reliable information.

DR. KLEIN: Since you are both clinicians and since you have been working on this for 15 years, what minimal sensitivity would you recommend?

DR. JACOBS: I think we presented the data as clearly as we could based on the data that we have. 10^3 would be fantastic, 10^5 would be great as well, because that prevents the vast majority of serious complications, and all the cases where we had deaths.

DR. YOMTOVIAN: I Guess I would add, I know Mark Brecker is here, who has said many times, and I have said it myself, we shouldn't let the perfect be the enemy of the good.

Anything now would be better than what is currently available for the rapid screening tests which are notoriously not just bad, but they are wasteful, such as pH and so forth.

DR. FINNEGAN: Can I ask the flip side of Dr. Kuehnert's question? For your three breakthrough

cases, what was the physiology of the host. In other words, the person who died and the person who had to get admitted to the ICU, were they immune compromised, or were they regular people?

DR. YOMTOVIAN: The one staphoryous case, I already admit to not knowing the detail, because that platelet, we serve as a depot, that was shipped and unfortunately that information, for whatever reason, hasn't been forthcoming.

The first case, the serratia, was a neonate who was very sick and obviously very immunocompromise. The staph. epidermidis case was also an oncology patient.

DR. JACOBS: Just to add a few more details, the serratia case was a patient in the ICU. The coag negative staph patient was an outpatient receiving platelets for chronic -- during chronic hematherapy.

DR. ALLEN: Thank you very much. Our final speaker in the open public session is Dr. Steve Kleinman, who is representing the AABB. Dr. Kleinman, I understand you also want to briefly present data from a real life situation of bacterial testing and platelets given current methodologies.

Agenda Item: Presentation by Steven Kleinman, AABB.

DR. KLEINMAN: Thanks, Jim. I was just asked to

maybe summarize some of the current blood data. I would point out to the committee there is a paper that was published by the American Red Cross that has quite a lot of data on about 360,000 aphoresis platelets that were cultured.

Recently, through a consulting role I have with Blood Systems, we have analyzed Blood Systems' data and submitted a manuscript for publication.

In that data -- and both the Red Cross report and the BSL report are very consistent. In both of those systems, using bacti-alert cultures, aerobic bottles only, for ml inoculations, the positivity rate is about one in 5,000. This is with inoculation after 24 hours, as has been described. So, that is the confirmed positive rate.

One additional finding from the BSL experience has been that, in their 21 positive isolates, 20 were detected prior to 24 hours, and only one was detected after 24 hours, and that was about 27 hours in culture.

So, again, for the aerobic organisms, most are detected relatively rapidly. I believe in the Red Cross data, maybe not all, but almost all were detected within 24 hours.

You do detect some positives after 24 hours. They turn out to be primarily false positives, and in addition there are some that are classified as indeterminant,

meaning that you have a positive result, but the unit has already been transfused, as I mentioned previously.

In the BSL data, there were about 26 of those, about the same number as true positives. Just judging by the organisms, they were, I think, more likely to be false positives than true positives.

So, we have, in summary, actual experience about one in 5,000 rate, and most of the positives, I would say at least 90 percent come up within 24 hours of culture.

So, to go on to my prepared statement, this is on behalf of the AABB, and an inter-organizational task force convened by AABB, which has been set up for the last several years on bacterial contamination of platelets.

I just want to tell you that that task force is composed of experts representing both transfusion services and donor collection facilities, representing AABB, America's Blood Centers, American Red Cross and DOD, and with liaisons from various government agencies, including CDC and I believe FDA. This task force has provided a number of guidance documents along the way to AABB membership.

To address the issues before the committee today, the AABB strongly supports development of rapid, sensitive and specific non-culture assays to detect bacterial contamination of platelets, using an approval scheme that

does not unduly delay their licensure.

Our most urgent need is for technologies to replace the -- and I am echoing Dr. Yomtovian's comments here, to replace the insensitive, non-specific and unregulated surrogate methods such as pH and glucose dip sticks currently being used to test platelets from whole blood.

Second, we must also agree on an estimate of the sensitivity required to prevent or substantially reduce residual episodes of clinical sepsis and infection that continue to occur even after implementation of a standard that requires these methods.

Again, I would say that the presentation we just heard is the best data that I have seen about the potential sensitivity levels.

Up until now, there has been no agreed upon sensitivity standard for rapid tests performed shortly before the platelets are issued for transfusion, and the informed opinion has been that, when used as a pre-transfusion test in the hospital blood bank for the goal of preventing clinical sepsis, the bench mark should be in the range of 10^3 to 10^4 CFUs per ml.

There is broad understanding that rapid tests now in development will not have analytic sensitivity equivalent to culture based tests, if the new assays are

used early during storage, before the time for bacterial proliferation sufficient for detection.

When used later, especially as we have heard today in the transfusion service at the time of distribution, rapid tests should be able to identify units in the target range and prevent adverse clinical events.

The FDA must find a regulatory scheme that is not unreasonably constrained by consideration of the current culture based tests as predicate devices.

It is known that some bacterial contaminated platelet units may be culture negative, so-called false negatives, using the approved quality control devices, and some estimates suggest that such negative culture results may occur in up to 25 percent of bacterial contaminated units.

The initial utility of rapid tests will be for use just prior to transfusion to detect either these falsely negative units, or to use on units that have been untested by culture.

Furthermore, as surrogate testing methods may detect only a minority of contaminated units, perhaps as few as one third, licensure of rapid tests for use immediately before transfusion will improve transfusion safety in comparison to the current insensitive and nonspecific approaches used to test whole blood derived

platelets.

Reasonable sensitivity and the expected specificity of rapid tests, we would suspect, would represent a marked improvement for prevention of clinical events.

A kinetic approach as outlined by FDA can be reasonable if a developer seeks approval for a QC indication similar to the current culture based systems, but emphatically not as an indication as an adjunct to culture to be used near the time of issue for transfusion.

The suggested kinetic approach seems likely to hamper development of this latter indication, resulting, for example, in unneeded delay in implementation of methods to test platelets from whole blood.

We recommend that the FDA seek an alternative route to labeling rapid tests for this specific indication. A possible approach could be to, as in the QC approach, establish the performance characteristics of the rapid test based no serial dilutions of a spiked unit.

For the standard quality control indication, demonstration in a parallel clinical study that the applicant test can detect contaminated or spiked units that are identified by the currently licensed systems at a given point in time seems a reasonable criterion.

For example, if a unit is spiked with one CFU per

ml at collection, stored for 24 hours, inoculated into the predicate and applicant systems, and detected after 24 hours in both systems -- so that would mean in the applicant system the test was actually done at that 24 hour later time period -- they might be considered equivalent.

In summary, the most urgent uses for the kind of assays under consideration are to replace current surrogate approaches widely used for testing platelets derived from whole blood, tests that are known to be insensitive and nonspecific.

Approval of rapid tests offers the opportunity for pretransfusion testing of whole blood derived platelets to prevent a proportion of residual platelet associated sepsis.

Accordingly, the approval criteria should not require equivalents of the new approaches to culture based testing, but rather should be based on an agreed upon sensitivity that will accomplish the clinical goal.

Approval for a more standard quality control indication should likewise demonstrate focus on the prevention of clinical sepsis without necessarily insisting on a single approach. Thank you.

DR. ALLEN: Thank you, Dr. Kleinman. Any comments or questions for Dr. Kleinman? Okay, the open public hearing session is now closed. We will move to discussion,

or a summary of the questions to be posed to the committee, and we will initiate our discussion.

Agenda Item: Open Committee Discussion. FDA Perspective and Questions for the Committee.

DR. VOSTAL: Okay, thank you very much for your presentations, and if we could back to the questions, the first question that we have is, is the proposed three tier regulatory scheme for clearance of rapid bacterial detection tests acceptable.

The tiers, with increasing data requirements, include clearance for quality control indication, adjunct release test indication, and a release test indication.

Agenda Item: Committee Discussion and Recommendations.

DR. ALLEN: Dr. Vostal, the order and the wording is somewhat different from what is presented in our issue summary. Can you briefly explain what the changes are, and why the FDA is doing that?

DR. VOSTAL: You mean the order of the questions?

DR. ALLEN: The order of the questions and the wording is slightly different.

DR. VOSTAL: I actually don't think the order matters that much in terms of how we start to discuss it.

DR. ALLEN: Okay, we will accept that, that the questions are essentially equivalent. Dr. Kuehnert, do you

want to open the discussion?

DR. KUEHNERT: May I ask a question about the last question? I am trying to understand this kinetic comparison, and it is confusing me.

So, maybe just explain it very simply. I am just worried about comparing apples and oranges about what is being compared.

So, you are looking at a culture based test, it gets inoculated, it takes, let's say for the sake of argument, three days to grow, and you get a positive on day three after inoculation.

Then you are comparing it to an immediate use test. So, then you are comparing the result at day three to day three; is that right?

DR. VOSTAL: That is what Dr. Epstein was pointing out.

DR. KUEHNERT: So, given that, when you are talking about organism load, and what the sensitivity is, are you comparing the organism load at point of inoculation for, let's say, the bacti-alert test, or are you talking about the organism load at the time the buzzer goes off for the test, because that makes a big difference.

DR. VOSTAL: I think we are comparing it at the point where it becomes positive, where the culture test becomes positive.

DR. KUEHNERT: But how many organisms are in that blood culture bottle at the time --

DR. VOSTAL: No, what we are saying is, we want to have equivalence for the devices to be able to detect a contaminated unit.

So, if it takes 10^6 CFUs per ml in the culture bottle to set off a signal, that doesn't come into play. That is the technology that works in that detection.

I think the sensitivity you are looking for is the sensitivity in the contaminated platelet product. If it starts off at 10 CFUs per ml and the culture bottle can detect that at day two, and it takes day three or day four for the rapid bacterial detection device, that is the comparison that we are looking for.

DR. VOSTAL: In other words, in a real live situation, if the platelet unit is contaminated at the time that it is drawn, the bacteria begin to proliferate at a variable rate.

The culture sample is taken at about 24 hours. The bacteria continue to proliferate. The rapid test would then be used not at the 24 hour sample, but at the continued growth, looking at it over a period of time, and that is a different question than actually spiking the unit with a known level and doing your immediate rapid test.

The kinetic model would be looking at more of a

real life, except using a spiked unit instead of one that is naturally contaminated.

I think among the committee's deliberation, the data that Dr. Kleinman just presented on the actual contamination rates found in real life -- recent real life situations, coming up close to the one in 5,000 -- it certainly has to factor into, if you are going to require extensive in use testing, that will be very different than with a contamination rate of one to two thousand.

DR. KUEHNERT: That difference is probably the difference of volume with the second bottle. So, if they use two bottles, you are probably going to see a different rate. I just want to make sure everybody on the committee understands that.

DR. DOPPELT: The plan would be to spike with different concentrations and using fast growers and slow growers?

DR. ALLEN: My understanding -- that is obviously an open point for us to discuss as part of this. My understanding is that we have been presented with different lists of 10 to 15 organisms that include both gram positives and gram negatives, primarily aerobic but some anaerobic bacteria.

Certainly the caution from my perspective, from a real life situation, you would want to take the bacteria

that are known to cause the most significant clinical problems, but there is an array of bacteria out there. My understanding is that all of them would need to be tested to understand how the system worked.

DR. SZYMANSKI: I understood that you are going to make many of this to determine the CFU per milliliters as comparison.

If you really culture the units that you took a sample of on day two or day one, you know, you have really fantastic conditions for growing of bacteria.

When you have the unit of platelets, and let that stand at room temperature, they are two different conditions, as was already pointed out here.

So, I don't think there are really very good comparisons between these two tests. You should actually determine how many CFUs you have in a culture test when it becomes positive, and also how many CFUs you have in the rapid test, to be positive. Then you could say at what rate it detects. Do you understand what I am saying? You don't.

DR. ALLEN: I understand. I think I haven't decided in my own mind exactly what the answer is. I agree with you, they are not necessarily going to be comparable.

DR. KATZ: I have been confused every since I got the briefing packet. That is not unusual, as you are aware.

So, as I understand it, this kinetic approach, particularly for the QC, which would replace bacti-alert or EBDS, we would stop doing cultures for the QC.

What it would tell us is how long we had to hold the platelets in inventory before we can test and release them for transfusion to the hospital.

DR. VOSTAL: Let me just back up to the -- all right, so this is what we are proposing for the quality control.

We like to see initially analytical sensitivity of the device. For culture based devices, we ask for this up front.

Basically the study is, you spike in known amounts of bacteria and you test to determine if the device can detect that.

So, the culture based devices have like 10 CFUs per ml sensitivity. So, if you do a head to head comparison between a culture based device and a rapid test device, currently the rapid test would lose out. So, you couldn't declare them equivalent.

So, what we would ask of the rapid test devices is to first define their analytical sensitivity in a spiking study and, as we probably anticipate, this will be a 10^3, 10^4.

Then we would go to this kinetic based study

where we would try to figure out at what point would the two devices be equivalent in detecting a contaminated unit.

So, it would be like you were saying. Maybe for a rapid test device you would have to wait three days before you test the product, and then find out whether it is contaminated or not.

DR. SZYMANSKI: I think you want to test the product by the rapid test at the time of issue, which might be two days, or one day.

DR. VOSTAL: Right. We might be mixing different indications. This would be an indication for quality control to make sure the process is working.

Now, if you start talking about release tests, we have different criteria for validating it as a release test or as an adjunct to another test.

So, for example, if we think that the rapid test devices could be cleared as an adjunct to a release test, we would ask them to do the spiking studies that we require for a QC validation, and so we would know what the sensitivity is, and about what time the platelet products should be sampled.

We would be willing to approve it for that adjunct release indication, providing there is a commitment to do a postmarket study. Actually, I am sorry, this would not be a postmarket study. This would still be a

preapproval study.

We would then ask them to go look at clinical units, to see if these devices are capable of detecting contaminated units that have already been declared by the culture system.

DR. SZYMANSKI: If you find that the test detects 10^3 CFUs, or 10^4 CFUs, why can't it be then used right away, and not have to go through all these testings.

DR. VOSTAL: For a release test, we have always considered that we need something more than just this spiking study, because the products are contaminated clinically. They have a lot lower initial contamination. So, the growth pattern could be different from a laboratory type experiment.

So, for a release test -- and this was true for seven day platelets -- we would like to see data on performance on clinical units.

DR. SZYMANSKI: Dr. Yomtovian showed beautiful data that, if you have 10^3 CFUs, you could really prevent all adverse reactions -- most.

DR. VOSTAL: Right, she did show very nice data, but what we are interested in is if the devices that are coming to us for clearance are capable of detecting those units with their sensitivity. So, if they are capable of detecting clinically contaminated units.

DR. CRYER: I guess the rationale that you are proposing seems good. I mean, I think it will figure out if the test works or it doesn't.

I am a little concerned about the feasibility of it. If you have to get all these contaminated units, how many of them are out there to test? It doesn't sound like very many. We had some number like 450,000 in the paper. That seems kind of ridiculous.

DR. VOSTAL: The 450,000 number was the sample that were sampled for quality controlled testing. That doesn't mean that they were all positive. Those are just the ones that were sampled, and we know the results on those negative or positive.

DR. CRYER: Does the company have to then go test all 450,000 or just the ones that you know are positive?

DR. VOSTAL: This type of a study, where we wanted to test only positive units, that would require that they get hold of units that have been declared positive by another method, which is a culture based system.

The study you are asking for is, once we clear them for quality control indications, they start collecting data at the blood centers.

We would like to see that data brought to us as part of a submission for something that gets closer to a release test, like either adjunct to another release test,

or stand alone release test.

So, it would be some kind of performance that is already out in the clinic to show us that this device can detect contaminated units.

DR. DUNKIN: I am Robert Dunkin. I am from the division of emerging transfusion transmitted diseases of FDA.

As a reviewer on a number of these devices, I just want to make a couple of points about how we are thinking about this discussion.

The first one is on the question of comparison to a predicate device and substantial equivalence, and just reminding the committee that substantial equivalence doesn't mean identity, that we are not looking for the exact same detection limit in CFU per ml, and that is why we are trying to develop these ideas about ways of comparison that could be considered.

Dr. Vostal covered it pretty well, but just keep that in mind, that that is what we are looking for, is agreement on the idea of finding ways of making the comparison that are fair.

The other point is on the question of going to a release test. The problem is clinical sensitivity. In all device review, we differentiate analytical sensitivity from clinical sensitivity.

Analytical you can get from a spiking study. Clinical sensitivity is testing units in a clinical setting, and having enough positive units to be able to make a calculation.

The study would have to be massive, and we have been fighting that for a long time, but we still would not want to approve a rapid device until we have been able to get some indication that that analytical sensitivity of 10^3 is reproducible in the clinical setting. That is what this is about.

DR. QUINN: Just a quick question on that, because I think you just hit upon -- in the very last statement you made, it would be a huge study to show that clinical sensitivity, and may be beyond the scope of what some of these can do. You just made that statement, and yet you said you are going to still require it.

DR. DUNKIN: The point is, to approach that in any way is the kind of scheme that we have got here, with a coming in with QC testing with a large number of samples, and then proposing a postmarket study. So, the large study could happen postmarketing, rather than require that up front.

DR. KATZ: I think there is a fundamental disconnect about what those of us taking care of the product and the patient want and what the FDA wants.

I don't think that any of us looked at rapid testing for a QC indication seriously as the first use. We wanted to pick up what we are missing, and it shouldn't take the kind of study that I am -- unless I am missing something -- is being proposed by FDA.

DR. EPSTEIN: Two things. First, if I could attempt to disentangle the issue of the apple and the orange, what are you comparing to what and when.

The distinction that needs to be made is what can you learn from a spiking study, what can you learn from a clinical study.

In a spiking study, you can start comparing the readouts immediately, and then you can compare the culture readout to the rapid test readout. You can do it on day zero, day one, day two, day three, and that is unbiased. In other words, you are not making any presumptions of which one is better than the other. That is the spiking study.

The problem that you get into with the clinical study is that, if you want to do an unbiased comparison, then you have to start doing the rapid tests on very large numbers of negative units in order to arrive at a comparison with the small number of positives.

Instead, what is being said is, let's just make sure it is no less sensitive than the culture. So, that question is being framed as, when you get a positive

culture, would you have at that same time also picked it up by a rapid test.

So, it is a culling phenomenon. It makes the study more efficient. At the same time, it has to be realized that it will take quite a while to accumulate even 60 culture positives at a rate of one in 5,000, but that is feasible. It is not going to take five years.

That is where the distinction lies. I think the issue, as it is being framed from the industry point of view versus the FDA point of view, really comes down to whether we ought to be giving approval as a release test based solely on an analytical demonstration of sensitivity, either by comparing the kinetics in a spiking study or by some other analytical measure of sensitivity relative to the spike.

I think that is something on which the committee may want to advise the FDA, but it would be unusual for us not to look for a clinical comparison, and I think that is what you are hearing the FDA say.

DR. ALLEN: Let's let Dr. Klein respond to that, and then we will get back to our --

DR. KLEIN: Actually, it is a question I have for Jay. In our institution, I have no problem because we use all aphoresis platelets. So, we have a system that may not be great, but it does basically what we want it to do.

For the 25 percent of platelets transfused in this country that are pooled, random or whole blood derived platelets, we are testing them with pH dip sticks which, as I said before at this meeting, are great for swimming pools and hot tubs, but they are really useless for platelets.

I guess what I am asking is, can we separate these two issues and try to get something in place to deal with the 25 percent of platelets being transfused that are not being tested in any way, really, for bacteria.

DR. EPSTEIN: All I would say is that we have the same goal in mind, and what is in front of the committee is how to get there.

DR. FINNEGAN: I have a simple math question. We said that one in 5,000 is contaminated, and how many units are put out in the country in a given year? That will tell you how many years it will take to do this study you are suggesting.

DR. EPSTEIN: There are about four million platelets per year and one quarter approximately platelets from whole blood.

DR. ALLEN: Dr. Kleinman, the data you presented on the one in 5,000, those were essentially all aphoresis?

DR. KLEINMAN: Essentially, yes. In the Red Cross experience, about 360,000 units, which I think was only about six months of their data, and in the BSL experience,

120,000 units, which was about two years of their data.

MR. DUNKIN: Do we have somebody in the audience who has a calculator, who can figure out how many years it would take to get this route to --

DR. ALLEN: One in 5,000 for the aphoresis, and it may be a higher contamination rate for the random donor platelets.

DR. KLEINMAN: It shouldn't be any higher. The per unit risk should be the same.

DR. CRYER: I would just like to clarify the second step, where you go and they now have to trust the known positive units, the clinical units.

That seems ridiculous to me for the following reason. It is already culture positive. Since there is a time lag, by the time you get it back, the bacterial colonization rate in that unit has to be extraordinarily high by the time you would be able to test it with the device.

I mean, if it is a negative result, I can see how that is useful information. If it is a positive, won't they all be positive? I guess I just don't understand why you would do that study.

DR. ALLEN: I think even if it is not being tested on an established basis, if the decision to test the unit is made only with the positive culture, you probably

are losing some information.

The other side of it is, what is the specificity of the culture methods that are currently being used, and is the culture system at 24 hours missing some units that, in fact, may be positive, and that these tests done at a later point might pick up the rapid test?

It is not a simple study to do in terms of the numbers, because the rate is going to be extraordinarily low, but it is an important question.

DR. SZYMANSKI: You started doing the AIDS re-testing, NAT testing, as an experimental test, and everybody had to test the donors with this experimental test until enough data was collected. So, why not do the same here, to start testing for bacterial contamination with this new rapid test, and see how it functions?

