TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRAITON

BLOOD PRODUCTS ADVISORY COMMITTEE

58TH MEETING

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

BLOOD PRODUCTS ADVISORY COMMITTEE

58TH MEETING

Friday, March 20, 1998

8:00 a.m.

Doubletree Hotel
Plaza I and II
1750 Rockville Pike
Rockville, Maryland

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P R O C E E D I N G S

DR. SMALLWOOD: Good morning and welcome to the second day of the 58th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary.

Yesterday I real the statement of conflict of interest. That statement applies to today's proceedings. If anyone is interested in that, it is available for your review. I would ask that in the interest of fairness, that if anyone has anything to declare any or the proceedings taking place today, that they do so now.

Today, two of the members that were present yesterday, Dr. Martone and Dr. Verter, will be absent today. However, there will be a quorum so that this committee will be able to take care of the business before it.

Today, our first agenda item, classification of blood establishment computer software -- for this particular topic the committee will be sitting as a medical device panel. At this time, I would like to read a brief statement regarding this responsibility to the committee:

The charter of the Blood Products Advisory Committee permits the committee to sit as a medical device panel when it is necessary to review or discuss issues related to the seeking of advice, recommendation for approval, or reclassification of medical devices which are regulated by the Center for Biologics Evaluation and Research. The Blood

Products Advisory Committee will sit as a medical device panel to consider classification of blood establishment computer software as a class II device.

Products classified as class II are those where there is insufficient information showing that general controls alone would ensure safety and effectiveness, but there is sufficient information to establish that special controls would provide such assurance.

FDA is proposing that blood establishment computer software be classified as a class II device with general controls. Because the manufacture of blood and blood products are governed by specific blood regulations which exceed those safeguards covered by medical device general controls, FDA's reviewer guidance, published in 1997, will be considered as a special control. Accordingly, the advisory panel will be asked to provide opinions and recommendations as to whether blood establishment computer software should be classified as a class II medical device.

The questions for consideration by the advisory panel will be presented by FDA personnel, and will be restated by the panel Chair, at which time you may discuss them or request further clarity, as necessary, and provide recommendations.

Are there any questions at this time? Hearing none, our Chairman, Dr. Hollinger, will continue with t he

proceedings. Thank you.

DR. HOLLINGER: Thank you, Linda. We have three important topics today, besides this one where we are going to be sitting as a medical device panel. This will take us until about eleven o'clock, when we will break for lunch. Then, later on this afternoon, we will start around noon, on relative safety of solvent detergent-treated plasma, and finish with a proposal for donor deferral related to xenotransplantation.

So, we will start the proceedings this morning with the classification of blood establishment computer software, and the first presenter is Boyd Fogle, who will talk about inspectional findings.

MR. DUBIN: Blaine, just a question. Based on the agenda, I have scheduled a 5:30 flight out of Dulles. I just wanted you to know that. I did that based on the agenda I got.

DR. HOLLINGER: My hope is that we will be finished in time. We are going to try to do that.

MR. DUBIN: All right.

Classification of Blood Establishment Computer Software

Inspectional Findings

MR. FOGLE: Good morning.

[Slide]

What I have been asked to do for you this morning is to

present a brief overview of the background concerning regulation of blood establishment software, and then to focus on some of the more significant inspectional findings.

Provided to you previously was a more comprehensive listing of some of the deficiencies that we have found in inspections of device manufacturers. When we say device manufacturers, those are the manufacturers of the blood establishment computer software.

[Slide]

To focus our discussion and to refresh our recollection on the background, a letter was issued to all registered blood establishments in April of 1988. It was a recommendation from CBER and it was asking that blood establishments have systems that will be able to trace the history of donation forward and backward; that there should be implementation of a computerized system as a major change, to be reported to CBER under licensure.

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Also, prior to implementation the blood establishment will evaluate the computerized system for evidence of validation that the programs consistently perform, as required and within preestablished limits.

To refocus the time period for 1988, 1988 is when the agency went to 100% inspection of blood establishments.

[Slide]

So, our initial thrust in terms of regulation of blood establishment software was through inspection of blood establishments, and 100% inspection began in 1988. We updated this guidance and expanded it by issuing additional requirements for computerized blood establishments. In this situation it was not recommendations. What we were articulating was the requirements that apply to blood establishment software systems, computerized systems used in blood establishments.

We specifically articulated, in a memorandum of September 8, 1989, that we believe that the 211 provisions of the CFR applied in addition to the 606's. The 606's are the blood GMPs, the 211s are the GMPs for pharmaceutical manufacturing. It was also at this point in time, while we were focusing, that the computer system should meet the same standards for equipment that was contained in 606.60, and also the standards for records in 606.160. We were specifically focusing that we were going to apply 211 authority initially with 211.68 which talks about validation of automated systems. We felt that that was appropriate also because blood is a drug.

[Slide]

In November of 1989, there was also available the FDA policy for the regulation of computer products. This policy was an agency policy, spearheaded out of the Center for

Devices and Radiological Health which provided general guidance on the regulatory requirements for computer products. Computer products which are medical devices are subject to one of four levels of regulatory control, depending on their characteristics.

[Slide]

It was focusing on the definition of a medical device and bringing that to focus on where software as a product would fit into the device regulation. For your information, again, the term device means an instrument, apparatus, implement, machine, contrivance in vitro reagent or other similar related article, including any component or accessory which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease. That is contained in Section 201 of the Food, Drug and Cosmetic Act.

[Slide]

Also from the Center for Devices and Radiological Health was a guidance document for submission of 510(k)s for software-controlled devices, and this was issued in August of 1991.

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Contained in that, it also stressed CDRH's and the agency's concern that 510(k)s should include a hazards analysis for the device's software, along with a level of

concern in relation to the following areas: One would be functional requirements and system specifications; also, software design and development; verification and validation data; and test results and analysis.

[Slide]

So, what we were doing was addressing the concern that we were seeing coming out of blood establishment inspections, an increase in the use of computerized systems, an increase in availability of stand-alone software to be used by blood establishments. We were seeing that from the biologic side.

At the same time, we were trying to then put those issues and concerns into the existing regulatory format that existed under the '89 software policy and existing guidance. Again, we believe that the computerized system in blood establishments consisted of hardware, software, peripheral devices, its personnel and documentation. We had clearly felt that these computerized systems met the standards for equipment and the requirements had to be met as 606.60 and 211.68 which included system validation. We also believed record-keeping requirements were applicable in 606.160. SOPs were appropriate and required in 606.100, and personnel was required in 606.20.