DR. ALLEN: I think that is one of the proposals, but it would not be done solely because it is still an experimental device. The others are already in use.

DR. KLEINMAN: I thought it might be useful to sort of look at the operational way that such a test might be used. I could see several areas that are worth considering.

One is the whole blood derived platelet area that we have been talking about. So, FDA would want an analytic sensitivity claim and would say, once units grow out to two

days or three days, this is a reasonable test to do because it is likely to pick up the clinically important units.

In reality, probably the way the test would be used on whole blood derived platelets is that they would be tested at the time of issue.

If the time of issue happened to be three days for that unit and three days actually indicated that you had appropriate sensitivity, you would do the test and you would be fairly confident that you wouldn't be missing a result.

If you happened to have whole blood platelets, and they were transfused at a day and a half, you would still do the test in reality.

It wouldn't be labeled as a release test, but then again, neither is culturing of aphoresis labeled as a release test and yet, as everybody knows, we are doing 100 percent QC.

This is where there is a regulatory disconnect. I know the FDA doesn't like 100 percent QC because, by default, you are doing what you would be doing with a release test, except that you are not putting that on the label.

In actuality, if the rapid tests were allowed to be used in the field, and you were operating a transfusion service, wouldn't you say, gee, I am ready to release this

platelet, I am going to test it whether it is 24 hours old, 48 hours old, 78 hours old. Maybe I will get lucky and it happens to be at a high level.

So, I think the analytic sensitivity is important, because at least you could say, I am releasing this platelet early and, yes, there might be low levels of bacteria because it is early, but it usually doesn't have a clinical important. I think that is one use.

The second use, which I hadn't thought of until Jaro presented it is, would you take a culture aphoresis product that got released to your hospital and would you say, in addition, now I have it in my inventory, I have saved it for a day before I have transfused it, I know it has a negative result by culture. Should I once again do this rapid test just to see whether something happened in the last 24 hours that wasn't picked up by the culture system.

I guess that is a second indication as an adjunct test. I am a little unclear about how to handle that situation.

I think some transfusion services would elect to do that if the test was available. Others would say, I rely on the culture, even though we know the culture is not 100 percent.

I am not sure that is the one we should get hung

up on but I think, as Lou Katz said, the important thing is to have this test out there to replace pH and glucose.

I think the goal is the same but, in actuality, it doesn't matter what the claim is. Once the test is out there, transfusion services are going to use it, provided it is appropriately priced, and it can be used on non-leukoreduced platelets.

DR. ALLEN: As Dr. Yomtovian and Jacobs pointed out, even detection at a level of 10^5 bacteria per ml would eliminate virtually all of the -- at least in their experience -- all of the fatal transfusion reactions, and a very large percentage, two thirds or more, of the ones that cause significant clinical illness.

So, there is a large potential clinical benefit here, even at a relatively low level of sensitivity. Very quick comments, please, from the floor microphone. Identify yourself.

DR. SAZAMA: My name is Kathleen Sazama(?). I am a professor of laboratory medicine at the University of Texas MD Anderson Cancer Center.

I believe it is a safe statement to make that we transfuse more whole blood derived platelets per day than most institutions do in a month. We transfuse 500 equivalent doses per day.

We use whole blood derived platelets because we

have a huge difficulty getting aphoresis platelets that meet our clinical needs, and I would like to focus this to the clinicians on the committee.

Our clinicians participate in more NIH approved protocols for experimental therapies for cancer than any other institution in the country.

Because of that, they have made it a requirement for our transfusion service that we transfuse platelets that are, on average, less than two days old.

We can't begin to meet the culture requirements. Even if we had the will to do that, we would not be able to satisfy our clinicians' needs.

I am just raising that as an issue. Clinically -- Jaro, could you go to your next slide about the growth curves?

Clinically, we are talking about detecting the problem that occurs between what is shown there as between day one and day two, namely, the heavily contaminated units of fast growing bacteria that could cause real harm to our clinical patients.

To be absolutely crass about it, we don't care if there are other organisms there, or if the organisms are there at a very low level.

By the time we acquire the information, the patient has already benefitted from the transfusion, and we

do not see the need to go about trying to determine whether every unit of platelets has bacteria in it.

In fact, they do, and I don't think anyone on the collection side would disagree with me. They probably all have bacteria in them.

We have just heard very good data that suggests that up to 10^4 at least CFU units per ml are clinically acceptable.

The other bit of data I would like to share with you is that MD Anderson, for decades, we have not had a serious transfusion reaction, nor have we had a death. I suspect it is because we transfuse very fresh platelets.

We are stuck in exactly the conundrum that Steve Kleinman described, which is that we have no reliable method of finding those very rare -- but they do happen -- units of platelets that happen to have a very fast growing, very potentially harmful organism in them.

So, we are stuck. We need one or more of these rapid methods out there. We don't prefer to use dip stick pH meters or other surrogates. They simply are no better than blowing on it.

So, we really need the committee to understand that we would like to protect our patients, and we transfuse, as I have just shared with you, lots and lots of platelets to very sick patients.

The second point I would make is, the reason I believe we don't have serious transfusion reactions is because virtually all of our patients being transfused are loaded up with antibiotics. So, there is that other piece of the coin.

I, for one, because I happened to have been the person who said, yes, we are going to do the standard for AABB, I believed in the safety measure of doing testing, bacterial testing of platelets, but don't throw us out of all of this.

We want to be compliant with what needs to be done, but we are transfusing at that zero, one and halfway to the two point. So, we need something to be acknowledged, recognized.

Appreciate the fact that we are not trying to find if every platelet unit has bacteria in it. That is not the goal.

The goal is, when we decide to issue that for a patient, is it safe enough for that patient to receive that unit. Thank you.

DR. ALLEN: Thank you for that information and those comments.

DR. BENJAMIN: Richard Benjamin, chief medical officer for the American Red Cross. I wanted to update the committee on the Red Cross experience with the current

licensed bacti-alert test.

We have now transfused 1,250,000 tested units over the last two years. I wanted to address especially the false negative rate with this test.

As pointed out, we get true positives at a rate of about one in 5,000. In the last two years, we have also had 17 reports of septic transfusion reactions where we have proven that our culture system has missed a truly positive unit. That includes two deaths.

That rate is about one in 74,000 transfusions causing septic transfusion reactions, despite using aerobic bottle only with a formal inoculation.

One in 74,000 is not statistically different. It is 36 percent lower than the rate reported in the Bacon study.

At this point, it is my belief that we are only picking up about half of the contaminated unit with this test. We are moving to increase the sensitivity and change the way that we are doing the bacti-alert test based on these data. Thank you.

DR. ALLEN: Thank you. Very quick.

MR. WAGNER: Steve Wagner from the American Red Cross. I just wanted to offer perhaps another way of thinking about it.

I think from the regulatory framework, it might

be a bit more difficult, but I think if we look at the rapid tests as tests that would be mandated to be done within four hours of transfusion or some reasonably short time of transfusion, then you really don't have to dissect the kinetics of bacterial growth and all sorts of other difficult things to be able to investigate scientifically.

Of course it brings the regulatory burden down to the level of care, which would be at the hospitals, and that may bring in some regulatory issues that might be more difficult than regulating blood centers. In reality, as I look at a rapid bacterial test, that is how it might best be performed.

DR. ALLEN: Dr. Vostal, can we go back to the first question that was asked there? Are there other significant comments that the committee wants to make, or are we prepared to go ahead and take a vote on this?

Is the proposed three tiered regulatory scheme for clearance of rapid bacterial detection tests acceptable. The tiers, with increasing data requirements, include clearance for quality control indications, adjunct release test indications, and a release test indication.

I will qualify it by saying, I think the committee has been overwhelming in its support of the need for rapid approval of useful tests from a clinical perspective.

I think we have heard from blood collection agencies of the importance of this, as well as from clinicians in practice, of the importance of this.

With those caveats, are we ready to vote? Okay, why don't we go ahead with that.

MR. JEHN: For question number one, Dr. McGee?

DR. MC GEE: Yes.

MR. JEHN: Dr. Szymanski?

DR. SZYMANSKI: No, if I understand. I think this is too complicated as proposed.

MR. JEHN: Dr. Quinn?

DR. QUINN: Well, I think they have been reversed, and therein lies the problem. I think some of the quality control stuff is in two and three, is it not, and then -- I think the debatable issue, if I understand it right, is this term called adjunctive release tech indication.

The way I read this, if the rapid test says negative, then in post marketing the manufacturer needs to then do a culture on that negative test and see how many come up positive to see how it would compare to the blood culture tests, ultimately. Is that right? That is how you have it described in your document to us, number two.

DR. ALLEN: My understanding is that the adjunct testing would be that this test, until it is fully accepted

-- sorry -- that this test alone does not meet the AABB requirements. Am I correct about that, Dr. Vostal?

DR. VOSTAL: The adjunct test would be used -- so you would test the unit with a culture based device up front, in actual clinical use. That would meet AABB standard.

Then, at the point where you are going to release the unit, you will re-test it again with a rapid bacterial detection device, to make sure you didn't miss something up front. So, you would try to catch the breakthrough cases. That would be the idea behind that indication.

DR. ALLEN: So, in other words, you would do the culture testing at 24 hours and then this would be done immediately prior whereas, under a release test indication, you would not have to do a prior culture. There would be sufficient data, you would have sufficient confidence, and it would be -- this test alone, the rapid test alone, could be used as the only test for release indication.

DR. QUINN: Then just a point of clarification. Number two, in addition to the sponsor needing to commit to the follow up postmarket study, that is irrelevant to these three issues here?

DR. VOSTAL: No, that is relevant.

DR. QUINN: The way you describe it there is that, where the product is tested by the device and

released as no bacterial growth at release will be now re-tested with a culture based device, at out date, to confirm the initial test results, and then you get the statistics for that. The way you are describing it, it is the flip.

DR. VOSTAL: So, which slide would it be on?

DR. QUINN: It is on our document that we were given at the outset. This is wrong.

DR. ALLEN: Let me interpret this. What I would suggest that the committee do is to vote on the words that are on the question, with the understanding that the FDA is going to take all of the comments and the discussion that they have heard and modified the scheme as appropriate.

What we are saying is that the tiered approach does make sense. In other words, for quality control only you need less data than you do if you are doing adjunct release, and you need much more data to be certain if you are doing release testing only with this rapid device, regardless of the scheme.

DR. QUINN: So, I would say yes, except that I am uncertain about this adjunct -- it is clear there is a lot of confusion over this adjunctive testing. So, I will do a qualified yes, we need more clarification on adjunctive testing.

MR. JEHN: Dr. Finnegan?

DR. FINNEGAN: My vote is no. I think that it

does not answer an urgent clinical need and it is too restrictive on the industry.

DR. CRYER: I will give a qualified yes as well.

DR. BALLOW: I will say yes as well. Initially I thought the adjunct testing was kind of onerous because the incidence is one in 5,000. After hearing from the Red Cross and others that it may be possible in a fairly short amount of time, six months, to accomplish that part of the assay, I feel more comfortable.

DR. KUEHNERT: I can only split my answer into three parts. For the quality control indication, I would say yes. For the adjunct release test indication, I would say no. For the release test indication, I would say maybe.

I like the post-marketing aspect of it. I think that is very important. Some of the other aspects I would have to look at more closely.

DR. MANNO: I agree with what Dr. Finnegan said. I Think the adjuvant release test indication makes this too cumbersome, and I vote no.

DR. QUIROLO: For the two previous reasons, I vote no.

DR. WHITTAKER: I also vote no.

MS. BAKER: I also vote no.

DR. DAVIS: Yes.

DR. DOPPELT: I will make it simple. Yes.

DR. KLEIN: I would vote yes for the philosophy of a three tiered system, requiring more data for each of these, with the large and important reservation that, for whole blood derived platelets, we have nothing, and one shouldn't wait for all three tiers in order to do something about that problem.

DR. VOSTAL: If I could comment on that, you know, the easiest way for a company to get on the market is to do the quality control indication.

That is what we did with the culture based devices, and you can see what happened with those. So, we are not going to wait to see all three indications come to us. We are going to take the easiest one that comes, and the easiest one would be QC indication.

DR. ALLEN: Ia m going to vote with a qualified yes also. I think that Dr. Klein's comments are appropriate. I am voting strictly on the question which is a tiered system, different levels of data for the tiered system.

The question itself does not necessarily say the design of the clinical studies, and I am going to separate my answer on the clinical studies from the answer to the tiered system.

MR. JEHN: Dr. Katz, do you have an opinion?

DR. KATZ: I will only make the point that there

is no adjunct release test for platelets derived from whole blood. There is no test. Dipsticks are not a test.

I don't care about aphoresis platelets at this point. I couldn't care less. We are testing them, and that is fine, and I think if I ran a transfusion service, and a device sensitive at 10^3, 10^4 was available to opick up what I had missed, I would use it that way. I don't care whether it was QC indicated or otherwise.

I think that the analytic sensitivity data that is being accumulated on these proposed devices, plus some reasonable amount of specificity, should be all that is required for a point of issue indication for whole blood derived platelets.

DR. FINNEGAN: I know it is lunch time, but can I ask a question? Is there any way to IND this to make it a little more rapid for the pooled blood? I don't know what an IND is, but you talked about it with west Nile virus. I am assuming it is like a phase III clinical trial. Could you do an IND for the fueled platelets?

DR. VOSTAL: So, an IND would be for a clinical study, a clinical application. We heard a lot of comments about clinical studies here.

It would be doable, but it is a major hurdle. I think it is easier to go through a 510(k) application where you demonstrate substantial equivalence.

DR. FINNEGAN: That was my question. Is there something you could use as a model for the 510(k)? I am not making myself understood. Could you do a mini-clinical study within the 510(k) structure that would address the pool of platelets, which is the biggest immediate concern?

DR. ALLEN: We are really short on time. I think your point has been well made. I really don't care what the FDA's response is right now. They have heard your message and that is the important thing. Would you go ahead and summarize, please?

MR. JEHN: Yes, in summary we have nine yeas -- many are qualified -- and six nos.

DR. ALLEN: Okay, we do need to get to -- if anybody wants lunch, we are going to need to break soon. Can we move on very quickly? I am willing to take five minutes, because we have had discission of the other questions, to see if we can come to conclusion quickly.

Number two, what would be the minimum sensitivity for detection of a contaminated platelet unit. Can we just go around and let everybody say what they would accept, rather than spend a lot of time on what the recommendation would be. Is that a satisfactory answer? It is not a yes no.

I want to go around the table and just ask people to give a response to what the minimum sensitivity for

detection of a contaminated platelet unit should be for one of these rapid detection devices.

DR. MC GEE: First, I haven't the slightest. Based on the little tiny bit of data, I would have to say four, N^4.

DR. SZYMANSKI: I think 10^3 would be fantastic, 10^4 would be acceptable and 10^5 would be okay.

DR. QUINN: To get something out there rapidly, 10^4.

DR. FINNEGAN: 10^4.

DR. CRYER: 10^4.

DR. BALLOW: 10^4.

DR. KUEHNERT: I am really not trying to be difficult, but it is a little ridiculous to put all bacteria into one category and start shouting out numbers. I just really have a problem with this.

I think each bacterial species has to be looked at separately, and you want to obviously go before the log phase. So, that is the point at which you want the minimum sensitivity to be.

DR. MANNO: 10^4.

DR. QUIROLO: 10^4.

DR. WHITTAKER: 10^4.

MS. BAKER: 10^4.

DR. DAVID: 10^4.

DR. DOPPELT: 10^4.

DR. KLEIN: Just going by Dr. Kuehnert's remarks, between 10^4. and 10^5.

DR. ALLEN: I don't think we have any microbiologists on the panel. It wouldn't have made it this far in the discussion.

I am going to go with a preferred level of 10^4. 10^5, I think we have heard data indicating that would be useful, and my guess is that we certainly don't want to put any absolute limits on it, because I think that the first generation of tests are not going to be as sensitive as the second and third generation. I would suspect, if we start out at 10^4 to 10^5, we are going to get improve in that over time.

DR. KATZ: I will not quote Voltaire again, somebody beat me to it, but 10^4 sounds like a pretty reasonable starting point to me.

MR. JEHN: It looks like 10^4.

DR. ALLEN: And the final question is the kinetic comparison time sampling, spiking study and appropriate design of an equivalency demonstration between culture based and rapid test devices. That I am going to take as a yes no. Any comments or discussion before we vote on this one? Again, I think we have had time for discussion on it. Let's go ahead with the vote.

DR. MC GEE: A qualified yes. If it is designed right, I think it can be an important step.

DR. SZYMANSKI: Yes.

DR. QUINN: Yes, with that same qualification. It has got to be designed right, and I think data that was presented from one of the manufacturers was in that right direction. So, yes.

DR. FINNEGAN: Yes.

DR. CRYER: Yes.

DR. BALLOW: Yes.

DR. KUEHNERT: Yes.

DR. MANNO: Yes.

DR. QUIROLO: Yes.

DR. WHITTAKER: Yes.

MS. BAKER: Yes.

DR. DAVIS: YES.

DR. DOPPELT: Yes.

DR. KLEIN: I believe that will give you the scientific data that you want the answer. I would say yes.

DR. ALLEN: Yes, with some qualifications, as have been explicated in the discussion.

MS. JEHN: Dr. Katz, do you have an opinion?

DR. KATZ: Yes. I have an opinion, and it is yes.

MR. JEHN: A unanimous yes.

DR. ALLEN: Dr. Vostal, any final words for us?

DR. VOSTAL: No, thank you very much.

DR. ALLEN: All right, we are adjourned from the morning session. It is 1:20. I would ask that people be back here if possible by 10 minutes after 2:00 so we can get not too delayed start on the afternoon. Thank you.

[Whereupon, at 1:16 p.m., the meeting was recessed, to reconvene at 2:15 p.m., that same day.]

A F T E R N O O N S E S S I O N (2:15 p.m.)

DR. ALLEN: The second topic that we have for discussion, which will be this afternoon, is -- sorry, we have got an update first. Committee update, current considerations on implementation of new recommendations for donor eligibility, Dr. Allen Williams.

Agenda Item: Committee Update: Current Considerations on Implementation of New Recommendations for Donor Eligibility.

DR. WILLIAMS: Thank you, Dr. Allen. Good afternoon, everyone. I have had a lot of questions about what this update is about.

It is really pretty simple. The committee has heard a lot of discussions on the progress of the inter-organizational donor history task force, and development of a streamlined donor questionnaire.

Then, FDA's subsequent review of these materials and acceptance of the donor history questionnaire or DHQ, in draft guidance.

As FDA works its way toward finalizing that guidance, there was one other strategic goal that needed to be met, and that is what I am going to cover today.

That is simply on the odd chance that a new donor eligibility criteria comes along some time in the future, how to interact that with the process that is established

for task force review of the history questionnaire and FDA's acceptance of that process.

The draft guidance for industry was actually issued in April of 2004, identifying an acceptable full length donor history questionnaire and accompanying materials for use in screening human donors of blood and blood components.

This was prepared by the interorganizational donor history task force, and it encompasses the entire collection of materials related to donor screening including the full length questionnaire, a user brochure, a medication deferral list, and blood donor educational materials.

Through this draft guidance, the history questionnaire or DHQ, is recognized by FDA as an acceptable mechanism to collect donor eligibility information for manufacturers, in order to comply with the donor suitability requirements in 21 CFR part 640.

One of the key elements to signal FDA's encouragement for blood establishments to use a standardized process was that manufacturers implementing the DHQ could include that change in the annual report as long as the questionnaire instrument was used intact, either by self interview by the donor or by administration face to face with donor staff.

Additionally, if blood establishments included more restrictive questions or changes to the questionnaire, that also could be reported as an annual report.

Similarly, as other changes would potentially be made to the document, the reporting category would step up a little bit.

Computer assisted administration would be a CD30 and other modifications to the form, or the questions themselves would need to be reviewed as a prior approval supplement.

The use of the DHQ, however, is not required or even recommended formally by FDA, but it certainly is encouraged, and licensed manufacturers can continue to use previously approved donor questionnaires.

The DHQ is, in fact, quite widely used throughout the blood collection community now, and experiences are beginning to be exchanged about its use but, for the most part, the reaction is very positive.

So, the question is, if there are future donor deferral recommendations issued by FDA, how will this be handled

Currently, the DHQ user brochure specifies that any new questions are to be added to the end of the instrument until a task force can review and comment.

Clearly, donor questionnaires do change over

time, and particularly when FDA issues new recommendations. So, we wanted to pre-define a strategy to both fulfill FDA's regulatory mandate, but also to maintain a synchrony with the DHQ task force goals that have already been established.

These include maintaining the standardization and integrity of the DHQ, providing timely cognitive assessment of proposed new donor questions or other screening mechanisms, and integrating new questions into the existing DHQ structure in a logical manner.

There are some factors that need to be considered. First of all, legally, FDA can't recognize the DHQ as continuing to be acceptable in a draft guidance until the DHQ actually incorporates the new recommendations of that guidance or an acceptable alternative. In other words, there needs to be a synchrony between the history questionnaire and any new recommendation that comes out.

Secondly, guidance content cannot be legally shared outside of the agency unless it is done uniformly to the public, the publication, or discussed publicly with notice, which limits the availability for a group like the task force to do pre-review of the materials.

Thirdly, portions of the blood community and particularly AABB have expressed a preference to proactively define appropriate donor screening mechanisms

to meet donor eligibility that is defined scientifically.