[Slide]

As we have progressed throughout the process, we were

principally regulating through blood establishments. We did not feel that that was appropriate. What we felt was more appropriate was to start regulating the software at the design phase. Using the procedures that existed, we then initiated a more proactive approach by issuing a letter, on March 31, 1994, where we stated that FDA considered software products intended for use in the manufacture of blood and blood components or for the maintenance of data, the personnel making decisions regarding the suitability of donors, and the release of blood and blood components for transfusion or further manufacturing to be devices under Section 201(h) of the Federal Food, Drug and Cosmetic Act, again, using existing regulations, bringing them to focus on the issues of software as a device. Again, it was a critical component of computerized systems used in blood establishments.

Also, circa 1993, we had increased our emphasis on blood safety. There was also a congressional hearing in terms of FDA's initiatives in blood safety and to be more proactive in its initiatives for quality assurance, and also assuring that the nation's blood supply was as safe as it possibly could be. One of the initiatives that was announced at that hearing was our proposal to more proactively regulate blood establishment computer software as a device.

[Slide]

The culmination of those actions was in this March notification to the industry. It also indicated, over and above the fact that we now considered blood establishment software to be a device under the Act, that establishment registration and device listing would apply; cGMPs for devices would apply. Those are contained in CFR Part 820. Also, medical device reporting was applicable, and the manufacturer will be responsible for submission of the 510(k) or PMA for each device that was not in commercial distribution prior to May 28, 1976, which was enactment of the original device amendments to the Food, Drug and Cosmetic Act.

[Slide]

Also at this time, when we had issued the requirement for manufacturers to submit applications, we also believed that t here were suitable predicates that the industry could draw on. So, we also felt that that mechanism of a 510(k) was a quite viable alternative as far as predicates existing for similar intended uses.

As we were moving forward in this initiative, we also found that it was appropriate to give an extension so that there would be an orderly transition for blood establishments, and a one-year extension was given to software manufacturers, and there was a letter issued on

February 10, 1995 which gave a revised schedule for compliance, a one-year extension of the premarket submission deadline to March 31, 1996, and that there should be notification to CBER by letter if a premarket submission would not be completed and filed by the September 30th deadline.

[Slide]

Focusing on deficiencies that we found in inspections of software manufacturers, again, we had done a 100% inspection of blood establishments starting in 1988. As we saw problems in blood establishments, we then initiated inspections of the vendor developers which we call "for cause" inspections. Again, refocusing in the '94 letter was to give us a more proactive approach. But going back to inspections, as far back as 1989, we did find problems with respect to design defects and programming errors.

[Slide]

With respect to design defects, and also focusing also on outcomes and impact on blood establishments, in the area of design defects we determined that unsuitable units had been released and test data had been lost. Reactive results were not transferred to donor deferral records, and these reactive results were viral marker testing and other results that are used for product quality and donor suitability decisions. There is also assignment of inaccurate sample

identification numbers, and this assignment was controlled by the software. There were no deferral donors with positive test results, and these functions which were to be performed by the software but they were not, and they were tracked back to design defects.

[Slide]

Also in the design phase, we determined that there had been programming errors which relate to permanent deferral status being deleted if temporary deferral status was removed. There was no quarantine of reactive units; units suitable for labeling without completion of all testing, and loss of data when merge function was used.

In summary, we believe that the regulation of blood establishment software should begin at the design phase and that a course of regulation over time has been appropriate. Since 1989, there have also been 16 recall classifications of blood establishment software, involving 10 firms. Of those 16 recalls, 6 were in the area of design defects; 8 were in the area of program errors; there were 2 others that related to the distribution of faulty diskettes; and another situation involving inadequate directions for use.

In furtherance of the process that we have described, starting back in 1988 and 1989 as far as our regulation of blood establishment computer software, we are now pursuing the process of formal classification.

Our next presenter will be Molly Ray, who is in the Division of Blood Applications, who will give you an orientation to the classification process.

Device Classification

MS. RAY: Good morning. I am Molly Ray. I am a consumer safety officer in the Division of Blood Applications, and a software reviewer.

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I have been asked to present you with an overview of device classification.

[Slide]

The items that I am going to discuss will include the current status of blood establishment computer software. Boyd just presented the background information so I won't go into that again. I will go over the classification procedure. I will identify what the question is that will be submitted to the Blood Products Advisory Committee. I will provide an overview of the device classes, and provide you with a summary and the recommendations.

[Slide]

Current status -- blood establishment computer software is currently unclassified. Inspectional findings, discussed by Boyd Fogle, indicated that some flaws exist in blood establishment computer software that is currently in use in blood establishments. We are here this morning to formally

classify blood establishment computer software. We are asking for the committee's input and recommendations as far as the appropriate classification.

[Slide]

Title XXI of the Code of Federal Regulations, or CFR, Part 860 codifies the device classification procedures identified in Section 513 of the Federal Food, Drug and Cosmetic Act. These regulations state that devices are to be classified into one of three regulatory classes based on the amount of regulation that is necessary to provide a reasonable assurance of the safety and the effectiveness of the device. These regulations also state that devices should be referred to the appointed panel to make recommendations for the appropriate device classification. This Blood Products Advisory Committee has been appointed as that panel.

[Slide]

After the FDA presentations and the open public hearing, this committee will be asked the following question, does the committee agree that blood establishment computer software be classified as a class II medical device?

[Slide]

The appropriate device classification is based on the amount of regulation that is necessary to provide a

reasonable assurance of the safety and effectiveness, as well as the risk for potential harm. Most devices can be found in Title XXI CFR Part 862 through 892. There are approximately 1700 device classifications within 16 medical specialties. Of these 1700 devices, 45% are class I, 47& are class II and 8% are class III.

[Slide]

Class I devices are subject to the lowest regulatory controls since they present minimal potential for harm, and are often simpler in design than class II or class III devices. The class II determination may be made when there is enough information to determine that general controls are sufficient to provide reasonable assurance of the safety and the effectiveness of the device. Class I devices are not life-supporting or life-sustaining. Examples of class I devices include elastic bandages, examination gloves and blood bank centrifuges.

[Slide]

I want to make a note here that the number on the left-hand side of the overhead denotes the specific section of the Federal Food, Drug and Cosmetic Act. All device classes are subject to the following general controls, for which I am providing a very basic overview that only addresses the relevant items for today's discussion. This overview is not intended to be all-inclusive of the provisions addressed by

each of the sections of the Federal Food, Drug and Cosmetic Act.

Section 501 states that a device is considered to be adulterated if the device is not manufactured in conformance with Good Manufacturing Practice requirements.

Section 502 addresses misbranded devices. One of the provisions in this section states that a device is considered misbranded if the labeling is false or misleading, or does not contain adequate directions for us.

Section 510 of the Act states that medical device manufacturers must register and submit a listing of devices being manufactured. Each person who is required to register under this section, and plans to begin delivery of a device into interstate commerce must submit a premarket notification submission or a 510(k) at least 90 days before such introduction.

Section 516 of the Act states that devices that are found to present substantial deception or unreasonable and substantial risk for illness or injury may be banned from human use.

Section 518 of the Act states that there are three actions that the agency can take if a device presents an unreasonable risk of substantial harm to public health. One of these actions is notification of the device users. This option may be considered if no more practical means are

available under other provisions of the Act, such as recall, seizure or injunction, and notification is required to eliminate the risk.

The device manufacturer under certain circumstances may be required to repair, replace or refund the purchase price of a device if notification would not be adequate to eliminate the risk. Another alternative under this section includes ceasing distribution and use of the device.

Section 519 of the Act states that medical device manufacturers must establish and maintain records and reports, and provide this information to the agency to assure that the device is not adulterated or misbranded, as well as safe and effective. The medical device reporting regulations can be found in 21 CFR Part 803.

Section 520 of the Act contains the general provisions for the control of devices intended for human use and includes the Good Manufacturing Practices requirements. They have been codified in 21 CFR Part 820.

[Slide]

Class II -- this is the device classification that we are recommending for blood establishment computer software. Devices are classified as class II if general controls are insufficient to provide a reasonable assurance of the safety and effectiveness of the device, and there is sufficient information to establish special controls. Class II devices

are subject to general controls and special controls.

Examples of class II devices include transfer sets, empty blood bags, blood bank refrigerators, blood bank freezers and powered wheelchairs.

Section 5 of the Safe Medical Devices Act of 1990 amended Section 513 of the Federal Food, Drug and Cosmetic Act and introduced special controls as a means of providing reasonable assurance of the safety and the effectiveness of a device. Special controls include performance standards, postmarket surveillance, patient registries, guidelines and/or guidance documents, recommendations and recognized standards.

The FDA Modernization Act of 1997 created an alternative procedure for demonstrating substantial equivalence to 510(k)s. Section 204 of this Act states that FDA will recognize all or part of an appropriate standard established by nationally or internationally recognized standard development organizations to which manufacturers may declare performance in lieu of submitting an element of a premarket notification submission. The Center for Diseases and Radiological Health has established 13 specialty task groups to evaluate standards for potential recognition. One of these specialty task groups has been assigned to evaluate software standards, and has CBER's participation.

Approximately 175 consensus standards have already been recognized and published in the Federal Register. No software standards have been recognized yet, but these standards are actively being evaluated for recognition.

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Class III is the most stringent regulatory class. Class III devices are usually life-sustaining or life-supporting devices for which there is insufficient information to assure the safety and effectiveness through general controls or special controls. Class III devices require a premarket approval, or PMA. Regulatory requirements that implement Section 515 of the Federal Food, Drug and Cosmetic Act for PMAs, or premarket approvals, can be found in 21 CFR Part 814. Examples of class III devices include pacemakers, replacement heart valves and respirators.

[Slide]

Summary and recommendations -- blood establishment computer software is currently unclassified. The new quality system regulations in 21 CFR Part 820 include pre-production design controls that are considered to be a part of general controls. Compliance with these regulations is not evaluated by FDA until the device manufacturer is inspected. This inspection does not occur until after the design of the device has been completed and the product is

already on the market.

Boyd Fogle summarized FDA's continued inspectional findings of design flaws that indicate that FDA needs regulatory control during the design phase and general controls are insufficient to provide the reasonable assurance of the safety and effectiveness of blood establishment computer software.

Based on the above and the risks that are inherent with the intended use of this device, for example, the release of unsuitable blood, FDA is recommending that blood establishment computer software be formally classified as a class II device. The risk or potential for harm is greater than class I devices, such as bandages, gloves and centrifuges, but less than that of class III devices, such as pacemakers and respirators.

Nancy Jensen will now present the review of the guidance document that is the basis for special control.

Special Control for Blood Establishment Computer Software

MS. JENSEN: Thank you, Molly.

[Slide]

I would like to speak this morning regarding the special control for blood establishment computer software.

[Slide]

In the previous presentations you heard that the critical decision-making capability of blood establishment

computer software involves the inherent risk of releasing unsuitable units of blood for transfusion. FDA has proposed classification of blood establishment computer software as a class II medical device since a special control is needed to establish safety and effectiveness.

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FDA proposes that the reviewer guidance for a premarket notification submission for blood establishment computer software, which was issued April 12, 1996 for comment and published January 13, 1997, be considered as the basis for development of a special control for blood establishment computer software in addition to declaration of conformance to recognize software development standards.

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The reviewer guidance identifies those elements to be included as part of the special control. Declaration of conformance to a recognized standard may be submitted in lieu of submitting these review elements as part of the 510(k). The applicable review elements include the functional requirements, the software requirement specifications, the hazard analysis, and the verification of validation and testing.

[Slide]

The functional requirements should include the intended use functionalities, and a reference to the applicable blood

regulations found in 21 CFR Part 600.

It should be noted that FDA cannot dictate what functionality should be included in the software design. However, if the manufacturer claims a certain function, the manufacturer should ensure that the appropriate blood regulation is addressed either by the software design or by a work-around.

The limitations of the software system are to be identified in the 510(k) and in the labeling for the device. The functional requirements should also include an identification of the safety critical requirements, the design safeguard employed in the software, and a trace matrix to the software requirement specification, the hazard analysis and verification of validation and testing.

[Slide]

The software requirement specification should include a detailed design specification document which describes how the functional requirements are implemented into the software design. The design specification should be traced to the functional requirements, the hazard analysis and the verification validation and testing.