However, at the agency, we frequently are asked by other portions of the blood community to give them specific instructions as to how to implement recommendations.

So, we have a little bit of a dichotomy within the blood community as far as the degree of FDA's prescriptiveness.

So, current considerations are that, with any new draft guidance, FDA will include an implementation method that is acceptable to the agency.

That draft guidance, unless it is done on a public health emergency basis, would have a comment period. That length of comment period might vary with the importance of putting the new question into place.

The DHQ task force, as well as anyone else, is encouraged to respond with assessments, particularly with data, suggesting modifications to comments by submitting them to the docket.

In the event that the task force does not have modifications and accepts the strategy that is proposed in the guidance, upon publication of the final guidance, any new questions would be added to the end of the DHQ, appropriate modifications to the user brochure, educational materials would be made, and no further changes until the

next DHQ version issues.

If the task force requests modifications based on review and cognitive studies, FDA will review these for acceptability and incorporate them into the final guidance.

Finally, we need to cover the contingency that if the task force, for some reason, is not able to review the proposed materials, FDA will go ahead and publish the final guidance based on procedures that are proposed in the draft. Thank you. That is the end of that topic.

DR. ALLEN: Thank you, Dr. Williams. Any comments or questions from the committee on this issue?

MS. GREGORY: My name is Kay Gregory. I am from the AABB, and I have the staff responsibility with the donor history questionnaire task force.

I think what Allen is proposing is perhaps very good, but since we hadn't seen it until today, it is a little difficult for us to say how well we think that is going to work.

So far, we have had a good relationship with FDA in developing the questionnaire. I certainly hope that would continue.

DR. WILLIAMS: Thank you, and we would agree.

DR. ALLEN: Other questions or comments? I will just say that I think that the development and steps that have been taken to implement the uniform donor history

questionnaire are extremely important, a big step forward, and I would encourage the FDA to work as rapidly as possible on getting that fully implemented. All right, thank you. Anything else on the update, Allen?

DR. WILLIAMS: No, that is it.

DR. ALLEN: We will then move forward to topic two, which is public comments on the guidance for industry and FDA review staff, collection of platelets by automated methods draft, and Dr. Williams will present that.

Agenda Item: Public Comments on Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods. Introduction and Review of Comments.

DR. WILLIAMS: Thank you again. While we are waiting for the slides, FDA recently issued draft guidance on automated platelet collection, which was intended to modernize the outdated standards which, in fact, dated back to 1988.

The draft proposal addressed issues of donor safety and product efficacy, really for which data had been lacking, regarding current practices, despite the fact that the practices had become widespread.

As FDA finalizes the guidance, we are of course very interested in the many, many comments received by the docket, the deliberations of the committee at this session, and if any other future discussions are indicated.

I would also say that the agency is highly mindful of any potential impact on supply of platelets or other components and, as usual, will act carefully to balance issues of safety, efficacy and product supply.

The draft guidance has a number of different sections. It addresses donor selection and management, information provided to the donor, component collection and management, process validation, quality assurance and monitoring, processing and testing, labeling, reporting changes to an approved biologics license application, and an appendix which proposes one potential way to address a statistical approach toward quality assurance monitoring.

There were numerous comments to the docket, which opened in October with publication in the guidance and closed just in December.

So, in fact, the agency has had a somewhat limited time to consider the docket comments, particularly given the breadth and complexity of some of the information.

However, some common threads were immediately apparent, and we felt it was important to give them some rapid attention, and bring them to the Blood Products Advisory Committee as soon as possible.

Some of the current considerations relevant to some of the internal discussions will be presented today.

Three of these issue, we will present current considerations based on internal discussions and include them as voting topics for the committee to consider.

These are validation procedures for bacterial contamination, donation frequency, which includes a number of components donated per year, as well as intervals between different types of aphoresis platelet components, and donor deferral for medications that impact platelets and potentially impact the therapeutic benefit of a platelet component.

I just want to particularly stress that all comments to the docket are being considered carefully, they always are, and there remain multiple issues still to be discussed within FDA. So, those will be mentioned, and I will make some reference to the comments coming in, but just to advise you that we are not going to have all the answers as current considerations today.

The first issue is with regard to medical coverage. The draft document made a statement that FDA's interpretation of having a physician present on the premises at the time of the aphoresis platelet collection would be interpreted as a qualified physician able to arrive on site within 15 minutes in the event of an emergency.

Comments to the docket reflected that, based on

extensive current practice, aphoresis is, in fact, a safe procedure, that physician available within 15 minutes is simply not feasible for mobile collections with aphoresis devices, and this would have a trickle down supply impact that could, in fact, be major because the number of mobiles able to have that support would be diminished.

The comment was also made that staff who are aware of emergency medical interventions such as CPR and emergency calls to 911 are likely the more appropriate action than having a physician there on site within 15 minutes.

So, current thinking within FDA is to delete this recommendation. The CFR already states that licensed supplements are for licensed manufacturers, and blood establishment SOPs are to specify emergency responses, and that is specified in the regs.

There is also an issue of target yield when aphoresis devices are set up for individual donors. It considers the donor's body mass and some existing platelet counts to do a target yield.

FDA, in the draft, proposed that target yields should be set separately for doubles and for triples, $6.5X10^{11}$ for doubles and $10X10^{11}$ for triples, in order to yield individual transfusable components with a content of at least $3X10^{11}$.

Comments to the docket really stressed that this was unnecessary operational detail, that the target values and the performance of the machines were really unique to the collection devices, and that the targets should be both facility and device specific, and that the final transfusable component content was what really mattered.

So, the current consideration within FDA is to target the final transfusable component to be greater than $3X10^{11}$ platelet count.

Process validation. This also received a lot of comments, and this is one area where the discussions really still need to take place in earnest.

The FDA draft recommends that a pH meter be used routinely for pH measurement. The draft also continues the view of the regulators, not only in the United States, but I think in the European community as well, to try to move validation and quality assurance processes toward more of a statistical basis, so that a product meeting a certain standard can actually be defined as meeting that standard within certain confidence intervals.

So, for validation it was proposed that for validation of platelet yield, pH and residual white cells, that there be 95 percent conformance with the standard at 95 percent confidence intervals, and one could get at that in a fairly straightforward manner using a binomial

distribution, and tables are readily available to do that.

Comments to the docket, there still needs to be a lot of interaction with respect to this movement toward a statistical basis for validation and QC.

Often, using a statistical basis is even more efficient than some of the non-statistical measures that are in use out there, and I think it is really a back and forth discussion and some education needed that, in fact, these are not something to be wary of, that in fact, they can make the process more efficient, ultimately

Strata which are subjected to validation arose as a concern. For instance, if you have an SOP that has 13 different points, at what point od you need to stratify to consider your validation paradigm.

It is expressed by some that the criteria of 95 percent conformance and 95 percent confidence is just too strict for biological systems, that 90 percent is more realistic, given the inherent variation in some of the measures, such as platelet counting and pH measures.

So, the current considerations are yet to be determined. They are under consideration. I think it is important to note that the FDA does recognize the need to ensure comparability with performance parameters that were there for the cleared devices, and some of these clearances go back a good number of years. So, we need to make sure

that everything harmonizes with those.

The issue of bacterial contamination is the first discussion item for the committee. The FDA draft states that bacterial contamination with cleared bacterial detection systems, cleared by CBER for use with platelets, should be used to determine that 99 percent of cultures are shown to be negative within a 99 percent confidence interval. This can be accomplished by doing quality control of 500 components with zero failures.

It meets the statistical criteria, but it appears in practice that that is not necessarily easy to achieve reproducibly.

The FDA rationale behind this, I think, is important. There is a mean contamination rate for aphoresis platelets of about one in 2,000 but there are much lower rates and much higher rates that have been observed. Some of these could, in fact, be procedure related, particularly when starting up a new component preparation procedure.

It is important to remember that bacterial contamination of platelets is the third leading cause of post-transfusion fatality, and the leading cause of post-transfusion related infection fatalities.

There is a current industry standard for 100 percent QC of platelet components, but it doesn't specify the use of cleared culture procedures, which would

presumably be the most sensitive way of doing this.

For aphoresis procedures, we are aware that culture with the cleared devices is in common use, but the full extent of use in the blood community is not known.

I think part of the rationale includes the fact that culture using devices cleared for the purpose provides an important early stage detection of any improper procedures that may be in place that could result in gross contamination of components. It is simply a validation of the fact that the procedures are not introducing any sort of gross level of contamination that would exceed one percent.

There were numerous comments that came in to the docket. The leading one is that, particularly since blood establishments typically don't have laminar flow hoods, that zero failures in 500 cultures, even against the background of one in 2,000 or one in 3,000 through contaminations is problematic, in light of both the false positives that one gets with culture, and simply failures related to units that really are contaminated.

The point was made that platelet sterility is not an FDA requirement and that there is an industry standard in place that requires 100 percent quality control for platelet components, and this would make validation unnecessary.

So, what are some of the current considerations? I think FDA still retains the viewpoint that early rule out of high level component contamination due to improper new procedures is important.

The false positive issue is somewhat moot, since the validation refers to confirmed positive cultures which would, by definition, be repeated cultures from the same container.

FDA does recognize that recommending validation based on zero positive cultures out of 500 may be unduly stringent, since if you figure out the mathematics, there appears to be a 14 percent likelihood of finding one positive sample in a set of 500, when the true contamination rate is one in 3,000.

Therefore, the current consideration is that it might be more operationally feasible to allow, at most, a single failure in 500 tests, which would provide 99 percent conformance, the same conformance level, but with a 95 percent confidence interval.

So, the question for the committee is, do BPAC members agree that bacterial testing of 500 consecutive collections is appropriate for validation of the aseptic process. If not, what sample size and/or acceptance criteria does the committee suggest.

There is an extensive section on quality

validation processes.

The draft specified that QA monitoring should, in fact, have a statistical framework, not a specified one, but generically one with at least .05 alpha, and more than 80 percent power, the ability to detect greater than five percent non-conformance rate.

There was an appendix to the guidance which described a procedure known as scan statistics. This is actually based on some work developed within CBER, in which a rolling version of a statistical approach can be used to both be conservative in terms of the amount of sampling that is done, and yet be rigorous in terms of not having distinct cut offs for samples that are collected and used to determine whether a process is within conformance.

There obviously won't be time to go into detail with that today, but there does need to be further interaction on the whole statistical approach and scanned statistics in particular, because the comments to the guidance characterize scan as complex, unnecessary, and no basis for requiring it which, in fact, the FDA didn't require it, it was simply included as one possible way to approach it in an appendix.

Current thinking, there is a slide presentation on the CBER web. This is a talk that was put together for a recent set of conferences called the evolution of

statistical process control applied to blood product manufacturing.

I gave a number of these talks. I have to say, once this was explained, we got some pretty good interaction going on how this might, in fact, work within a blood establishment operation, and some sites expressed an interest in doing some pilot testing.

So, I would say give it a chance. Take a look at the slides, and hopefully there will be opportunities to discuss this further.

The scan statistics was offered as an example only. Parameters are generic, the alpha and the power. There are several published approaches to achieving that, particularly for things like residual white cell measurement.

In any quality assurance that FDA does eventually issue in final, FDA will provide those options in a user friendly table, not in a series of formulas that blood establishments have to figure out for themselves.

We recognize that the more user friendly and simpler it is, the more reliable and useful it will be to the end user.

However, specific to scan, FDA acknowledges that there currently is no supporting software for the procedure. There has been some interest in some pilot

studies, but currently no data available.

This is the second issue for the committee to consider, and it relates to the general area of donation frequency.

The draft guidance specifies that establishments should collect no more than 24 total platelet phoresis components in a 12-month period.

That is not collections. It is components. So, a triple would count as three components, et cetera, versus what I think is current practice, that 24 collections can take place in a year.

It also specifies, no more than two procedures in a seven day period, a seven day interval between double platelets phoresis and a 14-day interval between triple platelet phoresis, as well as a post donation platelet count.

I think, as I started off in the earliest introduction, this was based on some preliminary concern on some early literature, and was really a reaction to the fact that there was widespread use of many of these high volume aphoresis procedures, but no data which really addressed safety to the donors over the long term.

Fortunately, we did receive quite a bit of data into the docket. So, I think that will help to address this issue.

The rationale, the 24 collections per year, was specified in the 1988 guidance, that that predated the technology to collect double and triple collections.

Collections have since been maximized through the use of automation and a single publication, notable publication, by Ellen Lazarus in Transfusion demonstrated lowered platelet counts after repeated aphoresis procedures. This was concentrated in those who had less than 7.5 donations annually.

There are very limited data available regarding the long-term health impact of repeated maximized platelet aphoresis, and one cannot really rule out adverse events as a reason for cessation for donation.

If a donor simply doesn't return and one has no information as to why, you can't rule out that there might be some sort of health impact.

This is a very brief summary of the Lazarus paper. I believe Dr. Katz, in his talk, is going to also reference it.

It is a four-year prospective study studying 11,000-plus collections in 939 donors. The study assessed mean differences in platelet counts between the first and the last observation.

In fact, for frequent donors, typically there was a 50,000 platelet count difference per microliter, compared

to whole blood donors. There was also a nine percent deferral rate for low platelet count which was generally reversible.

Despite that observation, these are platelet counts that are diminished over time but still within reasonable levels.

The conclusion of the paper was that platelet counts decreased 10 to 20 percent over time in frequent platelet aphoresis donors, but the decrease is not clinically significant, at least within the bounds of that study, when conducted with proper monitoring and deferral policies.

Nonetheless, this paper was out there and gave some pause for thought about any future data that might come to bear on this.

Comments to the docket. Controls provided by the integration of pre-donation count and volume with donor height and weight, it is viewed by most of the commenters that these provide adequate safety controls, that aphoresis frequency is well established in practice without observed adverse events, that such a curtailing of donation frequency, particularly among some of the high volume donors, will impact platelet supply and estimates very broadly, the low is around 12 percent, the high was about 50 percent.

Important, I think there were quite a few data submitted to the docket which support stable or even in some cases increasing platelet baseline counts for long term aphoresis donors, well beyond that 7.5 annual donation frequency, and I think Dr. Katz is going to present a summary of some of these data.

There was also a comment on the post-donation count, that it potentially would require repeat phlebotomy of the donor and is unlikely to be accurate anyhow, due to volume dilution and some other factors.

So, current considerations for the committee to deliberate. FDA is considering a minimum pre-donation count of 150,000 as appropriate, which should be based on prior actual determination, post-donation count from a previous donation or a facility mean.

A minimum targeted platelet count for the machine setting at the end of the procedure should be 100,000 post-donation.

There should be consideration of modifying or removing FDA's recommendation for 24 component per year donation limit based upon review of submitted safety data. That review is just beginning. We are very interested in the talks today, but there is a consideration of modifying that.

There is a consideration that a maximum

collection for a new donor who lacks a pre-donation platelet count should be a double unit, obviously if they are eligible for that.

It would be appropriate to have a seven-day deferral for collections that are greater than a single unit, recognizing that there is a potential operational problem to this, because donors are often scheduled at the conclusion of a procedure. So, one might not, in fact, know whether that unit is going to be made into a single or a double.

FDA has already spoken with several in the blood community to solicit additional safety data for factors beyond platelet count, such as diminished plasma proteins.

FDA tends to agree that the recommendation for collection of a post-donation platelet count may not be appropriate.

So, this issue is being brought to the committee for discussion and recommendations. I think the important component of this will be Dr. Katz, representing the blood collection community, and his talk, potential impacts on availability of the draft plateletphoresis guidance on collection facilities.

A question for the committee is, do the BPAC members agree that the proposed recommendations on donation frequency, interval between donations and numbers of

components collected per year are appropriate to protect the safety of the donor pending the availability of additional safety data on larger volumes of collection. If not, please comment on limits that would be more appropriate.

Finally, I am going to defer to Dr. Vostal, who you have already seen quite a bit of today, who is going to present some of the FDA's comments to the dockets, and considerations with respect to donor deferral for medications that might affect platelet therapeutic function.

DR. ORTON: Allen, could you go back two slides, please? I just wanted to note that the minimum pre-donation platelet count of 150,000 is based on prior actual, and that shouldn't say post-donation count.

The other option is an average of several pre-donation counts or the facility mean. I just wanted to make that clear.

DR. ALLEN: I am sorry, Sharon, give that again, an average of what?

DR. ORTON: Several of the manufacturers recommend first a pre-donation platelet count. If you can't get that, you can take an average of several pre-donation counts that are historic.

So, if someone has been in three, four or five

times, you could take that average or the facility mean, not post-donation.

DR. ALLEN: Going back how far?

DR. ORTON: I think most of them, they have either two or three previous historic is what they say. So, it is right in their operators' manuals as the recommendation for platelet count.

DR. ALLEN: And the pre-donation count would need to be done on a separate venepuncture -- a specimen from a separate venepuncture?

DR. ORTON: Yes, a pre-donation count. One of the other things that came up was, did you have to have the count before you started the machine, because often you start the machine and, again, the operators' manuals do allow you to start the machine before that count gets entered. So, that is also taken into consideration.

DR. ALLEN: Questions for Dr. Williams on his presentation? Allen, I had a question with regard to the process validation, the 500 consecutive unit collections.

The initial guidance had zero failures, zero out of 500, and the recommendation was that that might be too stringent. So, you were considering one failure would be acceptable.

If you kept it at zero, zero out of 500, what would be required if somebody had one out of 500, or if you

accepted one, if they had two out of 500.

This would trigger a review of the entire quality assurance -- the protocols in the quality assurance process? I mean, what does that mean when you find that level?

DR. WILLIAMS: Given that this is at the validation stage, yes, that would produce evidence on a statistical basis that potentially the process has a problem with it, and one should go through and try to determine if there is a root cause and correct it.

DR. ALLEN: Then they would need to go through the 500 again?

DR. WILLIAMS: Yes.

DR. SZYMANSKI: You talk about validation, and to me, validation sort of means before you can start doing some procedure.

Now, there are many centers that are collecting aphoresed platelets for years and years. How do you -- this conflicts, sort of.

DR. ALLEN: I think it would be an ongoing quality assurance process. So, I don't think you would have to stop everything.

DR. WILLIAMS: The validation really would be relevant for a new procedure, a new machine, or some other new process for which there hasn't been extensive prior

experience.

DR. SZYMANSKI: But you want to run it on procedures and machines that they have been using up to now, the validation, don't you?

You know, they have been using, let's say, a Gambro machine for 10 years, and so now they have to count 500 consecutive collections; right? You don't have to start procuring platelets; right?

DR. EPSTEIN: Maybe I could clarify, because the whole idea is that it is okay to use a unit that was cultured and found negative, or using some other suitable test, you know, a 510(k) cleared quality control test.

So, it is okay to be in the manufacturing mode as long as you are doing the testing and releasing only negative units.

The nuance here is that, if you pass this validation procedure, that you could go on to a surveillance form of testing for quality control, because there is no requirement to be testing every unit.

So, the way it is set up, you don't stop production while you are looking at these first 500. That is okay. It is just that, once you have validated that, you can continue, and you don't have to test every single one. We would permit surveillance type procedures.

It is also the case that what is being said is

that, if it fails the test of no more than one per 500, what is in question is aseptic processing.

So, you would be looking back at, are your skin antisepsis solutions sterile, are proper procedures being followed prior to phlebotomy, are there problems with equipment, breaches of sterile connections, et cetera, et cetera, et cetera.

So, yes, you would want to look very thoroughly at the entire quality control scheme, because we don't expect rates greater than one percent.

That is kind of a soft test. You are only looking for outlier contamination frequencies above one percent, when we think that a fully state of the art aseptic procedure should yield contamination rates no greater than one to two thousand.

DR. SZYMANSKI: A 500-unit culture was not a previous recommendation.

DR. EPSTEIN: This is a new recommendation.

DR. FINNEGAN: Dr. Williams, one of your questions, the one on the proposed recommendations for donation frequency, et cetera, you are asking us to vote on something that you have already said you don't think is really good, and this is a draft of a document that you haven't actually done the final guidelines on yet. So, can you clarify that for us?

DR. WILLIAMS: I think that is a little bit of a fact that some of the materials have to be made available while the FDA is still making current considerations.

I think Jay may wish to comment, but probably the most relevant discussion for the committee is to address the current considerations that are being presented, rather than the recommendations in a draft guidance.

We have already started the thinking process, and we would like some go-no-go in terms of current thoughts. Hopefully that addresses the current concern.

MR. WAGNER: Steve Wagner from the Red Cross. I noticed that there was a requirement for machine settings on an aphoresis instrument of 100,000, as an end setting.

The comment I have is that there is a lot of data already now in the literature that, for one of the aphoresis manufacturers, that setting does not take into account splenic mobilization.

When you take splenic mobilization into account, a final count of 80,000 is a more appropriate setting, because with one of the instruments, there is no taking into account the platelets that go into the circulation while you are donating them. So, I was wondering if you had thought about that at all.

DR. ORTON: I am aware of that data. It is something that we will take into consideration, but

basically, from what we have available, from what has been submitted to us at this time, we thought that this was an appropriate cut off. So, we are still evaluating everything.

DR. LEITMAN: I want to go back to the bacterial contamination. The industry has clearly already self-imposed a standard for release of a platelet aphoresis component, which is that there shall be a test to assure that bacteria can't be detected.

So, the industry has 100 percent testing of its aphoresis components. So, FDA seems to be calling that process by a different name, calling it process validation, but there doesn't seem to be a need for that based on the industry standard.