[Slide]

The requirement specifications include a description of the hardware platform, the operating system and databases used, and a listing of the interfaces.

[Slide]

The hazard analysis should include the clinical intended use hazards, the implementation hazards which are those resulting from the implementation of the functional requirements in the computer and software environments, a description of the hazard, cause of the hazard, the method of control used to mitigate that hazard, and a trace matrix to the functional requirements, software requirement specification and verification, validation and testing.

[Slide]

The verification, validation and testing should include a test plan and results summary of the unit integration and system level testing. This is the alpha testing performed in the developer's environment. It should also include a test plan and results summary of the system level testing performed in the user environment, which is the beta testing. It should also include validation from both alpha and beta testing for the donor deferral, labeling, quarantine release and laboratory testing functions if these functions are included as part of the software application.

[Slide]

The unit level test plan should include a narrative description of the review addressing both the functional and structural testing. The functional testing addresses normal and invalid inputs, boundary testing and stress testing.

Whereas, the structural testing includes statement, branch and path testing.

[Slide]

The integration test plan should address both internal and external interfaces. Internal interface testing would address module to module, whereas, external interface testing includes peripheral devices, any other application software or networks employed.

[Slide]

The system test plan should include the alpha testing which validates the intended use functions tested in the developer's environment, and the beta testing which validates the intended use functions tested in the user's environment. The developer is responsible for designing the beta test plan, which should not be used as the test of record at the beta site.

[Slide]

The results summary should include a summary of results for the safety critical functional requirements at the unit integration and system levels for both alpha and beta environments, a description of deviations from expected results, any corrective action taken and any retesting that was performed.

[Slide]

The validation data should include alpha and beta

system level testing for the applicable functions if these functions are included as part of the software application. These functions include donor deferral, labeling, quarantine and release, and laboratory testing.

[Slide]

In summary, the reviewer guidance for a premarket notification submission for blood establishment computer software is being proposed as the basis for a special control for blood establishment computer software. A class II medical device becomes eligible for the new 510(k) paradigm, providing for a win-win situation for both industry and FDA whereby review times would be shortened and software upgrades would reach the market in a timely fashion.

I would now like to introduce Heather Rosecrans, from CDRH, who will describe the new 510(k) paradigm. Is Heather here?

DR. HOLLINGER: If not, I think we will go ahead and come back to her. Let me know when she gets here. We will go into the open public hearing. The first person that has asked to speak is Kay Gregory, who is a regulatory officer for the AABB. I know Kay is here.

Open Public Hearing

MS. GREGORY: Thank you, Blaine.

I am speaking this morning on behalf of the Information

Systems Committee of the American Association of Blood Banks. The American Association of Blood Banks is the professional association for approximately 2200 institutions engaged in the collection and transfusion of blood and blood components, including all American Red Cross blood service regions, independent community blood centers, hospital-based blood banks and transfusion premises, and more than 8500 individuals engaged in all aspects of blood collection, processing and transfusion. Our members are virtually all of the blood collected and more than 80% of the blood transfused in the United States.

The AABB's highest priority is to maintain and enhance the safety of the nation's blood supply. The AABB Information Systems Committee appreciates the opportunity to speak on classification of blood bank software. In order to ensure the safest possible blood supply, it is our contention that new technology must be improved and implemented as quickly and safely as possible. Consistent with the goal of rapid approval and implementation of new technology, AABB specifically encourages the acceptance of international standards and simplification of the approval process.

We understand that currently blood bank software is not classified, and we are very pleased to see that FDA is not recommending classification as a class III, which would have

required a PMA.

We understand their proposal is to classify software as a class II device, and it is intended to decrease the significant paper review which is currently performed by substituting an abbreviated 510(k), in which conformance to an FDA recognized standard or special control can be stated. The guidance for reviewers would then be considered a special control.

We expect that this approach will permit a more rapid approval for new software. Moreover, as we understand it, the current inspection process for design controls allows for adequate inspection and review by CBER.

Likewise, under a class II classification, changes or modifications to existing blood bank software would require submission of a special 510(k), declaring that the modifications in design conform to the design control standards rather than the current lengthy paper review. Again, the inspection process offers adequate inspection review opportunities for CBER.

As we understand it, the purpose of this classification helps to lay the groundwork for future implementation of the new CDRH paradigm in which CDRH is planning to recognize consensus standards, such as IEEE and ISO that are recognized both in the United States and internationally. We are concerned, however, that CBER's initiative may be

premature in light of the ongoing effort for CDRH to classify all software. We encourage CBER to ensure that the approach to device classification and approval is consistent with CDRH, and to work closely with both CDRH and industry on software classification.

Finally, a cautionary note, all of the ramifications of the classification are still not clear to us. Accordingly, as CBER proceeds under good guidance practices to further develop this initiative, AABB encourages more communication on the issues among FDA, the software industry and blood banks to ensure that the most appropriate approach is adopted. Thank you.

DR. HOLLINGER: Thank you, Kay. Any questions for Ms. Gregory? If not, the second person that wanted to speak is with the Health Industry Manufacturing Association, Carolyn Jones.

MS. JONES: Good morning. My name is Carolyn Jones. I am a director in Technology and Regulatory Affairs at the Health Industry Manufacturers Association. HIMA is a Washington-based trade association and the largest medical technology association in the world. We represent more than 800 manufacturers of medical devices, diagnostic products, and medical information systems.

I am here today, speaking on behalf of HIMA's Blood Bank System Task Force. We appreciate the opportunity to

address the committee regarding device classification of blood bank software. Blood bank software has been an integral part of clinical laboratory software products since the 1980s. Current blood bank software is designed to serve a variety of functions, including donor recruitment, donor scheduling, patient transfusion histories, labeling, inventory control and donor reentry. Blood bank software has had a long and exemplary track record.

As you know, four years ago FDA formally notified manufacturers of blood bank computer software that the agency considers such software products to be medical devices. Accordingly, stand-alone blood bank software became subject to device controls such as premarket notifications, also known as 510(k)s. Even though FDA had not classified blood bank software, the agency set a March 31, 1996 deadline for submission of 510(k)s for those software products.

In essence, the process has frozen the deployment of new products and the advancement of current products. Approximately 50 510(k)s were submitted on or before March 31, 1996, most of which were for blood bank software products already in use at blood banks and blood centers. In two years, we understand only 16 510(k)s for blood bank software have been cleared by FDA. As a result, the blood supply cannot be protected by the newest and most advanced

technologies. This is to the detriment of the patient care and the medical community.

CBER is now considering formally classifying stand-alone blood bank software. The HIMA task force has several concerns about the classification of blood bank software that we believe deserve serious consideration by this committee and CBER.

We understand that the main reason that classification is contemplates is to give CBER the option of using alternative procedures for reviewing and clearing 510(k)s for blood bank software. These procedures are found in a CDRH draft proposal called the new 510(k) paradigm.

The goal of the new 510(k) paradigm is to conserve the agency's review resources while facilitating the introduction of safe and effective devices into interstate commerce. The HIMA task force fully shares this goal, and is very interested in exploring the use of alternative approaches such as those described in the draft new 510(k) paradigm. We believe that such an approach will ensure that CBER's limited review resources are not wasted, and the introduction of new blood bank software products and modifications are not delayed. However, we do not believe that formal classification is a prerequisite to utilizing the new approaches outlined in CDRH's new 510(k) paradigm or other approaches to facilitate review.

By way of background, we note that the new 510(k) paradigm proposal suggests two approaches for demonstrating substantial equivalence in a 510(k). One approach is called a special 510(k). This would be submitted in lieu of a regular 510(k) for certain device modifications currently requiring a new 510(k). This alternative would allow FDA to take advantage of verification and validation testing requirements mandated by the agency's quality system regulation in determining substantial equivalence.

The second approach, called an abbreviated 510(k), would be submitted in lieu of a regular 510(k) for devices that adhere to consensus standards recognized by FDA, or for which FDA has developed a special controls guidance document. This proposal is consistent wit, but not mandated by the FDA Modernization Act, which generally requires FDA to recognize and use consensus standards.

It is HIMA's understanding that CDRH does not intend to exclude from the 510(k) paradigm unclassified devices that have been found substantially equivalent under the 510(k) process. This reflects the fact that there are a many pre-amendment devices that were overlooked during FDA's initial device classification process following enactment of the Medical Device Amendments of 1976, and that FDA has subsequently cleared hundreds of additional 510(k)s for new or modified unclassified devices claiming substantial

equivalence to the earlier unclassified devices. Indeed, it would be entirely inconsistent with the goal of the new 510(k) paradigm -- conservation of review resources -- for CDRH to require all of these devices to be classified before they could qualify for the alternatives under the new 510(k) paradigm.

We have confirmed this with Heath Rosecrans, Chief of the 510(k) Section of the Operations Staff in CDRH's Office of Device Evaluation. Ms. Rosecrans advised that any device for which a 510(k) is required, whether that device is classified as class I or class II, or is unclassified, will be eligible for the special 510(k) and abbreviated 510(k) alternatives under the yet to be published final new 510(k) paradigm.

The HIMA task force believes that any blood bank software device classification initiative is premature in light of longstanding, ongoing efforts in CDRH to develop a new regulatory framework within which medical software may be classified and regulated. CDRH has been working on this effort for almost 10 years, and has developed a great deal of expertise in the software area. Accordingly, we believe it is essential for CBER to work in conjunction with CDRH to ensure that any classification proposal builds on CDRH's knowledge and that classification decisions are generally consistent between the two centers. It is also essential

that CBER communicate and work closely with industry and CDRH to ensure that panel recommendations and FDA-proposed classifications are based on consistent classification policy and complete and accurate information to prevent unnecessary delays.

We are making this point not because we oppose classifying stand-along blood bank software, but because formal device classification is a very involved process that requires great care. Classification involves, among other things, the collection of information concerning the safety and effectiveness of the device; review of the information at a pre-announced panel meeting; publication of a proposed rule in the Federal Register; an opportunity for public comment; and publication of a final rule in the Federal Register.

Accordingly, it is generally a very slow process. For example, FDA convened the Radiological Devices Panel to review a proposed classification for five medical image management devices, commonly called PACS, on August 29, 1994. FDA published the proposed classification in the Federal Register over two years later, on December 2, 1996. Fifteen months have passed and a final classification regulation has not been published. Thus, we are concerned that the classification process would, if anything, delay the implementation of potentially efficient alternatives to

traditional 510(k) review.

The classification process is also complicated by the fact that given the many different types of blood bank software with varying levels of risk, not all blood bank software products merit the same level of regulation or the same classification. In this regard, the HIMA task force believes that software that performs only record-keeping and/or inventory functions and poses little or no risk to donors or recipients, compared to the risk posed by the use of paper records, is a candidate for classification into class I, as well as exemption from 510(k) requirements.

Examples may include software that maintains on-line card files of patient information about previous blood types, antibodies or transfusion; software that creates a list of donor records but does not provide assistance in determining donor suitability; and, software that provides on-line inventory of units, blood type, and known antigen information.

Class I devices are those for which general controls, including quality system regulations, registration and listing, and sometimes 510(k)s, are sufficient to provide a reasonable assurance of safety and effectiveness. According to Heather Rosecrans, the final new 510(k) paradigm will not be limited to class II devices, but will include class I devices that are not exempt from 510(k) requirements.

Therefore, there is no reason that all blood bank software should be designated as class II.

In contrast, the HIMA task force believes that software that contains algorithms or truth tables and manipulates data to assist blood banker's decision-making may be a candidate for classification into class II. Class II devices are subject to special controls in addition to general controls. An example of a possible class II device would be software that contains a database of deferral reasons and alerts the donor center staff to existing deferral when a donor presents for subsequent donations.

It is also important that CBER and industry discuss other software that may be used in the blood bank environment which is not the subject of this classification discussion.

Finally, we se the need for further guidance in two areas, whether as part of a classification effort or otherwise, in order to conserve agency resources and to speed review times.

Many changes can be properly regulated under the quality system regulations design control requirements and, therefore, do not require a new 510(k). We plan to help clarify what types of updates and enhancements to blood bank software require a new 510(k). To accomplish this task, we plan to prepare an interpretation of CDRH's modifications

document, deciding when to submit a 510(k) for a change to an existing device, specific to blood bank software.