You could define an acceptable level beyond which the facility should look carefully at its practices, but there seems to be no need to give this a name for a process that is already going on by a different name.

DR. WILLIAMS: I think the answer, like with the fact of differences in methodology, producing validation is a cleared culture system for aphoresis platelets.

We are aware that these systems are used commonly in the field for aphoresis platelets, but we don't know how extensively, and potentially measuring pH or other measures might not serve adequately for validation of a procedure.

That was the thinking, to make use of the devices that are cleared for quality control testing of aphoresis platelets, because there is a range of testing out there.

DR. EPSTEIN: I would add that there is also a distinction that FDA has been making between 100 percent quality control testing and release testing.

Technically speaking, products can be released before you have results of quality control, and quality control can also be done on outdating units. So, there is a real difference.

If people are doing quality control testing, 100 percent, pre-release, that is good, but it still leaves open what is the implication in terms of labeling.

We have been trying to move the system toward a validated label. So, if we say we had a negative culture, we know what that means, as far as the predictive value, that a unit release will have less than some amount of risk of, and level of, contamination.

Those data will only be forthcoming when these phase IV studies are completed. That is why we have maintained a distinction between what is a release test and what is a quality control test.

Of course, FDA is happy if people are doing testing before product release, because that is making blood safer. We are not against that.

The debate is over what label does that product get in relation to what that test meant. We are still trying to sort that out.

DR. ALLEN: This validation, do you have certain requirements for a culture as far as volume and bottles and all of that? It is dawning on me now that you are requiring something different. It is more than quality control.

DR. WILLIAMS: It is using a cleared device according to the labeling for that device. By labeling we are saying the package insert, the instructions, et cetera.

DR. ALLEN: So, you are. They have to change what many blood collection facilities are currently doing.

DR. SZYMANSKI: I wasn't clear about this document as to when you require the culture to be done, on day one or at out date, if you count the 500 units.

DR. WILLIAMS: I didn't get all the question, I am sorry.

DR. SZYMANSKI: I didn't understand what is the time required to culture the units? Is it day one or at out date?

DR. ORTON: It would be following the directions for the devices the way they are cleared. Each of those devices for quality control gives you parameters on when the bag should be cultured, and how long a time period,

what volumes, et cetera, and they are different. So, it is per the directions for which the device is cleared. That is the best way I can describe it.

DR. SZYMANSKI: So, the manufacturer determines this?

DR. ORTON: There are three devices that are cleared for quality control testing for bacterial contamination of platelets.

DR. SZYMANSKI: Yes, but this is not for quality control. This is for the validation.

DR. ORTON: Right, but we are asking that, for the validation you use a device that is cleared for QC and use it in the way in which it was cleared, use the procedure for it.

DR. ALLEN: I think we do need to move on. Dr. Vostal, are you up next?

Agenda Item: Introduction and Review of Comments

DR. VOSTAL: So, I am going to talk about donor deferral due to intake of antiplatelet medications, and I first would like to acknowledge Dr. Orton's input into gathering the background data for this presentation.

As part of background, I am commenting on the guidance for industry that was released in September 2005, and this guidance included new proposed deferrals for some medications that would affect platelet activity.

Now, what is our rationale for looking for new donor deferral guidelines? We think that the rationale is that there have been changes in platelet transfusion practice that drive the revision of the deferrals due to non-steroidal anti-inflammatory drugs and antiplatelet medications.

For example, there is now a higher percentage of single donor aphoresis platelets transfused. That means if the platelets are inactive, this could lead to a decreased hemostatic performance when these are transfused.

Now, this is different than back when the original guidance came out in 1988. Back then, whole blood derived platelets were the majority of transfused platelet product.

These are transfused as a pool. If one of the platelet units out of the pool is inactive, there will be less effect on the overall performance of the pool.

So, back then, a donor that took aspirin, whose platelets were combined into a pool would have less of an effect on the performance of the transfused platelets.

Now, it is still true today that whole blood derived platelets are transfused as a pool. However, these pools are getting smaller.

It is more common now to see pools of four to six units as opposed to six to ten units that used to be done

in the past.

This could, again, lead to a higher percentage of the pool being inactive, if one donor has an antiplatelet medication.

Finally, there are now lower transfusion triggers, on the order of 5,000 to 10,000 platelets per microliter, versus in the past it used to be 20,000 per microliter.

So, here is a table that summarizes our proposed deferrals for these donors. For aspirin or aspirin containing drugs, we propose a deferral should be five days, for non-steroidal anti-inflammatory drugs it should be three days, for plavix, five days, and for ticlid, 14 days.

Now, there are a number of comments that were made to the docket aimed directly at these new deferrals, and here is a summary of a few of them.

For aspirin, the comments included that it was not based on current practice, there were no observed adverse patient events from aphoresis patients collected 36 to 48 hours after aspirin ingestion, and there are some references provided.

Another comment was that it would result in a significant donor loss, and that 10 to 30 percent of unaffected platelets are necessary for normal platelet

function.

For the non-steroidal anti-inflammatory agents, the comments were that the references were not peer reviewed, that the platelet effect is reversible, some drugs have no platelet affect and, again, it would result in a donor loss. For plavix and ticlid, deferral should be 24 and 48 hours.

Finally, general comments were that the guidance were too restrictive, and the donors were willing to stop medications for a few days, but not likely more than three days.

So, with that in mind, we actually went back to literature and started looking around for more documentation on the effect of these drugs.

We had to consider what the term reversibility meant. The reversibility of an anti-platelet effect is based on whether the drug effect on a target enzyme is reversible or irreversible.

Now, you have two situations. You have the situation of reversibility in the donor and reversibility in the patient after it has been transfused.

In the donor, if it is reversible, if the action of the drug on the enzyme is reversible, then you look at the time to reversal of anti-platelet effect.

The time to reversal of the anti-platelet effect

depends on the last drug ingestion, and then four to five plasma half lives of that drug. You have to wait until the drug is washed out.

If the effect is irreversible on the enzyme, then there is not much you can do, but you have to wait to replace the affected platelets, and this replacement takes place in about 10 percent of the platelet pool per day.

Now, in the patient, if the effect of the drug is reversible on the enzyme, the effect on platelets, the reversibility on the platelet depends on the rate of elution of the drug out of the platelets.

That means if those platelets have been sitting in plasma that contains the drug and then are infused into the patient, the patient does not have that drug on board. So, the time to reversal of the effect is dependent on how fast the drug can elute out of the cells.

However, if the effect on the enzyme is irreversible, then again you have to wait until the platelets that are inhibited are cleared from circulation.

So, just to review some of the drugs that we are talking about, for aspirin and aspirin containing drugs, the plasma half life of aspirin is actually relatively short, about 30 minutes.

However, it has an irreversible inactivation of the cyclooxygenase, both 1 and 2 and, since platelets have

cyclooxygenase 1, these are then inactivated for the duration of their life span.

For non-aspirin containing, non-steroidal anti-inflammatory drugs, these drugs reversibly inhibit both cox-1 and cox-2, and some are selective for cox-2.

The cox-2 inhibitors do not inhibit platelets. So, we don't really have to be concerned about those. The inhibition of cox-1 is reversed when the drug is not present in plasma.

So, since this is a reversible effect on the enzyme, you have to wait four or five plasma half lives since the last ingestion for the drug to wash out or, if you take the treated platelets and place them in a medium that doesn't contain inhibitors, as in transfusing into a patient with no drug on board, then you have to wait for the elution of the drug from the cells.

Finally, there are other anti-platelet drugs on the market, plavix and ticlid. These drugs irreversibly block platelet ADP receptor and inhibit platelet activation.

The platelet effect to normal, for plavix, the platelet effect to normal is five days, and for ticlid the platelet effect to normal is 10 days.

So, when you are searching the literature, you have to decide what you are going to use to assess the

effect of aspirin on platelets.

There are several in vitro studies or methods that you can look at. We focused on aggregation because it has been around for a long time and some of these papers actually date back 10 or 20 years.

The effect on aggregation is inhibited by aspirin, but aggregation alone is not predictive of platelet efficacy in vivo. So, you have to take some of these results with a grain of salt.

The similar is true for skin bleeding time. This is an experiment that is performed with a standard sized cut on the skin of the donor.

You can measure time to cessation of the bleeding from this cut. Now, this skin bleeding time is also prolonged by aspirin.

However, there has been a lot of experience with this methodology, and it has been determined that it is not predictive of surgical bleeding risk, and we don't usually use this to predict platelet efficacy in vivo.

So, these are two studies that suggest effects of aspirin, but they are not the absolute study that we could use to look at the effects of aspirin.

The right study to do would be a clinical trial, where you take thrombocytopenic patients and transfuse them with these either aspirin or other inactivated platelets.

The end point of these trials would be a bleeding based on something like a WHO bleeding scale. This would be similar to a study that was done for the S59 treated platelets in a sprint trial.

This was a very large trial of over 600 patients that looked at the efficacy of S59 treated platelets, and it would be the standard of other clinical trials that looked at the effect of drugs on platelets.

However, this is an expensive and burdensome trial. We don't think we are going to be able to get this to study the effects of aspirin and other non-steroidal drugs. So, we are really stuck with looking at the literature for tests such as aggregation and skin bleeding time.

Just a little brief review of what platelet aggregation is. This is a schematic. Platelet aggregation is done on platelets that are in suspension, usually in plasma.

The suspension is stirred, and then you add an agonist. As the platelets become activated, they start to stick together, and you get this nice aggregation curve.

So, for strong agonists, your curve is relatively sharp and goes to the maximum in a nice, smooth curve. For weak agonists, such as ADP or epinephrin, platelet aggregation comes in two phases.

You get an initial phase, this is followed by the secondary phase. The secondary phase is based on thromboxin production and the release of ADP from platelet stores.

Now, if you do disaggregation on aspirin or NSAID treated donors, for the weak agonists, you tend to eliminate the secondary phase of aggregation. So, you get initial phase and frequently you get disaggregation.

The effect of aspirin is not a strong agonist or a dual agonist. So, we focused our literature search for articles that talked about single agent induced platelet aggregation.

So, the basis of deferral of the non-aspirin platelet inhibitors, ideally the deferral period should be based on time to reversal of platelet inhibition in the recipient.

When this is not known, the deferral should be based on the reversibility rate, or the rate at which platelet function becomes normal in the donor after discontinuation of the drug or, again, the four to five half lives.

We have also looked at platelet function. The platelet function was assessed by a single agonist induced aggregation.

So, as I mentioned, we were encouraged to go look at some specific references. So, this is a reference by Dr.

Zeiler published in Transfusion in 2004.

This study looked at two groups of patients, group A, that was given 500 milligrams of aspirin 12 hours prior to donation, and group B that was given no medications.

They looked at the donors before and after they donated aphoresis products, and they did aggregation with several agonists.

I hope you can see, this is a low dose ADP agonist in a group that took the aspirin. It is about 40 percent aggregation, as opposed to the control group, which is about 73, 74 percent.

If you increase the ADP dose, you get higher aggregation, about 50, but still it lags behind the control group.

The same is true for collagen. Collagen is a strong platelet agonist. The aggregation is 63 versus 76. So, you can see that, before donation, the donors did experience or did demonstrate the effect of aspirin on board.

The same was true when they were tested again after donation. So, the donation itself did not affect the performance of the platelets.

The authors then went on to look at the aphoresis products collected from these donors, and they ran a number

of in vitro studies.

The one we are focusing on here is the aggregation results. Here they are looking at aggregation at day one, day three and day five.

You can see that, even at day one, there is already a difference between the aspirin treated and the non-treated donors.

At day three and day five, the authors declared that there was no difference between the performance of the platelets, because they were not getting any difference in their aggregation.

Actually, looking at the study, I am not sure that is a fair conclusion, because your assay, at this point is, insensitive to be able to detect any differences between the two groups. So, it is not clear whether the effect of aspirin goes out in three or five days.

Here is another study we were encouraged to go look at, and this was done back in 1972 in New England Journal of Medicine by Dr. Stewart.

They also looked at donors, and then thrombocytopenic patients, transfused them with the products of the donors.

They put these donors on 600 milligrams of aspirin, either one hour before, one day before, two days before or -- I am sorry, they put them on 600 milligrams of

aspirin, and they did a skin bleeding time, and they looked at the bleeding time at one hour, one day, two days and three days.

You can see that, comparing to the skin bleeding time without any medications, which is about four minutes, you get a nice effect that peaks at day one, and then it declines by day three. So, it appears that these donors clear the aspirin by three days.

These authors also looked at epinephrin induced aggregations, specifically for the presence of the second wave.

They graded the wave as present, equivocal or absent. You can see at the beginning, without any medication, all donors had a second wave aggregation, and this disappeared and started to come back at day two and day three. So, a nice aspirin effect.

So, the second part of the experiment was taking platelets from donors who were exposed to aspirin and, again, they are doing a skin bleeding time on these donors.

These donors are thrombocytopenic, so they have a prolonged skin bleeding time of greater than 20 minutes. When they are transfused with platelets from donors who had no meds, this is nicely reversed, and the skin bleeding time is now less than 10 minutes.

Now, if these donors had aspirin 12 hours and

then one hour before, the reversal of the skin bleeding time is not as obvious.

Now, if they took 600 milligrams of aspirin and waited 36 hours, the reversal of the effect of the bleeding time is similar to when they had no drug. So, it suggests that, by 36 hours, the effect of the drug has worn off in these donors.

Now, I think this is a very nice paper. The only issue that I had with this is the transfusion triggers for these patients was set at 20,000 per microliter, which is a little bit higher than what we would be experiencing now, and those platelets that the patients have on board actually a significant amount to reversal of the bleeding time.

So, the results may be different if the transfusion trigger in these patients was lower, 10,000 or 5,000 per microliter.

Another study we looked at -- this is a study that was published in the Scandinavian Journal of Hematology by Dr. Cronberg in 1984 -- they looked at donors who ingested different medications, and then they followed reversal of the platelet effect over a number of days.

They looked at this by a full single agonist induced aggregation. So, again, they are looking for the presence of the second wave induced aggregation by a single

agonist.

Before they took aspirin, five donors had full aggregation, this went away after aspirin and persistence, the absence of the aggregation persisted until day five. So, the reversal of the effect of aspirin took up to five days in this study.

They looked at some of the other drugs like puroxicam. The reversal took up to three days. Other drugs, such as naproxin was almost reversed by day one, indomethacin was reversed by day one, and ibuprofin also reversed almost by day one.

So, the next two tables actually summarize some of the results we found on the drugs in the literature. We were looking for the reversibility rate based on the platelet aggregation or skin bleeding times.

There is a lot of literature, and we were just trying to find out specific reversal rates for these drugs, and I am not really going to go over them, because you can look them up in your handouts.

So, finally, based on the comments in our review of the literature, we have revised our proposed deferrals. This table summarizes what we are proposing at this time.

So, the original proposal was five days for aspirin, three days for non-steroidal anti-inflammatory agents, five days for plavix and 14 days for ticlid.

We have revised the aspirin deferral to three days, and we have broken down the non-steroidal anti-inflammatory into three groups.

In the motrin group, which will be propionic acid derivatives, we don't think there should be any deferral. For all other non-steroidal anti-inflammatory agents, there should be one day deferral, with the exception of feldine, because this has a very long half life. So, we think that should have a deferral of three days.

For the cox-2 inhibitors, since they don't affect the platelets, we don't think there is need for any type of deferral.

Then for plavix and ticlid, those two drugs have irreversible effects on the platelets. They have a very long half life. We think they should stay long, five days and 10 days.

A final note, I think this is a very important note, the FDA does not believe it is appropriate for individuals to stop taking medications prescribed for clinical conditions in order to donate.

So, we don't want patients to go off their medications just because they think it is their duty to donate.

This is the question to the committee. Does the BPAC agree with the revised proposed donor deferral

criteria and, again, aspirin is three days, motrin group no deferral, all other NSAIDs one day, except feldine, that is three days. The cox-2 inhibitors, there is no deferral, and five days for plavix and 10 days for ticlid.

DR. ALLEN: Thank you. I am sure that industry and certainly the committee appreciates this update and revisions, based on the comments. Questions?

DR. SZYMANSKI: Yes, I congratulate this change. I am wondering about this ticlid and the other drug, because I don't think you should really even take these donors on plavix, because they need it, and they should not really stop them. All the other recommendations, i think, are just fine.

DR. VOSTAL: Right, we agree with that.

DR. CRONSTEIN: I guess I had a question about the aspirin data that you showed. That was a single dose of 600 milligrams, and actually you minimized -- the graphics minimized the effect, because there was a doubling of the bleeding time in those patients.

If you look, the Y axis is very different in the right hand panel than it is in the left-hand panel. So, there is a doubling, more or less, of the bleeding time and that really brings it outside.

I guess the problem is that there are a number of ways that aspiring is taken by people. Either they are

taking 80 milligrams per day for prevention, either primary or secondary, much in the way that they are taking plavix or ticlid.

Those patients probably should be excluded, I would think, for two reasons. One, the cumulative effects of aspirin over time are probably very different from the single dose that you put up.

If they are supposed to be taking this to prevent something, they probably shouldn't be stopping it for a period. I guess the more casual user of aspiring or aspirin-containing products is a different issue, and I would agree that probably three days is long enough.

DR. KLEIN: I guess we will be discussing this in great detail later, but I have a question and a comment. The comment first.

I think the word inactivation in platelets in the same sentence with aspirin is totally inappropriate. I have been taking aspirin for years. I hope all of my platelets aren't inactivated, or I would be bleeding like a stuck pig.

Clearly, aspirin does something to platelets, but it does not inactivate them. The question I have is, why did you select three days? What is the rationale for that?

DR. VOSTAL: The 36 hours that the 1988 guidance was based on is, I think, based on studies like this. As i

was pointing out, I think this may not apply to current transfusion practice, because these were transfused at 20,000. Current donors might have a lot lower platelet counts.

So, the fact that you get reversal after 36 hours here may not be true if you had someone with a lower platelet count. Their bleeding time may still be elevated.

So, we think it would be more prudent to wait a couple more days until the effect wore off, until they actually produced more non-aspirin affected platelets.

DR. KLEIN: I guess I would just say that, as you said earlier, that bleeding time model is totally irrelevant. It doesn't predict anything. So, I am a little reluctant to base the recommendation on having the effect of a paper from 1972 with a model that has been discredited. I guess we will discuss that in some detail.

DR. VOSTAL: If I could respond, you are right, that your platelets probably are working more than adequately now. However, if you were to undergo elective surgery, your surgeon would have you stop the aspirin, and that is because you would be at a greater risk of bleeding.

I think the presumption is that we are giving platelets to people who need them because they either are bleeding or are at greater risk or don't have sufficient other capacity to clot.

So, I think it is rather unfair to compare yourself to this, and I agree, we don't have very good functional tests for platelets. So, you sort of go with what you have got.

DR. ALLEN: In your table where you have the reversibility rate for several of the non-steroidals, what was the dosage of tordol(?).

DR. VOSTAL: I don't remember.

DR. ALLEN: The reason why I asked is, in many surgical procedures, the anesthesiologists love tordol because it gets the patient out of the pacu, but the surgeons aren't particularly fond of it. For big procedures now they often like to give tordol and that has effects on bleeding.

PARTICIPANT: I have a logistical concern. The more different numbers of days of deferral you give a screener in a booth, the more errors are going to occur.

So, some things are three days, some things are five days and some things are 10 days. They are going to screw up, I am sorry.

Right now I don't have a proposal, but I would just ask the committee and FDA to consider that. One very simple proposal would be for the agents that are for serious illness, the plavix and the ticlid, I think the only approved indications are coronary disease, stent, and

stroke or stroke risk. We don't want those donors in the donor center. So, you could make both of those 10 days and no one would argue or be concerned. The others are more problematic, and I would ask you to re-think that.

DR. KUEHNERT: I just wanted to ask for a point of clarification on this because I am not sure what blood collection facilities do when they ask about medication history.

If they find that a person is taking a medication for a known clinical disease, is that different than if somebody takes a medication because it is PRN for some sort of affliction that -- it basically is for pain management? Is that differentiated at all?

PARTICIPANT: It is probably all over the board. It is clear the AABB standard -- I can't quote it exactly, but the donor is not going to be the sole source of platelets if the donor is taking aspirin within the last 36 hours, and all the rest is probably at the discretion of the individual center.

So, for example, at my center we are not deferring for most NSAID use, unless it is a disease for which we defer. So, we don't need to be bleeding rheumatoid patients, because often enough they get anemic on their own, for example.

If somebody was taking therapeutic NSAIDS, it is

not so much the NSAIDs we are deferring for. It is the clinical condition. We have a longer deferral for feldine because it seems like a good idea. There is no data. It is probably all over the board and that is not probably. It is. If they are taking daily aspirin, they can't be a platelet donor. That is the AABB standard.

DR. KUEHNERT: I am asking if you ask why they are taking it because they may say, sure, I will go off it for a couple of days. That wouldn't be a very good idea for some things. I just wonder if that gets differentiated or not.

DR. BIANCO: The philosophy in medical history is that we don't defer because of the medication. We go after the underlying reason why the individual is taking the medication.

It gets more confusing with these over the counter things like aspirin, like everybody in the country is taking a baby aspirin. Some take every day or some take every other day, or some don't take it for whatever reason.

It is always the screener. There are so many questions that we look for heart disease, we look for lung disease, we look for are you feeling well, did you have a surgery, and that is going to be part of the screening process.

So, a patient with heart disease, it is unlikely

that a center will be willing to take that patient, even under autologous conditions. Many questions will be asked.

DR. VOSTAL: Let me point out that the current uniform donor history questionnaire does not systematically elicit this information.

The medication question is about drugs on the deferral list. Then there are questions about are you well and healthy and heart and so forth. So, any of these proposals require very, very careful thought about how we would amend the uniform donor history questionnaire.

DR. EPSTEIN: Just a quick follow up, a follow up to Susan's point about lumping versus splitting, part of FDA's original thinking in putting forward a three day deferral proposals for NSAIDS was lumping because we knew that there was an outlier which was feldine. We didn't know about other outliers at the time.

Of course, most of the comments came back, why are you doing that, it is just feldine. So, you sort of can't win either way, and I don't know the right answer, but that is why we defer to the wisdom and advice of the committee.

DR. ALLEN: Again, I think Dr. Leitman's point was a very valid one. On the other hand, to the extent that we are moving toward computer based screening data collection, and computer based algorithms, it will simplify

the decision making to some degree, but we aren't there yet.

DR. SZYMANSKI: I just want to remind everybody that when platelets are stored, even if they are taken from total non-aspirin-ized donors, they lose their ability to aggregate.

Therefore, when you test platelets that have been stored, you use double agonists, and then they function well. So, this could be the same for people who are taking NSAIDs or even aspirin, who knows. Why don't say that you can't transfuse seven day old platelets.

DR. KLEIN: As we know, aggregation is totally meaningless in terms of predicting bleeding. It is great for publishing papers, but in terms of clinical transfusion, no one has ever demonstrated that it is a meaningful measure.

DR. SZYMANSKI: But we are talking about NSAIDs. They must have some importance.

DR. VOSTAL: They obviously have some effect in vivo, because otherwise he wouldn't be taking his aspirin every day and everybody else wouldn't be. I imagine most of the people in the room are taking daily aspirin. So, it must have some effect. If it is an important effect, I don't know. That is up to you guys here.

DR. SZYMANSKI: I think that aspirin, platelets,

if they are taken very soon after taking aspirin, are not going to be effective in transfusing patients, in order to clot or not clot, or bleeding. The other effects, I don't know. This is a very complicated question, I think.

I would agree. As Dr. Klein has pointed out, there are no good tests of how well platelets will function once they get transfused.

DR. KLEIN: We have had this practice for what, 30 years? There is absolutely no evidence that there has been a problem here, I guess is what I am saying.

We have looked very carefully and some of us have, in fact, used four units of platelets as a standard dose for many, many years.

In the absence of a problem, I am not sure that you ought to change a standard of practice unless you have data. So, I am asking, where are the data.

DR. SZYMANSKI: Yes, I think so. AABB says that you can keep platelets, after taking aspirins for up to 36 hours, and I don't know if there are any harmful effects of that, exactly what you are saying.

DR. KLEIN: How would you know if there is a problem? IF you are giving the platelets and they sort of work mostly, how would you know that there is a problem?

Why would you change in the absence of seeing something. Why would you assume that there is a problem. I

am not recommending that we do a large scale with aspirinated versus non-aspirinated, as was done in the sprint study, at all. I am just asking why one would change in the absence of any evidence that there is a problem unless there are some new data that have been found, and I haven't seen any.

PARTICIPANT: I will just comment, how do you know, when you operate on someone, you know if they are taking aspirin or particularly plavix, they bleed, they don't clot, and it becomes troublesome every now and then.

The last thing in the world I would want to do is take platelets from a guy who was on plavix and give them to the guy who is on plavix that I am operating on as an emergency. It is like trying to put a fire out with an empty bucket of water.

I can't imagine that you would even accept somebody on plavix as a donor at all. As far as the aspirin is concerned, I would just concur with what you guys said over there.

Particularly when you consider the rigor with which the FDA requires things to be studied, that the data you presented today is certainly no reason to change anything you are doing.

DR. ALLEN: This is an interesting discussion between the perspective of the clinicians in practice and

the perspective of the component collectors.

I think we need to move on in our discussion. We will hear from the collector's perspective, Dr. Katz, potential impacts on availability of the draft plateletphoresis guidance on collection facilities.

Agenda Item: Potential Impacts on Availability of the Draft Plateleletpheresis Guidance on Collection Facilities.

DR. KATZ: I think I want to thank Sharon Orton for asking me to do this. Anyway, I guess the title is self explanatory, even if there is an extra word in it.

I am mainly going to deal with the issue of number of components and number of procedures, because that is what I was asked mainly to do.

I have this list of four bullet points before I saw some of the adjustments that FDA has made since the last time we discussed this.

I really think this is a perfect example of the sort of iterative process that regulation ought to be, and I think we are all moving closer together and I think it is actually kind of neat that we are meeting in the middle somewhere, where it is reasonable.

So, these were the issues, the NSAID deferrals, physician on site within 15 minutes and that one is gone. I am pretty sure I still don't understand this one, and I

will explain why in very brief comments, but this is the one I will spend most of my time on.

On the NSAID issue, this is the Stewart trial. This is the standard. The AABB standard comes from this. We have been doing it since the early 1970s, and I want to echo what Harvey said, which is that we believe that it is working pretty well.

The implications of changes may be substantial and I am interested in why we think it is broke. That is not a rhetorical question. It is, I think, a serious question.

This is not the only study. This is, of course, the bleeding times showing that, if you have stopped the drug 36 hours ahead, that the bleeding time is now normal. I think the caveats about bleeding times, aggregation studies and all of that are very appropriate.

This was a letter to the editor the same year in the New England Journal. They didn't give a lot of data but what they said is, they gave a substantial dose of aspirin 18 to 24 hours before phlebotomy, transfused, pooled aspirinated platelets into leukemic patients, and had a striking decrease, not further quantified, on the bleeding time, suggesting that potential donors need not be rejected because of recent aspirin ingestion.

This was not a huge study, nor was the Stewart

study. Then the only other one was this one by Cheryl Flicter and Harker from 1976, and this was a little bit different.

These people actually had aspirin on the day of collection. Those platelets were then pooled into a fairly profoundly thrombocytopenic patients, and they corrected the bleeding time after transfusion in all of these patients in four to 18 hours.

Now, remember, these people had aspirin on the day of collection. So, it is not controlled clinical trials, but it is how we got to where we are now, which we believe clinically is working pretty well.

The non-end-stage, you have heard all this from Jaro, and I think the critical issue is, we are giving treated platelets on occasion, that is true, but they are going into untreated recipients. So, the relevance of the half life of these drugs in the plasma of the donor is not kind of linear to me.

This is the same data that he showed you in tabular form, just demonstrates that for these the correction of epinephrine induced aggregation is pretty complete by 24 hours after the last dose, and in fact it is improving even sooner then that.

This is another study, this is the in vitro bleeding time, the PFA is a platelet function analyzer and

they measure what's called, I think it's a closure time, a capillary of some sort is plugged up by the platelets. And this is Ibuprofen, actually quite high dose Ibuprofen for a week, and by 24 hours after the last dose this parameter is normalized, so I think that's kind of where we are.

This was a little survey we did after the guidance came out and I recovered from my audible gasp, people who read the AP will understand that. 112, and we were asking specifically about NSAIDs other then aspirin. Two had stopped donating because they take them quite regularly for better or worse reason, 21 used occasionally, two regularly, and would need a reminder, 41 use occasionally but would remember to stop, 48 never take them, so there are some logistics and donor education efforts that will have to be made if we're going to have a series of formal deferrals. I think we can do this if we think it's the right thing to do, I just would like to think it's the right thing to do.

This is about physician on site within 15 minutes, and I only wanted to put it up to just ask the audience in a show of hands how many people want CPR by a pathologist?

[Laughter.]

Not I.

And then here's the culture issue and then I'll

move on to what I was asked to talk about. We knew from a survey that has been completed and submitted for publication that more then 90 percent of apheresis platelets are being tested with a culture based method and if required Mark Brecker(?) I think has more detailed information. The positives or successes in some funny sense are discarded, collection facilities have a very strong economic incentive to minimize false positives so we don't see that this is an area that requires regulation, we have every incentive that we need to make sure their arm preps and sterile connecting devices are working the way they are.

My platelets are cheap at $400 dollars, okay, so every time I have to throw one away because I contaminated the culture at some point in the process, contaminated a component, it's $400 dollars of real cash flow that my center cannot realize, so I don't think we require regulation in this issue. It's the false negatives that are important and we talked all about that this morning with regards in particular to platelets from whole blood.

So this is the Larazus study that's going to get us into the collections and Dr. Leitman is here as well who's a co-author on the study. Regular plateletpheresis donors develop sustained decreases in count, however clinically significant thrombocytopenia is unusual with

appropriate monitoring and deferral policies. And as you can see here, this is the cumulative number of donations during about a four year period from two up to more then 30, and you can see that in this aggregate group there was a decline at the beginning of the interval to the end of the interval of approximately 30 plus thousand and the FDA has looked at this data from 1994 to 1998 and asked the question are we overdoing it. And so I'm going to try and convince you based on some data from my center, the American Red Cross, Florida Blood Services, Gambro and Hemacare that we're okay and that platelet homeostasis takes care of the issues that we're concerned about.

So this is my system, 43 hospitals in three states, soon to be four states. We do, we distributed in 2004 I believe 11,232 apheresis platelets from four fixed sites, and just to point this out, one of them is three and a half hours from the main center, two of them are across the Mississippi River on bridges that are frequently non-compis mentis, and I'm the doc, so we would close three of four sites if I had to be on site, or we'd have to hire docs, I guess that's possible. We use a couple of technologies and in 2005 got one and a half products per apheresis setting across our donor base.

We have a group of donors that I'm going to describe to you that we call our 24 karat donors and they

give 24 times in a calendar year, so they do the maximum number of procedures in the calendar year and I want to describe to you a little data on those and then from other systems. In 2004 this was distribution of the number of donations, so you got your one and two and three and four time donors over here, and here's our 24 karat donors in the system. Now at the rate that the entire, that we were able to split, we know that we would lose components on average from everybody from 16 on up because one and a half times 16 is 24 and so if we're limited to 24 components we're losing them from here on up and that's 1400 products out of the 11,000 and change, so it was essentially one out of eight products is gone with the restriction as published in the draft guidance.

Now on our 24 karat donors the impact is even more extreme, from these 60 donors, these 60 donors that are 24 karat donors are at Davenport site, we got almost 2500 products, 20 percent of our total collections, 1.7 products per so they're really good donors, that's why they're 24 time donors, they have platelet counts that will sustain superb donations. We got 41 products from each on average in 2005 and we would lose 16.7 of those 40.7, or 41 percent of their donations with a restriction to 24. So it's a big impact.

This is my best attempt to figure out how many

more donors we would have to recruit if we fell back to these numbers and so for the less then 16 time donors I used our system average of one and a half products per donation, for the greater then 16 I used the 1.7 that we get from our best donors, and the calculation is very straightforward, it's to replace 1900, almost 2,000 products from the greater then or equal to 16 time donors with products from less then 16 time donors requires that 1,999 divided by 1.47 products per donation divided by 4.4 donations a year, or 309 new donations, the 4.4 is the average number of donations in the group that are not the real frequent donors. That's 33 percent of our current donor base approximately, there are some assumptions here but it's close enough, it's somewhere between 30 and 40 percent of our donor base would have to be replaced given the frequency of donation in the lower frequency donors and the number of products that we estimate we can get from them.

This is from the American Red Cross showing a histogram of their donation frequencies, and I think if Ann Eder is here and Ed Notari, no, we can get more detail if we want from the Red Cross. Their estimate from calendar year 2004 is they'd lose six percent of their components in the Red Cross system which is essentially half the blood supply, six percent, we were 12 and a half percent minimum

estimate.

When the Red Cross in six regions, of six of their 35 or 36 regions, 130,000 total products, 1.8 per donation from these greater then 24 component donors, 3900 of them. 33 products per donor they would lose there for 9.2 products per donor, that's 28 percent of that 19,000 or 35,786. That's a lot of platelets. We don't know, we think that's probably generalizable across their system, half the blood supply, but we don't have that data at this point.

This is data that was given to me by Larry Dumont at Gambro from a blood center that prefers not to be identified. These are donors of greater then 24 products, 102 donors, 3900 products, with a 24 product limit they would lose 1454 and then applying the additional donors required when they look at the distribution of donation frequencies and split rates is 863, half their donor base would have to be replaced at the center that gave this data to Larry Dumont.

These are pre-counts in our 60 24 karat donors and the male mean is 254, female 289, and compared to our community different platelet analyzer but our machine in this laboratory, community laboratory's machine are calibrated to the same standard, so these are pretty comparable. Well obviously 24 karat donors have high

platelet counts, that's why they're 24 karat donors, they have a high platelet count and can very nicely sustain repeated donation.

These are the pre-counts of the 60 donors and the ranges, this is a little cumbersome, I think the people on the committee can see this, these are just box plots, and it shows you 150,000 is where we would defer a donor, we deferred none of these donors during 2005 for a platelet count below 150k, they maintain their counts very nicely, they will occasionally get close to 150,000. The other thing you can notice is platelet homeostasis appears to work, the distributions in each of these individual donors are reasonably tight, homeostasis works pretty good. Remember, this represents, these box plots represent 1440 pre-counts, so that's 24 pre-counts on each of 60 donors and so they regulate their platelet counts within reasonable measures. The boxes are the 25th to the 75th percentile, the whiskers take you out to 1.5 times that range, so in most of these donors it's 90 percent plus of their platelet counts and so they do a pretty good job of maintaining their platelet thermostat so to speak.

Now these are the same 60 donors and these are the 2005 pre-count ranges by the donation, one, two, three, up to 24. So as you can see there's not really a remarkable trend over the period of a year where we were

drawing these people, essentially every seven to 14 days. These blue boxes represent their first three ever platelet counts at the blood center. Now I only have 30 of those and the reason that I only have 30 is that these donors have been giving at these rates for so long we've thrown away the records on half of them, we keep the records for ten years, so these are 1997 to 2003 on these, excuse me, yeah, these are '97 to 2003 that we have and haven't trashed yet. And the rest of these donors have been giving at rates comparable to this for as long as ten years and as you can see their platelet counts are very nicely maintained.

Look at it a different way, this is the change in the mean pre-count from their baselines to donations 22 to 24 of 2003, and it's not statistically different then zero. They're a little bit higher then they were when they first started donating with us but not statistically significantly different.

This is data that German LeParc at Florida Blood Services gave me, their baseline counts which were anywhere from 497 to January of 2005 and then up to 22 or 23 donations over 2005 and it really looks very much like the data that I showed you from my center so these platelet counts are really very well maintained.

This is from the American Red Cross and this is

the yearly rate of change in their frequent donors, this is 91 donors representing approximately a five percent sample from calendar 2002 from the same six ARC regions that I showed you previously and these are donors followed forward with an average, with greater then 14 average donations per year from January '02 to 10/05 in those six regions. Here's the median is minus three and as you can see it's pretty well distributed and pretty close to not much change at all. Decreases in 54 but increases in 37.

Now they've stratified those according to how many products they were able to obtain, less then or equal to 24, 25 to 36, 37 to 48, I cannot discern a difference between the single, double, and triple donors in terms of any change in platelet counts. And I think this is our data, stratified, the lines are the regression lines for our single, double, and triple donations, obviously the singles and doubles are much more common. The reason that we do so well is that if the platelet count is X they're a single, if it's X plus Y they're a double, and if it's X plus Z they're a triple, and they're very nicely stratified and we don't draw these donors down and don't really see any kind of strong trend. And remember many of these donors have been doing this for ten years.

This is a single center reported to Gambro once again, 12/5/04 to 12/5/05, 1500 donors, over 6,000 donation

sessions, here you see 15 percent triples, 43 percent doubles, 34 percent singles, and then we got our Q&Ss(?) here at 7.5, Larry, you need to teach these people how not to have Qs. The therapeutic doses were 10,000, donors with more then eight donation sessions 285, and this is their platelet count. So single products in eight donations here, triple products and eight donations here, the platelet counts of the people who triple are higher and you can see the same thing for 12 donations a year and 24 donations a year, it's because we use pre-counts, either a pre-count that's available before we start the machine, or an average in general of at my center it's three pre-counts from prior donations to target single, double, triple.

I don't know if I really need to show this, I think you've said that we don't need post counts, this is from Hemacare, some data from Hemacare where they actually did post counts, demonstrating that none of their post counts, single, double, or triples, got down to 100,000. So the way that the devices that we're using, the way that their package insert reads, really does a very good job of keeping us from over shooting and getting the platelet counts that we think may be unreasonable for the donors.

Now there's some discussion about what should the interdonation interval be and I can show with the interdonation interval this is significant, between one and

two weeks, these platelet counts are actually statistically different, the last five, one week, two week, three week, four, five, and greater then five week interdonation interval. The box plots get narrower as the sample size goes down so that you can see that most of our interdonation intervals are seven or 14 days. And these are statistically different, I would argue not clinically significantly different.

And then, this is hard to see, I apologize, but I was enamored of an upgrade to my statistics package. But my conclusion is there's no reason to specify interdonation intervals according to the number of components produced. So here we have our Q&Ss with pretty stable platelet counts, but here's singles, doubles, triples, one through six weeks of interdonation interval and they all look the same, triples have higher counts then doubles then singles but again the deferral cutoff is here on the white line and everybody is above it on all occasions so I don't think there's a need to look at interdonation intervals in a guidance.

Plasma volume loss has been brought up as an issue and I just want to reiterate what you've already heard is that if the FDA has concerns my center and many others will be happy to as rapidly as possible get any data that you think you need.

I think I'm getting to my conclusions, increased deferrals for ASA and NSAIDs are a little bit logistically problematic and the evidence base is not compelling. The no doctor on site in 15 minutes thing would close us down. We really don't understand the rationale for validation of 100 percent QC, it's the false negatives that we're really worried about and our economic incentive to deal with our processes is very, very substantial. We at our center would minimally lose 12.5 percent from the restriction on products versus procedures and don't see the need because of the data that I've shown you from I guess four different places that are collecting platelets including my own.

At this point 36 hours for aspirin is supported by limited data but it's better then any other data I think that I've seen today. None needed for the short half life NSAIDs and I guess we've come to an agreement on that. The need for a longer deferral for piroxicam and some of the others with somewhat longer half lives is not established, I do believe, it probably is something we can live with but we'd prefer that we were more evidence based. I think the likelihood of the kind of clinical trial data that we really need to answer the question, the likelihood is not very good. You've dropped the physician attendance requirements, we believe that you should drop the bacterial culture "validation" requirement, and drop the limit on

components collected, the devices that we use and the approaches that we use to establish our donor's platelet counts are robust enough that we're pretty sure we're not injuring anybody.

And I just want to acknowledge, Kim Palmer is a nurse at my center who locked herself up in a windowless room for over a week with boxes of paper records to extract our data, and then a whole bunch of other people from the other places that contributed data and I can take questions.

DR. ALLEN: Thank you for that presentation.

DR. KLEIN: Thank you, that was terrific, it's nice to see a lot of data and frankly I found it very compelling. I'd like to make one point and then ask you a question and that is the other issue with doing plateletpheresis is that as your platelet count falls of course you become much less efficient in collecting platelets with this machine so that we as well as people who take care of therapeutics patients with severe thrombocytopenia don't see bleeding ever. Now I see your counts were all above 150,000 so you wouldn't expect to but I would ask you whether you or anyone else in this room or audience has ever seen a plateletpheresis donor bleed. We haven't seen thrombocytopenic patients bleed when we do apheresis procedures such as plasma exchanges.

DR. KATZ: I certainly haven't, we've occasionally discussed what happens if we get a triple product off of somebody and they go out and crack their care into a bridge abutment and it hasn't happened yet. But our platelet counts are uniformly above 150,000, and it's not because we're smart, it's because we follow the approved device instructions, we use the devices as they're labeled and I think that gives us a lot of protection.

DR. BALLOW: I just need a clarification, what's the present policy again about the number of donations per 12 month period?

DR. KATZ: The current is 24 donations but no restriction on the number of components up to three that can be produced. The draft guidance would tell us it's 24 components a year so that if I do a guy who triples frequently eight times I'm done.

DR. ALLEN: And the current restrictions in terms of frequency of donation is no more then twice in seven days?

DR. KATZ: The only time we ever do anybody more then once in seven days is a dedicated donor for an individual in the hospital who for some reason those are the platelets that work, HLA match or a cross match.

DR. SZYMANSKI: I would like to support your data because we have looked at our donors who have donated 24

times double units and their counts have stayed the same as in your example. But where it brings a scientific question forward as to how many platelets can a person give, how many are you able to produce in your lifetime, is there any limit, and I was going to give you a mathematical calculation about that but after I hear all these other data I don't think it is necessary.

DR. KATZ: The homeostatic mechanism at least in our donors, and we're going to try and pull together these donors in a comprehensive fashion but it's an enormous manual task, some of these donors are 12 or 15 years of very, very regular platelet donation, maintaining things as you've seen them, and they all smile, they just love to do it, I often wonder what motivates somebody to bleed every two weeks.

DR. SZYMANSKI: And usually in one donation a person can give platelets that he can produce in two days.

DR. KATZ: Right, I showed you, it actually wasn't that close, we don't know how fast they return to baseline, we do know that they are essentially back to baseline between seven and 14 days, they are absolutely back to their baseline, but we have a large number of donors that we call them snow birds, they live in Iowa while the weather is warm and then they go someplace else and they want to get their 24 donations in before they go

south for the winter, so they give every week, essentially they give every week and they're included in that group and they do just fine.