Second, HIMA would like to work with CBER and CDRH to develop a guidance outlining the kind of information that should be submitted in a 510(k) to demonstrate substantial equivalence when a change or group of changes to a 510(k)-cleared blood bank software requires a new 510(k). The development of such guidance would further the goals of the 510(k) paradigm and would dovetail with the paradigm's special 510(k) alternative. HIMA believes that in some cases limited information about the specific changes would be appropriate to demonstrate substantial equivalence to a marketed device. Further guidance in this area would be helpful in order to prevent redundancy in the submission and review of information pertaining to parts of the software that have not been modified.

In summary, HIMA appreciates CBER's recognition of the need to streamline and speed up the 510(k) review process for blood bank software, and looks forward to working closely with the agency in this regard. The HIMA's Blood Bank Systems Task Force hopes that our concerns regarding the classification of stand-along blood bank software will lead to helpful discussion about these issues. We would be happy to answer any questions from the panel or FDA regarding these remarks.

DR. HOLLINGER: Questions of Ms. Jones? I have just one question. You mentioned that blood bank software has a long and exemplary track record. Does that mean that there have not been any problems?

MS. JONES: Mr. Fogle gave you an indication that there were 16 recalls related to blood banks. There is no other information regarding how many recalls FDA has had relating to other incidents as far as the blood banker errors, and so on. So, 16 since 1989, with the numerator information missing, I don't think that that is really sufficient information to base a lot of what we are doing on. But, yes, there have been problems with blood bank software. No one could deny that. As I said, we don't oppose classification, but we are saying that classification is not a prerequisite to using all the alternatives that are available to CBER at this time.

DR. STRONCEK: I agree with your general premise that we have to have regulated software but it has to be flexible. But a couple of specific points, you are proposing that some functions only be regulated as class I, and the examples you give tend to be things on the transfusion service side such as previous blood types of patients and previous information about the antigens. I must say, I disagree with that. We heard all day yesterday that the incidence of infectious diseases in donors is

really on the order of 1 to 100,000 positive markers. Yet, the problem with transfusions is that clerical errors occur on the order of 1 to 10,000. So, you know, we can do all this stuff with collecting and testing donors and if we make mistakes in delivering the products to the patients, then that is just as bad. All the other good work we have done has gone for nought. So, I guess for this particular example I take issue with only having class I regulations on some of the transfusion side issues.

MS JONES: You take issue because you think that a 510(k) review of a class I device would not be sufficient?

DR. STRONCEK: No, I think the implication of what you wrote is that these are not as important functions, and they don't need as much oversight. I guess that is what I am disagreeing with. Quite honestly, I think a lot of what you presented -- I don't quite understand the issues with the paradigm and what all these nuances are.

DR. HOLLINGER: Apparently we are going to hear that in just a second.

DR. STRONCEK: Maybe I am missing something, but I think that if you are implying that issues related to the transfusion of blood products need to be less rigorously programmed than issues around collection, I disagree with that. Maybe I am misunderstanding.

MS. JONES: I do not think that software manufacturers

will apply less rigorous programming, design control or any of that to that type of software. What I am saying is that FDA's review of that information need not be as rigorous as the donor deferral information and all of that, which has been primarily the focus of their reviews so far.

MR. DUBIN: I want to support what you said, doctor, because I think one of the things we have found is that in a lot of areas the technology is available and working, but the application of that technology sometimes may be problematic. As the doctor said, I am not sure that I agree with where you drew the distinctions in terms of what is software that FDA may need to have a more stringent regulatory stance for, and where that boundary should be drawn.

It seems to me one of the things that we, on the consumer side, are really looking at is some national standardization consistency, and we strongly believe that software is one of the places where that can happen to ensure that the technology available and the testing be applied and that that information get through the system so the job gets done. So, I am a little foggy, if you will, about where you make the distinctions and I, for one, feel pretty good about the class II distinction. I think if we vote that way we are not putting FDA on its most aggressive footing, but we are saying that least aggressive footing may

not be enough, and middle ground seems to be a place where we can be comfortable and feel like we are providing the kind of regulatory stance that will get the job done.

DR. KOERPER: I must say, I agree with the previous two speakers. I believe that keeping accurate records of a patient's blood type, antibodies, prior transfusion reactions, etc. is absolutely critical to ensure the safety of blood transfusions. Certainly, the focus has been on ensuring that we don't transmit viral infections, but if you give the wrong blood type and somebody has a fatal hemolytic transfusion reaction, that is an immediate threat as opposed to a delayed death due to a prolonged viral infection. I think we have to ensure that safety as well.

Based on what I have heard on the differences between the classes, I believe that this function of maintaining accurate records about a patient's antibody status etc. would fall into a class II level of regulation.

DR. HOLMBERG: First of all, Dr. Hollinger, I need to disclose that I am on a configuration management board for the Defense blood standard system, and also I am on a committee for the North American Technical Advisory Group for international commonality of blood bank automation.

DR. HOLLINGER: That is good; that is not bad!

[Laughter]

DR. HOLMBERG: Well, I just wanted to make that caveat

--

DR. HOLLINGER: Don't apologize!

DR. HOLMBERG: I wanted to make that known because I don't want it to appear that there is a conflict, and I would probably have to abstain from voting, but I do want to be able to share my opinions.

I have a lot of concern -- I picked up three concerns that Ms. Jones expressed, and I wonder if this would be the appropriate time for the agency to respond to that. I detected that there was concern about the time line for the classification. If we do classify this today or recommend classification as a class II, what is the time line before this becomes regulation?

Also, Ms. Jones expressed concern about the classification of all software, all blood bank software to class II. I can see the extremes of the last three speakers, you know, the concerns about something that may just keep tracking and not make any interpretation, and then I see the other extreme once we start talking bout interfaces and electronic signature.

Also, there appears to be distrust that there is no communication between CBER and CDRH, and I would like the agency to address those three concerns.

DR. BUCHHOLZ: I am a little confused here in terms of whether these applications are envisioned to apply to all

and any computer systems within blood banks, or are these focused on the so-called commercial systems that would be developed by a company for sale as a kind of turnkey application. Could there be some clarification on that?

DR. HOLLINGER: Yes, that is another issue we will get into in just a second. Yes, Dr. Ellison?

DR. ELLISON: The only concern that I have heard expressed was at the bottom of page 3, the statement where she expresses concern about the delay, and I would hope that the FDA would take this to heart and act on it because I would find that extremely frustrating, if something that we are proposing is going to be a block rather than a facilitator.