DR. BALLOW: Has there been any studies on the quality of those platelets, on those frequent triple donors?

DR. KATZ: I don't think that I am aware of any, I guess all I know is that my oncologists are very happy.

DR. LEITMAN: I want to thank Lou for just a beautiful presentation that I think makes it easier for this committee to consider the considerations before us, and I'd like to comment a little bit on the Lazarus paper because I was involved in putting that data together, we looked at every donor whose first donation was within that six year period, we didn't focus on the donors who were able to do what you've described, that's a different set. So if you look at everybody that ever comes into your center that chooses to continue to donate you will get serial decreases in counts and if you looked at the graph that Lou showed the very, the most frequent donors, the ones all the way to the right, had a very small decrement in their first to last platelet count and that's because they were deferred. So the conclusion of that paper remains a very important point that the blood center must have systems in place to monitor the pre-apheresis counts

and to show them to a health professional who by training is competent to make a decision that's in the standard operating procedures as how often to defer, how to defer, it's center specific, but such procedures safeguarding the health of the donor must be in place.

DR. KATZ: Right, this is a self correcting mechanism and it's very critical that everybody on the committee understand that if they have a platelet count of 149,999 they don't donate.

DR. ALLEN: Okay, thank you very much. It's 4:10, 4:11, we're supposed to have a break, I'm going to suggest that people get up and stretch or whatever as they need to and we're going to keep on meeting at the present time.

We need to go into open public hearing at this point, I've got a list of three speakers who had asked to speak, I will ask you to, you all know the questions before the committee, you know the three questions before the committee, we're not dealing with every topic that's in the draft guidance, you have an opportunity to submit written materials that can address anything you want but I would ask you please to keep your comments directed to the three questions on which the committee has been asked to comment. And I need to read the open public hearing announcement for general matters meetings.

Both the Food and Drug Administration and the public believe in transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting FDA believes that it is important to understand the context of an individual's presentation. For this reason FDA encourages you, the open public hearing speaker at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any company or any group that is likely to be impacted by the topic of this meeting. For example the financial information may include the company's or a group's payment for 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.

The first speaker that I have on the list is Dr. Celso Bianco, America's Blood Centers.

Agenda Item: Open Public Hearing - Dr. Bianco

DR. BIANCO: I will speak from here so to reduce the transit time. I'm Celso Bianco, I'm the executive vice president of America's Blood Centers, I represent 77 blood

centers, I'm a full time employee. I will reduce, the comments are one page but I'm going to cut it down to half a page. We were very surprised with the guidance, we are pleasantly surprised on the way that FDA has responded so far and on the way the discussion has gone, and we are very proud of having Dr. Katz as one of our members.

We hope that the committee will really consider and modify the issues in the proposed draft guidance, the issue of aspirin needs some more thought, we do not understand the requirement for 500 cultures with a maximum of one positive, we really don't, because we are committed 100 percent of the products are being subjected to culture, and by two of the three systems, it's either by the biomeria(?) bacteria alert culture system or by the DePaul(?) culture system.

We are very happy that white cell counts in post donation platelet counts have been removed from discussion, we were actually concerned that maybe we would require a hemoglobin count for patients that donated whole blood, which we haven't done for the 60 years that we collect whole blood.

And we thank the committee for the opportunity to present these comments.

DR. ALLEN: Thank you Dr. Bianco. The second speaker is Dr. Stephen Kleinman representing AABB, ABC, and

ARC.

Agenda Item: Open Public Hearing - Dr. Kleinman

DR. KLEINMAN: Thank you, Jim, I'll speak from here too and I'll consolidate the written statement and to just add a couple of things I think that will be in addition to what we've heard or maybe reinforce.

On the subject of platelet component collection, number of collections, I just want to point out there is a paper that Dr. Cheryl Slichter published in 1980 which analyzed the influence of daily or every other day plateletpheresis procedures over a five to 30 day interval on the donor's platelet counts and this was basically for donors who were family members and the recipient required that specific donor and this was 1980 when donors weren't routinely available. The platelet yield per procedure was comparable to that of a contemporary collection of a single unit apheresis product but the high frequency with which the procedures were performed, that is daily or every other day, simulates the current extent of platelet removal for donors who may donate two double products in a seven day interval.

Now in this study most donors showed a platelet count that dropped to about 70 percent of their baseline value after six to eight donations, however the platelet count then returned to the normal range and remained there

in spite of continued apheresis procedures at the same donation frequency. And only one of 61 serially evaluated donors had a platelet count below 100,000 per micro liter at any time during their donation course. In this study with very frequent apheresis no donors were put at risk either for short term complications or for any persistent thrombocytopenia. So basically this reinforces the fact about the collection intervals, we don't think there's any scientific or medical reason to restrict the interval between donations even when the collection section results in a double or triple platelet product.

On to the subject of the platelet inhibitory drugs, just to reinforce the issue about non-steroidal anti-inflammatories, obviously this group effect platelet function through a mechanism that is reversible and I think again its been said two or three times but the relevant information is not how long it takes to reverse in the donor but how long it takes to reverse in the recipient who presumably is not taking this medication, that should be much shorter then it would to reverse in the donor. And so we think these platelets should function normally upon transfusion to a recipient and then in fact there is no need for deferring donors who take non-steroidal medications at all. And if there is a longer acting non-steroidal anti-inflammatory that we're worried about then

we should focus that deferral on that specific drug rather then a whole class of drugs that aren't really related so much one to another.

And then finally on the bacterial, process validation for bacterial testing, just wanted to reemphasize that currently bacterial contamination testing is regulated as a quality control test, it's not a product qualification requirement. It seems to us that by making it part of the process of validation you're in essence making it a product qualification requirement rather then a QC test and so we think that bacterial contamination testing should be conducted as its currently conducted by the blood center after consideration of the AABB standards and any specific requirements by the device manufacturers. And so that will be done as part of QC and facilities should set alert and action levels for positive rates, which would then trigger corrective action based on their own plans and so therefore bacterial contamination testing should be treated for apheresis as part of a quality control plan and it should be removed from the process validation section of the proposed guidance.

So thanks for the opportunity to make those brief remarks.

DR. ALLEN: Thank you, Dr. Kleinman. Our third speaker is Dr. Richard Benjamin, American Red Cross.

Agenda Item: Open Public Hearing - Dr. Benjamin

DR. BENJAMIN: Richard Benjamin, chief medical officer for the American Red Cross, national headquarters, thank you for the opportunity to address this committee. I too am going to curtail my comments given the discussion we've had here this morning and the fact that Dr. Katz has presented the Red Cross data already.

I just want to make the point that the American Red Cross operates over 150 centers around the country that collect apheresis platelets and we have about 100,000 donors who come in every year and about 450,000 occasions every year. We split those donations to produce about 650,000 apheresis products and we have been doing 100 percent culture testing for almost two years now on those products.

We continue to see shortages, continue not to meet fully the needs of our hospitals. For this reason we are in the process of implementing triple platelet collections at this point that will we hope increase our availability by five to ten percent. The draft guidance as written would prevent us from doing that and also reduce our availability by some five to ten percent and I believe would really result in some crisis in availability for apheresis platelets.

Given the prior discussion the only point that I

want to address now is really the process validation for bacterial contamination. The draft guidance as written requires now that we test in the minimum of 60 consecutive products for each type of automated blood separator for the actual platelet yield, the pH, the volume, the visible red cells and residual white cells and percent recovery, and then goes on to add that we should perform bacterial contamination testing on 500 collections with zero failures and now we hear that be allowed one failure. As I said we do 100 percent culturing so that's not an issue, what is an issue is that if you consider the smaller collection centers how long it would take to do this validation.

In a good center you can perform about 50 collections per machine per month, so if you have one to two machines in a center it's going to take you six to 12 months to perform this validation. If you have a failure it's going to take twice as long. Until the validation is complete you cannot license that product, you cannot ship it across state lines although you can use it within the state, so this would really have an inhibitory effect on our ability to ship products across state lines.

The justification for the process validation in the issue summary was given that the rationale for the sample size if they show 95 percent confidence that your true bacterial contamination rate is less then one percent.

Based on published literature the bacterial contamination rate for a conforming process should not exceed one in 3,000, at this level the proposed validation test would be expected to yield a false result of non-conformance in fewer then three percent of determinations. I would like to make the point that the bacterial test is not a suitable test for performance validation of this process and I'd like to base that comment on the results that we have had in the Red Cross with this test.

I mentioned earlier that we have now tested some 900,000 collections resulting in about 1.3 million transfusions and we have extensive experience that we have published. The initial positive rate is pretty consistently about one in 1500 so if we're testing 500 products 30 to 40 percent of the time we will get at least one positive. We know that two thirds of those are false positives, they're due to contamination of the bacterial bottle at the time of inoculation and not due to apheresis process failure. In fact we have seen zero failures due to apheresis contamination or problems with product integrity in the two years we've been testing.

We have seen approximately 80 true positives for each year for the two years, so we've picked up about 160 true positives. But 80 percent of those are gram positives and about 20 percent are gram negatives. We assume that

there are two sources of those true positives, one is donor bacteremium(?), asymptomatic bacteremia, it's a biological true positive. The other is incomplete skin decontamination, the skin plug or a skin organism. Our problem is we can't actually tell the differences, we assume the gram negatives are coming from bacterium and the gram positives are coming from the skin but that's not true, we have no proof of that.

We have multiple cases of strepbovis(?) which is a gram positive but we also know that that's asymptomatic bacteremia associated with colon cancer and in fact we have picked up at least one donor who had colon cancer due to our screening which is an interesting finding. We have also picked up gram negatives that when we've gone and cultured the anticubidlefoca(?) of the patient there was a gram negative. So our problem is that when we get a true positive we can't tell whether, with as much root cause analysis as we like, we can't tell with certainty whether it's due to process failure of the apheresis process or whether due to a biological true positive.

I also commented earlier that we have a false negative rate and we do not have good data and we are waiting the Gambro and Baxter studies to know what the false negative rate is. But we suspect that with the way we're performing the test it may be as high as 50 percent.

DR. ALLEN: I'm sorry, as high as --

DR. BENJAMIN: 50 percent. So in conclusion with regard to this process validation we'd like to point out that positive cultures are common but they rarely indicate apheresis process failure, that we already have 100 percent QC in place to ensure sterility, that 500 cultures would unduly delay licensure of products, and we suggested the one percent cutoff as suggested by the FDA really has no clinical or medical significance that would be unacceptable for clinical practice. Plus it's suggested the criteria that are being applied here, the one in 500, are not being applied to the pH and the white cells and the red cells and the other process validation criteria. So we don't understand the 500 cultures, to make a recommendation we don't really see the point of doing this test at all in validation but if we're going to have to do a number make it the same as the other tests, the 60 tests we do for white cells and red cells and volume and make it in line with the other validation studies we have to do.

Thank you.

DR. ALLEN: Thank you very much. Questions?

DR. QUINN: We were just chit chatting over here while you were ending that, so you do the cultures on all of them?

DR. BENJAMIN: On all the apheresis --

DR. QUINN: What about the centers that don't do any cultures, should there be any recommendations for them?

DR. BENJAMIN: I think I made the point that the license tests are really not useful in my understanding for process validation because you can't tell whether they're true positives or whether they're process failures.

DR. QUINN: But then why do you do it on all?

DR. BENJAMIN: This is a QC test --

DR. QUINN: Correct.

DR. BENJAMIN: That we're doing to ensure sterility of the product that we transfuse, not to ensure the integrity of the process.

DR. QUINN: Which I do understand. I'm still thinking of other centers that don't --

DR. BENJAMIN: The AABB standard applies --

DR. QUINN: Then they do the AABB, I mean I'm just trying to get clarification because you're setting one standard that some other centers don't follow --

DR. BENJAMIN: No, the AABB set the standard and in order to be accredited by AABB you have to do it --

DR. QUINN: You have to --

DR. BENJAMIN: You have to prevent or detect bacterial contamination in all platelet products.

DR. SZYMANSKI: But the AABB does not, does the AABB say that it has to be a culture or dipstick, so that's

why I think it's a different thing.

DR. KATZ: Well, Mark, I don't know if you want to address this at all since you're the author of the survey data, you and Maryanne Silva, but I can tell you that within ABC our last survey everybody uses a culture based assay, everybody, that's half the blood supply, and the Red Cross is the other half of the blood supply, so if people aren't it's small programs outside our organizations or hospital programs, it's not very many. Is it 100 percent, I can't say.

DR. KUEHNERT: It's close, I don't know if it's 100 percent, there may be a couple --

DR. KLEIN: And we do as well which is a 100th of one percent of the blood supply --

DR. EPSTEIN: Well it's hard for me to understand why there's an objection to meeting a standard that is automatically being met, in other words if you're doing 100 percent culturing then you've more then met the minimal standard that FDA is putting forward and the minimal standard is a safeguard for those centers that might not already be doing it, so that's sort of the first puzzlement.

The second is that I think that there has been several times stated a significant misconception, we understand that there's a fairly high rate of false

positive cultures due to contamination at the time of inoculation of the culture but we're talking about a rate of true positives and they can be confirmed, you go back to the unit and you see if every culture is or is not positive, so we would not base validation on the false positive rate.

And then the third point is that well, it's true that one percent is arbitrary but this is part of a much larger issue which is trying to put quality control for blood components on a sound statistical foundation and when you look at sampling 60 for validation, 60 of whatevers, zero failures out of 60 is 95 percent confidence of 95 percent conformance. The problem with looking at that figure in terms of bacterial contamination is that a "allowable" rate of five percent is off the wall, so that didn't really apply and we were trying to balance what's a reasonable denominator with what's a reasonable cut for deciding that a process is out of conformance. And we looked at the literature and the early literature, and I don't know of Roslyn Yumtovian(?) is still here, but many of those data came from her center, you saw culture positive rates between one and three percent. So we know that before all this attention was focused on carrying forward the aseptic process with rigor and monitoring it rates of that level were seen.

So we believe that that's a threshold that triggers awareness that there is something wrong with aseptic processing and again, I understand fully that if you culture things long enough probably the vast majority of products have some level of contamination because you're putting a needle through skin. But we're talking here about pragmatic standards and the whole idea is to try to move it to a firm foundation, what's in the CFR as the quality control requirement is four units per month tested for various parameters and that's simply not meaningful statistically. So the whole thrust of the recommendations has been to try to move towards something that is meaningful statistically but again I don't understand why if you're testing everything you've therefore complied with that recommendation should it ever be finalized, where's the problem?

DR. ALLEN: Let me just get the first speaker at the microphone and then we'll come back here.

DR. GREGORY: Mark Gregory, UNC. I just wanted to summarize some of the data from the Inter-organizational Task Force since it has been thrown out here. In a survey in the fall of 2004 the task force did they obtained data on 959,000 apheresis platelets, that accounted for 66 percent of all apheresis platelets that were collected in 2003 based on previous 2001 data for the nation. 93.2

percent were collected in blood centers, 6.8 percent in hospitals. Both the hospitals and the blood centers responded that 88 percent used cultures but there was a bias in the study in that the American Red Cross and Blood Systems were each counted as one facility, clearly they're not, American Red Cross collected 37 percent of all platelets in the country, Blood Systems eight percent of all platelets in the country, so that the study concluded that well over 90 percent of apheresis platelets were tested by a culture, we don't have an exact number but we though it was probably on the order of probably around 95 percent or more, it seems like since that study was done more big centers have come online.

What I haven't heard here is what's been the actual impact on patients by doing these interdictions with cultures. In the Red Cross study they found looking at a time period corresponding to just before they began doing the cultures to the time period when they began doing cultures, they seemed to interdict 75 percent of probable septic transfusion reactions, but it may have changed a little bit, we haven't heard the data from Blood Systems, we heard the numbers that were put out there by Steve Kleinman but we didn't hear whether it actually impacted on septic reaction and I think that kind of information is important to this group.

And finally I think the AABB standard would require 100 percent use of an FDA approved test if there was a test that was logistically easy to use for random platelets and right now we don't have a system so we desperately need a system and an AABB standard would be upgraded to say that you need to use an FDA approved test.

DR. BENJAMIN: I just want to make a comment again on the false negatives, thank you Dr. Braco(?) for quoting Chang Feng's paper, we do have more recent data on false negatives that I did mention earlier but I will repeat them here. We have seen 17 confirmed septic reactions in the last two years where we have identified a bacteria in the bag that the patient received, those products had tested negative in our culture systems out through five days, 17 septic reactions including two deaths.

The rate there, of those 17 eight of the septic reactions in fact fulfilled the criteria laid out in the Bacon(?) study in which we were able to culture a bacteria from the patient, from the bag, and there was a reaction. If you take those eight and compare that to the Bacon study the Bacon study in apheresis platelets came up with a rate of ten per million septic reactions with a confidence interval that was something like 5.1 to 14, I can't remember the confidence interval but that was about it.

The eight we saw in 1.25 million transfusions relates to 6.4 per million septic transfusion reactions, so essentially we've seen a reduction, I should comment that the Bacon study, most of those transfusions, the majority, were from Red Cross. It has been criticized for under reporting but the data I'm quoting to you now suffers from the same problem in that we do see chronic under reporting to the Red Cross of reactions and in fact at least one of those eight reactions we found because the patient died, we went to look for the split product, went to the hospital, and found that that split product had been transfused, patient had suffered a septic reaction, non-fatal, which was never reported to us.

So we know under reporting is an issue, nevertheless Bacon said ten per million, we're now seeing 6.4 per million under the same conditions, that's less then a 50 percent reduction, it's within the confidence interval of Bacon, therefore not statistically different from the Bacon study. So we are seeing a persistent septic reaction rate despite the BACT(?) testing and despite removing 80 confirmed positives from the blood supply every year with the testing we're doing.

DR. ALLEN: Thank you, and the Bacon study was done in what period of time?

DR. KUEHNERT: '98 to 2000.

DR. ALLEN: Okay, thank you very much. Dr. Tomasulo(?) or Dr. Kleinman or Dr. Bush, do you want to speak to Blood System's experience?

DR. CAMPBELL: Hanni(?) Campbell from Blood Systems, since implementation of bacterial detection we have not seen any confirmed positives or for that matter false negatives resulting in patient septic reactions.

DR. ALLEN: And what about reported sepsis from the hospitals receiving product?

DR. CAMPBELL: We have not seen any.

DR. ALLEN: Thank you. Dr. Bianco.

DR. BIANCO: Celso Bianco, America's Blood Centers. I want to respectfully disagree with Dr. Epstein regarding the statistical approach that is being proposed, or the principle of a statistical applications here. I think that we have to look at these as biological systems that may not be as subject to statistical approaches as our aliza(?) assays, they're writing forometers(?), or spectrophotometers, variation is very big and you saw there donors that can give one unit, donors that can give three units, their levels are high and all. If we establish rigorous statistic parameters there we are going to have very elegant platelets, statistically elegant, but I doubt that we are going to have real benefits for the recipient of those products. Each product is a lot of a medication,

we count how many platelets are there, we culture these units of platelets, and that's the only product that we are going to transfuse if they have at least three times ten to the 11 platelets and if they don't have an excess of red cells and if they fit the criteria.

The next point on the 500, yes, we are doing it and we will continue doing it, so we can count until we reach 500. But Dr. Epstein, will all centers currently doing apheresis be grandfathered, or will every center have to start counting 500 platelets before their license is renewed or approved? The moment we introduce these no new apheresis facility will be able to ship products outside as Dr. Benjamin put very well, outside their own state, until they have their license. I don't have in front of me the numbers of platelets that fly around the country in exports but about, I believe that about 30 percent of the apheresis platelets are collected in one state and are transfused at a different state.

DR. ALLEN: Thank you very much. We are running out of time, I've got a few hands here among the committee members, I will try to get to you, we need to get to our open discussion.

DR. SZYMANSKI: I have one suggestion, I don't know if it's reasonable but we're talking about the difficulty in determining whether you have false positive

or true positive culture and I think it would be wonderful if the manufacturers would provide a pouch that would be interconnected with that system where you have the actual product and you would remove that pouch and then if you had a positive culture you could go back to that pouch even if the second unit would have been transfused.

DR. ALLEN: That's a suggestion for the manufacturers to consider.

DR. KUEHNERT: I had a question about this whole reason for validation process and we keep on hearing well the blood collection centers are already doing this but then I also hear they would have to follow manufacturer's instruction and according to what I understand that would mean that many of the major facilities would need to change what they're doing. So maybe we could get clarification for that at some point because I know that many use, it's not according to --

DR. ALLEN: Dr. Epstein?

DR. KUEHNERT: This is sort of a subtle way to encourage facilities to change what they're doing.

DR. EPSTEIN: Well, we'd like facilities to move away from dipsticks for sure but we don't intend to change the practices in centers that are already doing cultures, and I think that there's a serious misconception here that all interstate shipments stop until you've done your next

500, we're not saying that at all, because what we are saying is that as long as you are culturing you can keep releasing culture negative units. So the idea here is to if you will set a threshold for when you can go onto surveillance, now if you never want to go on to surveillance that's fine but since we don't have any requirement for 100 percent quality control testing we're trying to figure out well is there a threshold to permit you to go on to surveillance under the conventional model of quality control, and that's what this is all about. So it's really not very much targeted to centers that are already doing 100 percent, I think that we're not aware that such a large proportion of centers were already culturing but nobody said it's 100 percent. And I think that it would have the effect of pushing centers that do not culture to do cultures at least to validate and I don't think that that's wrong either. So again, I think part of the issue here is a straw man but the straw man shouldn't still be standing, we're not trying to bring current practices to a halt.