DR. HOLLINGER: We are going to finish the open hearing. Next is Linda Lewis for the Committee of Ten Thousand. She has a statement she would like to make.

MS. LEWIS: My name is Linda Lewis. I am an executive board member of the Committee of Ten Thousand. For quite some time the Committee of Ten Thousand has been concerned and pushing for an immediate consistent standardized notification system that would allow efficient technology and timely notification regarding accident error reports and recall notices.

We agree that there should be implementation of appropriate safeguards for information protection, and the

Committee of Ten Thousand also supports the classification of computer software as a medical device.

We feel the system should begin with a mainframe at FDA that will filter information throughout the system and to us, the consumers. Such a system would allow someone, as myself who lives in rural Missouri, to feel more secure and informed.

Here I would like to add a little personal thing. Last year, when we had several recalls coming through that the Committee of Ten Thousand was receiving, I called our county hospital to see what their system of notification was. They told me they had not ever received a recall since 1988 or any kind, for anything. This is really scary to me. They get them now because when I get one, they get one.

We feel it is the responsibility of all, from FDA, industry, collection centers, treatment centers, organizations such as ourself, and so on, to get the information to the people. We need this done in identical, efficient and timely information through a standardized notification system and the circle will be complete regarding blood issues.

Another personal part, I am the mother of an 18-year old boy who was here yesterday -- he was here this morning and he as getting kind of tire. He has been living with Factor IX hemophilia. He was born with it. He has also

been infected with HIV since he was toddler. I am also the sister of a person with hemophilia who died in 1989, at the age of 45, from AIDS complications. Had these systems been in effect years ago, my family would not be standing where I am standing today, and I think it is responsible to use the technology that America has today to help any more families from having to go through the tragedies that many of us have had to live with. Thank you.

DR. HOLLINGER: Thank you, Linda. At this time, we are going to go back to the initial format, and Heather Rosecrans is here. I would hope that as she discusses this today -- there have been a couple of questions asked today about the potential overlap between CBER and CDRH, the problems with whether it is commercial or other stand-alone software, and there were some other questions that were brought up. Perhaps you could also deal with those after you finish with your talk.

New 510(k) Paradigm

MS. ROSECRANS: Thank you. Sorry, I wasn't here earlier when you announced my name.

The Center for Devices and Radiological Health started a reengineering process last year, and one of the teams was the 510(k) team. On that team we had a member from the Center for Biologics, at first Lynn Wilson and then Cheryl Kochman. Together, the team developed a new way of looking

at 510(k)s, actually two alternative ways in addition to the traditional way of looking at 510(k)s. We call that the 510(k) paradigm.

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The 510(k) paradigm itself, the final guidance document is actually appearing on the Web today. It may have come on last night. It may be on later today, but certainly by Monday it should be up on the Web. It is a final guidance document. It is not a rule; it is not a regulation. It is still available for comment, but we did propose it. Last June it went on the Web. It was announced in the Federal Register in September, with a comment period. We got 13 sets of comments and we revised the document accordingly. As I said, CBER was part of that effort.

Our Center director asked us when we went through the engineering efforts to look at the new tools we had under the quality system regulation, as well as postmarket surveillance that came under the new Food and Drug Administration Modernization Act of 1997, along with our premarket, and see what new ways we could come up with. Some of these things were under discussion before the law actually passed. That is why I mention it that way.

As I said, besides the traditional way of submitting 510(k)s that we have had for years and years, we have added these two new routes, the special 510(k) and the abbreviated

510(k), as alternatives if the criteria fit, which I will describe in a second, as ways of submitting 510(k)s, and we will be accepting those starting today.

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First of all the special 510(k) device modification -- this is where a firm is going to modify their own legally marketed device. In other words, we have a guidance out on the Web, issued January, 1997, entitled, deciding when to submit a 510(k) for a change to an existing device. So, when you are getting ready to modify your own legally marketed device, one that you had on the market prior to May 28, 1976, one that has been reclassified into I or II, or one that has been a 510(k) previously, and you know that that change requires a 510(k) because there are many changes that don't, then you could consider a special 510(k) device modification.

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Basically, you cannot use this route if you are changing the intended use of your device, for a special. If you are adding any new use to that device -- your patient population, physiological difference, from prescription to over-the-counter, for any of those changes you cannot use this route. Also, if you are making a fundamental change in the technology of the device, something entirely different, for example if you had gone from a culture system to a DNA

probe, something like that, you cannot use a special.

So, when these are received we are going to flag them as specials, and that is the first thing we are going to look at, just to make sure there isn't a change in the use or a change in the fundamental technology. There is a lot of definition in the new paradigm that is out on the Web today about examples in the use and changes in fundamental technology/

[Slide]

What you are going to basically do in that 510(k) is that you are coming to submit it with a declaration of conformity to design controls. So, one other issue, I guess, with using the special is that basically in the quality systems regulation design controls don't apply to class I devices, for the most part. They do apply to software. So, in order to use a special you have to be using design controls. So, if you are a class I device you would voluntarily conform to design controls in order to use this route, if you choose to do so.

So, you would submit it with a declaration, and there are examples and the criteria is spelled out in the document. We are going to process those within 30 days. So, you can change your material to other materials that have been on the market. You can change your energy source, etc., and we are going to look at that within 30 days,

basically just looking at your declaration of conformity to the design controls, and we rely on that process for clearing the product.

[Slide]

This is the design control regulation, 21 CFR 820.3 that you will be conforming to.

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The abbreviated 510(k) route is applicable to all devices. It is not only for when you make a modification to your device. It is when you want to submit a 510(k) for a reserved class I device. As you probably know, the new law that passed last November says that all class I device, classified into class I, are exempt from 510(k) unless they are of substantial importance in preventing impairment of human health or preventing serious risk or injury -- I can't even think of it, risk or injury, something like that -- risk of injury.

So other than that, I think there are 62 devices that were reserved in class I, some of which specifically have footnotes about CBER. For example quality control material was reserved if it was used for donor screening, whether it was assayed or unassayed -- if it was for donor screening. I think that was the wording. And, for class II devices, and also it is going to be applicable for class III devices.

The device is going to be subject to special controls.