DR. ALLEN: Thank you.

DR. KATZ: I don't know if I'm confused or not, Jay, and I think you probably can unconfuse me if I am, we are looking at three new sites to bring up with platelet apheresis and as I understand this I cannot ship those

products out of Iowa until I have 500, 499 out of 500 negative cultures, and that's what I think I'm hearing. If that's not the case, it's already hard enough to get a license for a new site, it takes a long time.

DR. EPSTEIN: This is still being actively discussed but I think that the current concept would be that assuming you've met all other criteria we would approve you, you would be collecting platelets and culturing every platelet and at the point at which you could submit a statement that you had no more then one in 500 positives we would allow you then to be on a surveillance type of QC if that's what you chose to do. But we would see this as data that came into the agency later or that even you kept on site that we looked at on inspection. In other words this is about quality control, that's what we're talking about.

DR. ALLEN: Okay, we'll have one last comment in the open public hearing and then we need to close that down.

DR. WAGNER: Steve Wagner from the Red Cross, I just want to put into perspective a bit of what Dr. Benjamin mentioned about with respect to the 50 percent projected efficacy of culturing and I'd like to contrast that with the 100 percent hopeful implementation of sample first or sample diversion. There was a study published at

AABB by Hema Quebec which showed that there was a ten fold reduction in sepsis when they converted to sample first where they divert the first bit of blood for testing rather then the last bit of blood, and it's about a dollar intervention and it may have a far greater impact on sepsis in patients then all these tests that cost 25 times more.

DR. ALLEN: Thank you. Okay, the open public hearing session is now closed, we will go into committee discussion.

Agenda Item: Open Committee Discussion

DR. ALLEN: I've got two questions I'd like to start out with, Dr. Quirolo, you I think are the only hematologist on the committee today, sorry, Dr. Manno, I looked through my thing here and it has you listed as a pediatrician. For both of you, are you aware of any studies that would indicate in any way that there's a long term problem in multiple continuous, the 24 karat donors year after year after year? Is there any long term problem, assuming that the measured platelet levels stay at an acceptable levels, is there any problem with stressing the macrophage production system or whatever?

DR. MANNO: Do you mean is there a limit to how many platelets you can donate over a lifetime? We have no data to support that that would be a concern. Keith, what do you think? 24 seems like a whole lot to me but I am

convinced based on your data that there don't seem to be any adverse events associated.

DR. QUIROLO: I think the fact is though that people who do show any decrease in their platelet count they don't donate, so it's a self correcting system, so you don't have people with platelet counts of 100,000 who are donating at all so those people just fall out of the donation pool, so you can't really tell from that how many people fall out, I don't know if you know that.

DR. KATZ: The only people that have fallen out of our program in the past 12 months is a single male that was found to be leukemic because he ran 250, he came in at 125 and when I looked at his peripheral blood smear it was full of blas(?).

DR. ALLEN: Okay, Dr. McGee, would you, we've heard lots of statistical stuff thrown around, would you give us your opinion on the quality control collection --

DR. MCGEE: First, let me just say point blank I think 500 is too many and that there are ways that you can get that number down quite a bit, I think the approach which is this confidence interval approach, to use the example that you folks have done, it's true the upper confidence limit is about 1.1 percent if you get one out of 500, but the lower is one out of 20,000, so you've wasted some data to find out that the lower limit is one over

20,000. What you're really interested in is ruling out this higher side so if you did just a more classical statistical approach which is a one sided hypothesis test for example you immediately almost have that sample size. And if you want to drop the power to 90 percent which is one of the things you had in your slides I think the sample size goes down well under 200. Do you see my point? You're wasting data to get this lower confidence model, you're not interested in it, in this case you just want to pick a process that's out of control.

DR. ALLEN: Thank you. Any other open committee, no open, any other committee, general committee questions or discussions and once we finish that we'll go on to the specific questions.

DR. CRYER: Does anybody know how long it takes for a platelet from somebody who has an NSAID from a non-steroidal anti-inflammatory agent, it's a reversible process but how long does it take for that platelet to work once its been infused in a person that has normal, that doesn't have any NSAIDs in their blood? The reason I ask that, it's a completely different problem if you're operating on somebody and need to transfuse bloods and need immediate homeostasis compared to somebody who just has a low platelet count that you're transfusing because they're taking some medication.

DR. ALLEN: Dr. Katz, do you have any --

DR. KATZ: No, and I think the blood community recognizes the shortfalls of the data that's available. I mean the argument that we've been transfusing these platelets over this long period of time, everything seems to be okay, isn't an idea argument, we recognize that, and particularly the short half life drugs seems very probable to me they fall off the receptor quite quickly when they're put into the drug free medium of the recipient and it should be very quick, but that's not the same as knowing that.

DR. KLEIN: There's another point though that's very important and that is that you don't get immediate function from the platelets that are normally collected, and in fact if your platelets are five days old or seven days old they don't work nearly as well or as quickly. If you really wanted rapidly acting platelets you should store them at four degrees but then they only last for a very short period of time but they act right away.

DR. CRYER: Well what we want is fresh whole blood --

DR. KLEIN: You really don't, maybe we can talk about that later --

DR. ALLEN: We're not going to discuss that one today. Yes.

DR. BALLOW: I just wanted to make a comment about aspirin, in the real world I believe that a lot of perhaps your donors are taking low dose aspirin as prophylaxis and I am really shocked that there's no information in the literature, you have to go back to the '70s in order to pull out any information that was addressed this afternoon. And I would suggest that the FDA actually go after this and get some real time data on individuals who are actually using daily low dose prophylaxis aspirin, they could probably do this study in less then six months and then you'll have an answer and you'll know what to do with this issue.

DR. ALLEN: I was just going to suggest this is an issue that needs to be brought up to the NHLBI for funding I would think.

DR. KLEIN: I would just say that remember that the standard is that you can't donate on aspirin without a 36 hour interval, so nobody to our knowledge is donating who's taking aspirin although clearly people forget that they took it the night before for a headache. The problem with doing a study is what study to do and I think again as I tried to emphasize there aren't any good surrogate end points and trying to do a study looking at WHO bleeding time is never going to get done.

DR. BALLOW: There must be a consensus by the

hematologists though what studies to do, on a control basis you can do a whole range of studies, not only bleeding time but platelet aggregation, ADP, values and whatever, so there must be a consensus by the hematologists --

DR. MANNO: It doesn't, it really doesn't help to predict bleeding so all the fancy platelet aggregation studies in the world as Dr. Klein said before the bleeding time, they really don't correlate very beautifully with bleeding. So the big NHLBI sponsored study that's being done now looking at platelet dose is using the WHO bleeding scale as the end point rather then any laboratory end point other then platelet count.

DR. ALLEN: Dr. Szymanski brought to my attention there is a more recent Japanese paper from 2005 so perhaps there are some new data out.

Dr. Williams, would you present the questions or Dr. Vostal, who's going to do our revised questions?

DR. VOSTAL: So this is the question concerning the deferral of donors, and the question is does BPAC agree with the revised proposed donor deferral criteria? And the criteria is three day deferral for aspirin, no deferral for the Motrin group NSAIDs, all other NSAID one day deferral except Feldene which would be three days, COX-2 NSAID inhibitors would be no deferrals, Plavix five days and Ticlid ten day deferrals.

DR. ALLEN: Committee discussion. Dr. Leitman, you already expressed an opinion.

DR. LEITMAN: Very high IQ to get through that, both on the donor part and on the screener part, I'm not sure I have a suggestion to help that out.

DR. KUEHNERT: I just need a clarification from people who are a little closer to the clinical side then I may be on prescribing Plavix or Ticlid, these are not PRN meds, is that right? I mean these are prescribed for significant medical conditions, is there anything I'm missing here as far as the use of these medications?

DR. KATZ: What we think that we're starting to see at the blood center is that the drugs are getting used longer and longer, longer intervals after the stent goes in for example, and so while if somebody had had an MI we would just for the sake of donor safety say you're not going to be a donor for six months, which used to take care of the Ticlid and Plavix, may not anymore. And so I think that these drugs are for conditions serious enough you're not going to tell them to quit, that we probably just need to say when you're off the drug come and talk to us.

DR. KUEHNERT: So the most common use of these meds is after angioplasty to basically keep the stent open.

DR. DOPPELT: I mean in my experience patients frequently know that they're taking an NSAID but they may

not know which one they're taking and sometimes don't know how much they're taking, I'm just curious, do the blood banks do a formal medication reconciliation where they call the pharmacy and find out what the patient is really taking?

DR. ALLEN: Well in my experience usually there's a single question that's asked along where the drugs are grouped together and you've got about six seconds to respond to that and if you don't happen to know the answer the easy thing is to say no I'm not taking anything. I think the ascertainment of reality or truth is complicated by the number of drugs and generic names, trade names --

DR. DOPPELT: Exactly and I think scientifically from the data that we saw this makes sense but practically I don't think it's going to work, I agree it's a little complicated and maybe you need like just three days across the board except for the two that are longer.

DR. LEITMAN: It's not that bad because as we've heard from many different people this afternoon this pool of platelet donors is a committed family, they're committed to the organization, they're committed to donation, they understand what they're not supposed to take, they've been educated. We can teach them about those medications I think fairly effectively if we get a consensus on what to teach them. The first time donor will not know so you may

be deferring a higher percentage of first time comers to enter your plateletpheresis program.

DR. DOPPELT: Long term donors represented what was it 20 percent, so what about the other 80 percent, I mean they're donating, some are first time and some are several times a year, some are ten times a year, the regular high donors were only, were 20 percent --

DR. LEITMAN: Most centers find that a small proportion of donors donate the huge majority of platelets by plateletpheresis, I'm not sure what you were referring to, I think we find a core of 400 donors donate at least 70 percent of what we transfuse although our platelet pool population may be as high as 1200 subjects registered.

DR. ALLEN: Let me suggest to move, to simplify the process a little bit and move it on that we focus on the science base rather then the application base for the donation criteria, in other words we're being asked one question with multiple parts to it. Does anybody want to suggest that we need to break these apart and make a vote on aspirin, Motrin group and so on separately? Are you satisfied based on all of the data that we've had presented today that this is a satisfactory representation and let then the FDA wrestle with how it's going to apply it?

DR. CRYER: I think we ought to break them up, I don't have a problem with that certainly.

DR. CRONSTEIN: It seems to me that having just a single standard coming up with one would clear it for all of them, even the Motrin group which is the shortest acting because people forget they take it and it's over the counter, Naproxen is also over the counter, that's almost as long acting as Feldene, unfortunately Feldene isn't used very much anymore --

DR. ALLEN: What time period would you recommend if you were to go with a single one?

DR. CRONSTEIN: The current recommendation I didn't realize was a day and a half, 36 hours for aspirin, it would probably work for Feldene even as well because those tests were done where they just took the platelets right out, the platelet rich plasma, tossed it into an aggregometer and looked to see what happened. I imagine that once these platelets get into someplace where the ambient Feldene concentration is zero it's going to normalize their function a lot faster, I think 36 hours or three days, I mean it's kind of random and arbitrary at this point so pick a time that sounds okay with everybody and just say that for the whole thing.

DR. KLEIN: I hate to say it again but I don't think we should change current practice unless there's evidence of a problem or availability of new scientific data, it just doesn't seem to make sense to me to change

one relatively arbitrary standard for another relatively arbitrary standard.

DR. ALLEN: Let me ask for just an informal show of hands, who on the committee if you were voting right now as a block would vote for the recommendations that are on the screen? Can I see a show of hands? Okay, so one, that was one, two, three, about five, so about a third to 40 percent would vote for that. We've heard other recommendations ranging from keep the status quo to a single uniform date that for which there is no hard and fast data but something on the order of three days is not unreasonable. May I ask the FDA, Dr. Epstein, do you want us to continue to discuss this and vote on it or do you have sufficient guidance from the committee at the present?

DR. EPSTEIN: I'm not sure we have a clear guidance, I think we have two options, one is to vote specific measures, the other is to go around the table and see what members individually think.

DR. ALLEN: If we voted, my sense is if we voted on what is presented as such and did it as a single vote it would not carry although you would get as I said somewhere between 30 to 40 percent --

DR. EPSTEIN: You didn't poll for abstentions so we just don't really know.

DR. ALLEN: Okay, all right, let me then, let's

vote on the presentation as it is and if that does not carry we'll then look at a couple of other ways that we might provide some assistance --

DR. EPSTEIN: Could I suggest that if the proposal doesn't carry that we can then get comments around the table?

DR. ALLEN: Okay, that would be fine, and we'll do it, let me suggest that we do it with the exception that we'll break it into two parts, we'll do the aspirin/Motrin group, COX-1 and COX-2 as one group, and then the second question would be the Plavix and Ticlid, do that as a separate since I sensed that there was some difference there. Do you want to go ahead and call the question and we'll do it for the top group --

DR. KUEHNERT: Could you repeat that?

DR. ALLEN: Yes, does the BPAC, the way we're going to do it, does the BPAC agree with the revised proposed donor deferral criteria for aspirin three days, Motrin group no deferral, all other COX-1 reversible inhibitors one day except Feldene three days, COX-2 inhibitors no deferral, that will be the first vote.

MR. JEHN: Dr. McGee?

DR. MCGEE: Yes.

DR. SZYMANSKI: Yes.

DR. QUINN: Yes.

DR. FINNEGAN: No, it's too confusing and there's no science.

DR. CRYER: No.

DR. BALLOW: I say yes, the other point is that with, since we don't have the COX-2 inhibitors there's going to be more patients on the COX-1 inhibitors and it's going to make it more difficult, more complicated for the donors by having them off three days of their pain medication when they have arthrout(?) or arthritis or other rheumatoid conditions.

MR. JEHN: Okay, continuing, Dr. Keuhnert?

DR. KUEHNERT: I feel like to vote yes I'd have to see some compelling data so I'd have to vote no.

DR. MANNO: No.

DR. QUIROLO: Yes.

DR. WHITTAKER: Yes.

MS. BAKER: No.

DR. DAVIS: Yes.

DR. DOPPELT: Yes.

DR. KLEIN: No.

DR. LEITMAN: No, but I'll try and help out the FDA by giving them a suggestion, I think I would feel comfortable with either two or three days for aspirin, that's just a feeling because you've all heard the presentations today. I don't think there's any reason for

a deferral for any NSAID from what I know, from the last 30 years of experience, there's not a problem, there's no deferral right now, no one uses Feldene, I can't remember the last time I saw a person, a donor on Peroxicam(?), so I feel that's a non-issue, that's why I had to say no.

DR. CRONSTEIN: I would say no because I think you should just come up with a single time point for the whole bunch.

DR. SZYMANSKI: Feldene is also selected COX-2 inhibitor, more then COX-1, 33 times more COX-2 then COX-1.

DR. ALLEN: I'm going to vote no in large part because of the complexity of the scheme.

DR. KLEIN: I thought you were the one who said let's not worry about the application, let's just talk about the science.

DR. KATZ: Were I allowed to vote I would vote with Dr. Harvey Klein not to alter the status quo in the absence of a compelling new reason.

MR. JEHN: Okay, thank you. Nine no, eight yes.

DR. ALLEN: All right, let's take the second vote on do we want to recommend to the FDA a deferral of five days for Plavix and ten days for Ticlid.

DR. MCGEE: Can I ask the clinicians, you all know I'm a statistician, how do I vote on this? I mean the other ones I at least saw some data on, three days for

aspirin, this one, did I see any data?

DR. KATZ: I really think I'd like at this is why is the potential donor on the drug and while we need more donors I don't think we need donors who require these drugs and when they've been off if you want to make it five days for both or ten days for both, that's fine. But I really feel pretty strongly that somebody who has had a vascular event or a vascular procedure of the seriousness that required these drugs, we ought to wait until their docs feel they're good enough to be off.

DR. ALLEN: But that's not five or ten days.

DR. KATZ: It'd be five or ten days after they were off, or two or three days, I mean pick a number to clear the drug, I think it's arbitrary, it's not science, and I think this is why we don't generally drop people on therapeutic NSAIDs for rheumatoid disease, they got enough going on, they don't need to be donating.

DR. ALLEN: Does anybody disagree with that perspective?

DR. LEITMAN: I might make a plea just to make it the same number of days for both just for ease, that wouldn't hurt, it's easy enough, make the screening easier.

DR. ALLEN: Okay, I don't see a reason for a formal vote, I think the sense of the committee is that people that actively need to be taking these drugs should

not be accepted as donors and once they are off the drugs and they've cleared, if they're otherwise acceptable as donors in two weeks, ten days after they've stopped they can perhaps come back.

Dr. Epstein, do you want further discussion on these issues?

DR. EPSTEIN: I think we have the sense of the committee here.

DR. ALLEN: Okay, Dr. Williams, are you doing the other --

DR. WILLIAMS: So the remaining questions have to do with the validation studies for bacterial contamination and a donation frequency, I think because we're asking you to look at the current considerations I've asked for the larger talk to put up so I could just very briefly review what those are for the frequency issue because they went by you fairly quickly I think.

So let's take this one first. Do committee members agree that bacterial testing of 500 consecutive collections is appropriate for validation of the aseptic process? If not, what sample size and acceptance criterion does the committee suggest?

DR. MCGEE: I already said I didn't agree with the 500 so I would certainly vote no on that, but what I agree with is both Dr. Epstein's comment that something

should be put in to place and secondly it's probably going to be statistical long term. But instead of a specific sample size I think that the statisticians at Seaberner(?) should be involved in designing these studies, they can come up with something a little cleverer then this I hope.

DR. WILLIAMS: Dr. Allen, could I just make a quick comment? Is that appropriate? The other statistic is based on a binomial, in other words the 60/95, to determine 95 percent confidence interval, our single tail, I think the statisticians were involved in this one, I think they probably just weren't directed that a single tail analysis would be correct on this so that's a good observation.

DR. KUEHNERT: I just wanted to comment on this because it just seems really complicated and there's more behind this then meets the eye it seems to me. There were comments made about how for apheresis platelets we're basically halfway there with the current practice of what we're using with culture based methods and I think there are a couple of reasons for that. I mean I think one really is because there's one bottle being used and I think part of the, this is my speculation, part of the impetus of putting this forward is to get it closer to manufacturer's recommendations which would require more volume, and I think that's a good thing, I think that will get us closer,

I think have a diversion pouch would get us even closer but that's not what's being discussed here. I just wonder if there's a way to say that is a good thing to get us to ask facilities to use sufficient volume but it's sort of so imbedded in this question it's hard to suggest how to do that.

DR. KATZ: Jay's last clarification to me was very valuable, I have to ship, I ship 70 percent, more then 70 percent actually of our platelet products move interstate and so when we bring up a new site if we can only use those products in Iowa we've got a very, very serious problem. He's telling me that's not an issue, that I can license a new site or a new machine at an old site, new process at an old site, and do this after we've already got our license. So I think the objections that the blood community have to this are substantially less because of that clarification, Celso or anybody else want to disagree with that?

DR. KLEINMAN: It is really a question of clarification because, and Matt was getting to this, that this is going to require an aerobic and an anaerobic bottle which is what the product insert says in order to fit this requirement, virtually nobody is doing that now, maybe some people who are on the seven day platelet protocol are but not very many people are. So it could be a substantial

difference in the way cultures are being done and it would be useful to clarify whether that would be a requirement under this proposed scheme.

DR. EPSTEIN: The answer is no, first of all it's a recommendation, but it would be for use of a five tentay(?) cleared quality control test, so that includes the Paul(?) EBDS(?) and the scan system, and those don't require two bottles --

DR. KLEINMAN: Right, but the confusion, Jay, as you know, is if you're using bacti(?) alert the product insert says to use an aerobic and an anaerobic bottle, right, doesn't it?

DR. EPSTEIN: Not as a QC, can you clarify that Jaro?

DR. VOSTAL: It is a recommendation however we did approve the Paul EBDS system which is aerobic only.

DR. KLEINMAN: So I guess the clarification is you wouldn't have to do the anaerobic bottle unless you chose to.

DR. KUEHNERT: The Paul EBDS doesn't even have bottles so it doesn't even --

DR. KLEINMAN: Right, I'm talking about the bacterler(?), what form you would have to do it in and I think its been clarified, you could do it the way you are currently doing your cultures because that's comparable to

Paul EBDS only taking aerobic bottles.

DR. VOSTAL: If I could clarify that, for QC it's only aerobic is required, you don't have to do both aerobic and anaerobic for quality control indication.

DR. KUEHNERT: But the issue here isn't about anaerobics, it's about volume too, so is that, I mean regardless of the justification are you just saying one bottle is okay?

DR. VOSTAL: Yes, because that's, I mean the bacti alert was approved for a single bottle but in the labeling it's recommended that people use two but it's not required.

DR. FINNEGAN: I have a bigger concern, I think that what was stated before earlier by someone else trying to make a physiological system consistent with statistics is a dangerous precedent to set and I think that what the statistician has said makes a great deal of sense and this probably does not to go back to the statisticians and come up with a realistic statistical approach that can be reproducible for other systems that come up rather then trying to make this fit into a strict statistical model, I mean other then pure science there doesn't seem to be a good rationale for picking that statistical model.

DR. LEITMAN: There's only one other test that all manufacturers perform on every single plateletpheresis

component and it's a CBC, and so process validation includes 60 CBCs on your component to make sure you're doing things correctly, so if this is the other test that we hear clearly it's going to be applied to every component released why not apply the CBC criteria, 60 is arbitrary but I agree with what you just said so why not include it with the other things that one performs, 60 counts on 60 assessments for process validation.

DR. ALLEN: Dr. McGee? Other discussion? The second part is that if the 500 is not accepted what sample size and acceptance criterion does the committee suggest? I think the Dr. McGee has already given, without coming up with an absolute number has given a suggestion for how that can be done and it seems to me that there are some suggestion around the table overall that the whole validation process needs to be considered carefully. It seemed to me that one part of it certainly is validation of the skin antisepsis and the collection methods and everything else that goes into it, you don't want to just rely on the culture and I don't, I don't have a clear sense, I have to admit I looked through the document, I read through a number of the comments, I didn't read every single page in this so I don't understand the whole process of the validation procedure that was being proposed. But I guess my thought would be that it needs to be looked at

very carefully given the recommendations that have come back from the industry in their comments.

DR. SZYMANSKI: I just feel that actually the number 500 is not too many because there are so few contaminated units, you would never get it if you test only 100 units or something like that, I don't understand it. And I don't know what you really want now as to vote, do you want to vote for two bottles or one bottle and 500 or less then 500 or what is the vote?

DR. ALLEN: Well as has been pointed out there are many factors that go into, ideally you would have 500 negative cultures, you increase the probability, if there is true contamination of any unit you increase the probability that you will detect it if you one, increase the volume that goes into the bottles, two, increase the number of bottles, if you're only using an aerobic bottle you're not going to pick up anaerobic bacteria, I mean there is no final answer to that, it depends on what you want to accomplish with it. Other discussion? Are we ready to vote? Well, we vote on the question, bacterial testing of 500 consecutive collections. I believe that Dr. Epstein said two bottles was not required in this process, Dr. Vostal, do you want to clarify?

DR. VOSTAL: I think it should just be according to the manufacturer's instructions for each particular

device. If you follow the instructions and apply that device to your product that will be sufficient.

DR. SZYMANSKI: How could it be different for different manufacturers whether you want anaerobic or aerobic bacteria detected? I don't understand.

DR. KATZ: There are three devices that are approved for platelet QC, Biomerry(?) use bacti alert in fact gives you the option to do an aerobic and an anaerobic bottle. The Paul EBDS is in a pouch and is aerobic, it is not anaerobic, it cannot be made anaerobic. And Hemasystems scan system is visual assay basically similar to microscopy but automated and is neither aerobic nor anaerobic, so each device is different.

DR. SZYMANSKI: So assume you have one simple standard and it's the same all over the place and not different standards --

DR. ALLEN: There are different devices just as we heard this morning from five different manufacturers, each one using a different process, trust me, if they were all to be done on the same samples you would come up with different results from them and that is the way it is. Are we ready to vote? Let's go ahead and call the roll.

MR. JEHN: Okay, voting on as is the question up there. Dr. McGee?

DR. MCGEE: Assuming we're voting on it as it

sits, right? No.

DR. SZYMANSKI: I'm voting for 500, yes.

DR. QUINN: No.

DR. FINNEGAN: No.

DR. CRYER: Yes.

DR. BALLOW: No.

DR. KUEHNERT: Yes, I think so, but I think with the given platform the practice should be the same and there's so much behind this question it's really hard to say yes or no.

DR. MANNO: No.

DR. QUIROLO: Yes.

DR. WHITTAKER: No.

MS. BAKER: No.

DR. DAVIS: No.

DR. DOPPELT: No.

DR. KLEIN: No but I would like to add that I support the agency's search for a scientific method of validating, a scientifically valid method of validating the process, looking at perhaps a one tail or some other approach that would not require that kind of an end.

DR. LEITMAN: No and I state again that I don't understand the need for process validation for a test for which is 100 percent sampling for QC reasons, I just don't understand that but I would use the CBC analogy, we do the

same thing for another test and so I would use that approach and that number.

DR. CRONSTEIN: Can I abstain? I really don't understand the issues to be honest.

DR. ALLEN: No with comments very similar to Dr. Klein's, this is an important issue, if testing is being done on 100 percent of the samples that may take care of the issue adequately, there may be some collection areas where testing is not being done routinely and there needs to be some sort of a process in place.

MR. JEHN: Dr. Katz, do you have an opinion?

DR. KATZ: For the reasons that I said when I did my presentation I don't find this to be an emergent issue. Having said that because Dr. Epstein has clarified the licensure issues and Dr. Vostal has clarified the issue of requiring a second bottle or not and said that no, that was not the intent, some number and perhaps the one tail test I don't think we'll find onerous if there's adequate discussion.

MR. JEHN: Okay, so four yes, 12 no, and one abstention.

DR. ALLEN: I think we have had reasonable discussion on the second part, if not, what sample size and acceptance criterion, are there other comments that anyone on the committee wants to make with regard to that? All

right, lets move on to the third question.

DR. KUEHNERT: I think just on number two, I mean it sounds like people agree with the spirit but not the details.

DR. ALLEN: I think that's a good summary, thank you.

DR. WILLIAMS: So the final question is do BPAC members agree that the proposed recommendations on donation frequency, interval between donations, and number of components collected per year are appropriate to protect the safety of the donor pending the availability of additional safety data on larger volumes of collection? If not please comment on limits that would be more appropriate. And the preceding gives the current considerations if you'd like those reviewed briefly, Jim. So FDA's current consideration is that there be a minimum pre-donation count of 150,000 based on prior actual determination and I believe this was modified, a mean of pre-donation counts or a facility mean. There's a minimum targeted platelet count of 100,000 post-donation, consider modifying or removing the recommendation for 24 component per year donation limit based upon review of the submitted safety data, I think a good representation of which you saw today. A maximum double unit collection for new donors who lack a pre-donation platelet count, a seven day deferral

for collections that are larger then a single, recognizing that there could be some operational problems involving rescheduling of donors on site. Solicitation of additional safety data, for instance related to loss of plasma proteins over time. Elimination of recommendation for collection of a post-donation platelet count.

DR. ALLEN: Alan, could you clarify for me the seven day deferral for collections that are greater then a single?

DR. WILLIAMS: If donors donate a double or a triple unit they would be deferred for seven days.

DR. ALLEN: That was the original recommendation, this is the revised. Committee general discussion on this.

DR. KLEIN: Could I see the wording of the question again? Because again, I disagree with the wording of the question and what it says there is if you agree that the number is appropriate to protect the safety of the donor, well one donation every five years is appropriate to protect the safety of the donor, so I think it's appropriate but not necessarily ideal. I would simply recommend once again not changing anything without the current procedures, without any either data saying that there's a problem or that there's a better way to do it and I don't think we've seen any compelling data today.

DR. FINNEGAN: That was actually my question is

what pushed the FDA to get into this topic other then one study which said that there was some lowering over time but it actually didn't effect anybody?

DR. WILLIAMS: I think it was recognition that the standards had not been updated since 1988, that practice had changed substantially since that time, and although collection of higher volumes was in fact in frequent use there really were not data available to the agency at that point that supported the safety for donors. That's not to say there were observations of adverse events but just that the practices had changed and we actually hoped that there would be data submitted that would help guide the issue.

DR. QUINN: It's on the post donation, so the second line says you need to have a minimum targeted platelet count of 100,000 post-donation, then second to the last slide, or the last slide, an elimination of the recommendation for collection of post-donation platelet count, how do the two --

DR. WILLIAMS: The difference is target versus count, the machine is targeted to a post-donation count of 100,000, it's not an actual count.

DR. KATZ: I presume there's nothing in any of what we've discussed here that would impede my ability to use a dedicated match donor more frequently then this

presuming that I take due care.

DR. WILLIAMS: I believe there are provisions for that under physician oversight, that that be continued.

DR. ALLEN: Dr. Williams, the third point, consider modifying or removing the recommendation for 24 component per year donation limit based upon review of submitted safety, what is the agency's expectation there in terms of who will submit data and what is necessary? I guess my question would be why not leave it where it is until there is, and request that the collection agencies submit data that would validate that rather then --

DR. WILLIAMS: Well, I guess one interpretation of that would be that are the types of data coming in those that would adequately address donor safety, we're seeing long term trends in platelet counts and saying this is a self regulating biological effect, it doesn't give any indication of donors who may have dropped out, whether they dropped out for reasons that might be related to high volume apheresis donation, are the data that we're seeing that you saw today adequate to address safety issues that might be present in the donors.

DR. SZYMANSKI: -- you can make 24 donations double or triple? Yes?

DR. ALLEN: It's 24 components per year which would be if you were doing all triples would be only eight

times per year --

DR. SZYMANSKI: No, no, no, I thought removing that --

DR. ALLEN: It says consider modifying or removing it but the FDA has not --

DR. SZYMANSKI: Hasn't done it yet.

DR. ALLEN: Right, and that would be contingent upon submitting other data.

DR. QUINN: I think this is an important point because I'm seeing heads over there shaking one way and what I heard Dr. Katz present was different, he was saying it would cut down to just eight donations a year if you allowed triples, and yet some of you are sort of alluding that no, that's not the case, you can do a triple 24 times a year. The only thing I want to say, I mean we all want to ensure safety, the data that we heard Dr. Katz present didn't show any adverse events in his presentation, it looked like the safety was pretty good, I'm convinced with whatever they're doing, so this triple versus a single per 24 times is very important to us because he's saying it will cut them down to eight.

DR. ALLEN: Dr. Williams can you, on the third point could you clarify for the committee exactly what that means?

DR. WILLIAMS: I apologize, the wording is a

little confusing. This is a consideration which refers to changes in the draft guidance, the draft guidance as currently published limits collections to 24 components per year. The current consideration, which is point number three, is to modify or remove that restriction as stated in the draft guidance. I'm sorry it's a little convoluted.

DR. ALLEN: Well it says to consider doing that.

DR. CRYER: Can I ask what's allowed right now?

DR. WILLIAMS: 24 transfusable components, I'm sorry, 24 collections which can be as much as three ach.

DR. CRYER: It just seems to me from the data that we heard today that if we change that that we'll lose a lot of platelet donors and that we'd be doing it for some pretty soft data and it seems that the reason that we're doing it, doing pretty safely now, why change?

DR. SZYMANSKI: So if we vote for this we say that we don't agree what you said in your guidelines unless you modify it, but we don't know how you're going to modify it.

DR. ALLEN: There is a problem in that there are multiple issues up here and we're being asked one question and that's --

DR. KLEIN: As I understand it if you vote yes for this you vote yes for 24 components a year with the consideration that you go back to more if there's

additional safety data. I think we've heard all of the available safety data that we're going to get today and as we've heard from multiple people it doesn't seem to be an issue.

DR. ALLEN: That was my interpretation exactly too.

DR. EPSTEIN: I think if the committee were to make a recommendation based on whether the safety data presented appear on first blush to be adequate we could then remove that one line and vote the rest. Is it the sense of the committee that the safety data for as much as a 72 component collection per annum appeared to be adequate to support the practice?

DR. ALLEN: If I could summarize for the committee and anybody may take exception, I have not heard anything today that suggests that we should change current practice and I would suggest you continue to look at it, that's not, that should always be done, we should always be examining what we do, but I haven't heard anything that would suggest that there's a real safety consideration if we were to continue current practice. Do you want us to vote on that specific question?

DR. EPSTEIN: Why don't you just ask if anyone objects to that concept?

DR. ALLEN: Does anyone object to that? Okay.

DR. DOPPELT: Please state it again.

DR. ALLEN: That the current practice which allows up to 24 donations, platelet donations per year does not present any safety consideration for the donors based on all the information that we've heard and discussed today. Each one of those donations may be up to three components.

All right, I think the sense of the committee is that that is an acceptable position so with that understanding look at the rest of the things there and can we vote on the rest of the recommendation, does anybody have concerns about any of the other points that were listed there?

DR. SZYMANSKI: The interval, we did not agree with the interval either, questions, discussants --

DR. ALLEN: Okay, the interval is being changed from currently the interval would allow two donations within a seven day period, this change would be that once you have, if you've donated a double or a triple you would need to wait at least seven days instead of being able to donate one more time in that seven day period. Am I correct on that interpretation?

DR. KLEIN: Correct but again I don't think we saw any data to that point and since we actually test donor's platelet counts it's not intuitively obvious to me

why there would be a problem with the current practice.

DR. ALLEN: Dr. Williams or anybody else?

DR. LEITMAN: We saw a little data from Lou that suggested that when the interval was one week the count was statistically lower then if the interval was two weeks, and we've all had experiences where you had an HLA match sole donor or a family member and you did have to do a plateletpheresis of one or one and a half unit equivalence, as much as you could get, and the platelet count went down on the second procedure. So in a healthy volunteer altruistic donor if one is going to do more then one equivalent plateletpheresis component I feel we should wait a week, seven days.

DR. KATZ: The number of donations in our dataset, not just the 24 karat donor but I mean everybody in our donor base for 2004 that donated more frequently then seven days, it's microscopic and except for that dedicated donor where we're going to control it with a platelet count under any circumstance I don't see a problem with this approach.

DR. LEITMAN: So it has no operational impact.

DR. SZYMANSKI: But sometimes if you have a dedicated donor you might not be able to wait for seven days. That's excluded?

DR. LEITMAN: With the subject with the donor who

is specifically necessary for a matched need we always do that, I think that's a medical need --

DR. ALLEN: And these are recommendations so that if there's a medical indication and the medical director decides that it's safe for that donor to do that the recommendation can be overridden, am I correct? Okay. Dr. Quinn.

DR. QUINN: Next item on the list that for me just needs some clarification because I don't do this procedure, how often do you screen plasma proteins and what is that going to tell you in terms of safety? Is that line necessary then? It's out there for those people that do these procedures.

DR. KATZ: In the draft guidance are plasma volume limits that come from an old guidance on infrequent plasma donors as I understand it and I don't know why platelet donors would be different and it was okay for the others. Having said that if the FDA wants data in this slightly different setting we'll get it for them.

DR. KLEIN: But in point of fact the original, part of the original rationale for the 24 donations a year was in fact based on the plasma donor experience where a healthy human being losing that amount of plasma per year has no change in their plasma proteins or in their plasma protein electrophoresis, and so the infrequent plasma

donors do not have that kind of testing, the frequent plasma donors of course do.

DR. KATZ: My understanding talking to the agency was they just wanted to be sure this wasn't somehow different and I don't think it's a big deal, I mean literally for a thousand bucks I can get all the data and be done with it.

DR. ALLEN: Okay, other concerns or are we ready to vote?

DR. DOPPELT: Getting back to the previous section, the seven days and if you do like doubles and so forth, if the platelets go down some but there isn't a problem why are we considering changing it? I'm still not clear about that.

DR. KLEIN: I agree with you, why change a recommendation, a guidelines or a standard or God forbid a regulation based on no data and no problem.

DR. EPSTEIN: Well I think there's sort of a bigger envelope here which is you're talking about updating a guidance that dates back to 1988 which antedated all of these common practices of apheresis, and over that period of time the volumes collected and the number of platelets collected from donors has gone up considerably. And what the FDA was really saying in this draft is where are the safety data. Now any time the agency proposes to change

current practice there's going to be a firestorm but there's reason for it which is that there were no data, not a shred of data, no submitted data on patient safety for these much more aggressive practices. Now we've heard good data today and we'll certainly take a careful look at it and it's impressive but again, it must be understood that we were updating 1988 guidance antedating all of these practices. Its also been argued that the apheresis devices have gotten a great deal better and that we've learned a lot more about the parameters, we've learned that we're comfortable with a pre-count of 150k, we've learned that they can be set for a target end point of collection of 100k, we've seen data for the first time that intensively apheresed donors don't get below these parameters when the instruments are used according to their label. But it needs to be understood that we're hearing this information for the first time and really it's the sense, well, the question is whether it's the sense of the committee that we'll we've heard enough to allay our concerns.

DR. CRYER: I think what I'm hearing is is that you want data and it doesn't seem to me that the way to get that is to change the rules but just ask for the data. And it sounds like the companies can easily get that data for you so it'd be my proposal that we let them ask the companies or the data they want and then revise the rules.

DR. ALLEN: Let me suggest that we go ahead and vote and those who want to add a comment like that with their vote may do so. Dr. Szymanski, do you have one final comment?

DR. SZYMANSKI: Does the vote really mean that we limit the donations on a double apheresis into 12 times a year or not? I don't understand what we're voting for. Are we voting for that until the safety data has been collected?

DR. ALLEN: We're voting, the sentence that starts considering modifying or removing a recommendation, we've already discussed and our recommendation, the committee's recommendation to the FDA is to leave the current situation in place, so we're going to consider in one vote all of the rest of the issues there and the most contentious one being whether or not we want to change the current practice of allowing two donations within a seven day period to only one within a seven day period if it's more then a single unit collection.

DR. SZYMANSKI: Okay. So you still can donate 24 times a year if you do double donation, fine.

MR. JEHN: Dr. McGee?

DR. MCGEE: Yes.

DR. SZYMANSKI: Yes.

DR. QUINN: The wording has changed so

dramatically, yes, I would say yes, I think I would recommend that they not donate blood more then twice within a seven day period if they're doing multiple donations, if that's what's up there okay, yes, with the other caveats that we already made. I think what the committee is saying to the FDA is work with the blood donation facilities to collect safety data to influence these recommendations. So if it's just one line I'll vote yes, if it's all these others and it's with all these caveats I'd say no, it's totally been changed, I can't vote yes on the original writing. So qualified or whatever.

MR. JEHN: Dr. Finnegan?

DR. FINNEGAN: I vote yes, my comment would be I think one of the reasons the FDA hasn't seen safety data is because the people on this side of the table are a little confused because we haven't seen the problems that you're worried about and while no science would make you worry about safety I think trying to put safety regulations in with no science is no better then what you're thinking we were doing.

DR. CRYER: I'll vote yes just with the caveat that I think you ought to wait until you get the data to decide.

DR. BALLOW: I vote yes.

DR. KUEHNERT: Abstain, I just think it's

impossible to convey a vote on this one. I agree with the sentiment though, get the data, keep the recommendations, and then come back to the committee with the data and with very clear question yes or no about individual issues would be much easier.

DR. MANNO: I'm also confused and I guess I have to abstain.

DR. QUIROLO: I vote yes.

DR. ALLEN: Dr. Epstein, go ahead.

DR. EPSTEIN: Well, I'm very troubled, we don't have a meaningful vote if the committee members don't know what they're voting on, and I think what was proposed in specific is on the next slide, it's the entire set of straw man proposals minus the proposal on a limitation to 24 components, so it's exactly what's there minus the line that speaks, I guess it's line, sentence four, so it's everything else minus that sentence. But there shouldn't really be lack of clarity what we're asking you because what we've said is let's just deal separately with the issue of more then 24 components per annum and just ask if you otherwise concur with these conditions. So there shouldn't be any ambiguity about what we're asking and what you're voting on, because the other paragraph was simply a summary of this, it said do you otherwise concur with what's here, namely the FDA's current thinking.

DR. ALLEN: All right, given that, Dr. Keuhnert, do you want to reconsider your vote? We'll come back to you, that's okay.

DR. KUEHNERT: No, it's still six issues and I just think that they're all very complicated and I think it's difficult to process the information given.

DR. ALLEN: I think everyone respects that. Dr. Manno, do you want to reconsider? No, no, don't feel pressure, abstain is a legitimate decision.

DR. MANNO: I vote no.

DR. DOPPELT: I'm still confused, the number of donations that you can make within a seven day period.

DR. ALLEN: If you are donating a single unit you can donate twice, if you're donating more then a single unit the first time you have to defer for at least seven days.

DR. DOPPELT: Unless the medical director --

DR. ALLEN: The medical director can override that if you're otherwise qualified to donate again.

DR. WHITTAKER: Yes.

MS. BAKER: Abstain.

DR. DAVIS: Yes.

DR. DOPPELT: Yes.

DR. KLEIN: No, I vote not to change the current practice without either a perceived problem or scientific

data suggesting that this should be done, I don't feel that we should change one relatively arbitrary standard for another relatively arbitrary standard.

DR. LEITMAN: Yes, I agree with all those current considerations and the point that seems to be bothering many committee members is this interval of seven days between an apheresis donation that yielded more then one apheresis component and I just feel that, there's a point at which I feel uncomfortable asking a donor to do more and I know donors compete against each other, they're very nice people, they're donors who want to donate three apheresis on Monday, three apheresis on Wednesday, and just be the lead apheresis donors. And I think we ought to safeguard them against themselves and that's rationale behind that.

DR. ALLEN: I appreciate Dr. Klein's perspective, I will vote yes.

MR. JEHN: Dr. Katz, any opinion?

DR. KATZ: Well once again were I allowed the luxury of a vote I would vote no and only because I am not sure that the minimum target of 100,000 is appropriate and we're hearing from some of the manufacturers that if you in fact target 80 people tolerate donations better on one of the machines and this and that and the other thing, and then there was one other thing that I didn't like, maximum double unit for new donors lacking, oh it says lacking,

forget it, it's just that one thing.

MR. JEHN: 12 yes, two no, and two abstentions.

DR. ALLEN: Thank you. Any other comments that anybody wants to make, thank you all, we're adjourned for the day. And we reconvene at --

DR. EPSTEIN: I'm sorry but we have to hear the result of voting --

MR. JEHN: 12 yeas, two no, two abstentions.

DR. ALLEN: We reconvene at 8:30 tomorrow, is that correct? 8:30, okay, thank you all.

[Whereupon at 6:00 p.m. the meeting was adjourned.]