What you are going to do, you can declare conformity to a recognized consensus standard that we have recognized, instead of submitting the data to us for review, you are going to say you meet the criteria in the consensus standard, or you meet the criteria that we have identified in a guidance document, or any other special control that we have gone through. I think you went over that earlier to identify special controls.

Basically, that is what an abbreviated is. It is like a traditional but it is going to be this much quicker. We are going to have the same time frame, a 90-day time frame but we are going to rely on your declaration of conformity to a recognized standard, a guidance document or any other special control.

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There will be a summary of the information in that declaration, what you relied on and so forth. You can rely on just part of a consensus standard, and if you differ from the standard slightly you have to say why and address it in another manner. It is not that you have to conform to the consensus standard. There may be devices out there that are pre-amendment or have been 510(k) that don't conform to the standard and you may want to claim equivalence to those. That would be okay because if you are as effective as those devices, you may be cleared for marketing. But this is a

choice if you want to submit an abbreviated 510(k) and make this type of declaration.

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This is how we think the 510(k)s that we receive will fall out. We received a little over 5000 year, and we expect to receive around 4000 this year because we have exempted so many more devices. I might just add that any device that is exempt is exempt subject to limitations on the exemption, which say that if you have a different intended use or a change in the fundamental technology, you would no longer be exempt. You have to submit a 510(k).

So, with the traditional we are going to be looking at everything that is required, a truthful and accurate statement, 510(k) summary, labeling, all that, along with the description of the device and then the data, whether it be bench data, just comparing specifications, animal data or clinical data. A good 10% of our 510(k)s have clinical data.

The abbreviated, as you see, it is just the same with lesser amount of data because we will be relying on those consensus standards. Then, the special is going to be that declaration of conformity with the design control provisions.

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This is our slide just to show -- you know, we are

going to even those out statutorily. We use the 90-day time frame on 510(k)s. We have 30 days for the specials. For the abbreviated and the traditional we will still be using the 90-day time frame, but we think the abbreviated are going to go a lot quicker.

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We came up with this slide just because my son things I am in a race at work. He thinks I am in a 5 or 10 k.

[Laughter]

[Slide]

That is just what we expect in our Center about the 510(k)s that we get in each of these areas. They will probably shift over the years. People will become more comfortable with the paradigm approach. Again, they are just options. The traditional is still there. You are not forced into any one of these categories.

Are there any questions?

DR. HOLLINGER: Yes, now we can have questions. Dr. Boyle?

DR. BOYLE: Do I understand that all existing blood bank software will have to go in, presumably, under a special 510(k) for approval?

MS. ROSECRANS: No.

DR. BOYLE: No? They are grandfather'd in?

MS. ROSECRANS: Nobody has to do a special. I am

speaking for CDRH, but if Biologics chooses the same, this is how we laid out the options for the 510(k) program and the paradigm doesn't limit it as CDRH's 510(k) program.

DR. BOYLE: But all existing software would have to go in for some kind of approval at this point in time?

MS. ROSECRANS: Right, because all blood bank software is unclassified. So, until such time as we classify, which we should have done year and years ago, and we have lots of devices that we missed initially and we are still classifying -- we have to put them in one of those classes. You can submit a special 510(k) for a class II device, but not if you make any changes in that use or if you change the fundamental technology whatsoever.

DR. BOYLE: Okay. A specific question, if you have software that is approved, and let's say it is something that involves data entry, for instance recording something about donors, if somebody wants to add a consistency check or a range check to that software, what kind of approval do they have to go through to do that?

MS. ROSECRANS: I have to ask somebody here if that is a change in the use because I am not really a computer person. If it a change in the use they could not do that. Let me just say that. Otherwise, to do a special the design controls in our regulations are very laborious. We even got comments on the paradigm stating that they think that is

more work, to do the special, than it was to do a traditional. Therefore, I assume some people will not choose that route. But they have to have those records in place.

MS. JOHNSON: I am Nancy Johnson, from CBER. I would like to answer your question. As long as you are just adding a control check to the functionality that is already existing and, therefore, design controls should be sufficient regulation for that, you would not have to submit a 510(k).

DR. BOYLE: Thank you.

DR. HOLMBERG: Going back to technical changes, what if a software developer was changing the operating system from, let's say, Unix to Windows NT?

MS. ROSECRANS: I am sorry, my husband does computers; I am terrible. Harvey, do you know if that is a change in the use? It depends on if it is a change in the use. But we feel we are still going to have a very high level of review.

MR. RUDOLPH: Harvey Rudolph, CDRH. Generally speaking, if you make a significant change in the operating system, according to the guidance document when you submit a 510(k) for a change in an existing device, you would have to submit a 510(k). I am not sure what type of 510(k) it would have to be. But a change from Unix to Windows NT is a

significant change. I think it requires revalidation of the entire system essentially.

MS. ROSECRANS: I guess I would just like to say that whether it is classified or unclassified, all of these exist right now. I mean, if the device is unclassified they can use the traditional, special or abbreviated. If we have recognized a standard that would be applicable, they could use it.

MS. GUSTAFSON: Mary Gustafson, from CBER. One more comment on that. We have had experience with changing the operating system, taking commercial software and placing it on a new platform, and it has required a 510(k) refiling.

DR. STRONCEK: A little different question, what if there is a fundamental change in the function of the software? There are several issues that came up at this meeting that would require blood bank to change the way they do business, such as quarantine. If we passed this regulation -- you know, it is going to take long enough to develop new SOPs and new processes and then just develop the software. Once that change is submitted, how long is it going to take for the FDA to approve it? Couldn't we be in a position where we are waiting to implement a very important change in the blood bank and we have to wait because there is a 6-month, 1-year, 2-year delay in getting the software approved?

MS. GUSTAFSON: This is one reason that we want to take advantage of the new 510(k) paradigm, to allow vendors who have gone through the 510(k) process with us and who are comfortable and are confident that they can follow appropriate design controls, that they can certify when they make a change, that they can upgrade. If it is new functionality, completely new functionality, they will need to come through as a complete traditional 510(k). But by being able to use the special and abbreviated options for some of the other changes and some of the new software that we see, we will be able to direct our resources to the ones that have substantial changes in functionality.

DR. BOYLE: I appreciate that but, you know, I have been around blood banking for a while and in the old days they would have an information systems department in the blood bank or the transfusion service, and you would just do it; you would just make the software changes. What I am asking is what is the realistic time line? I mean, these changes that we are talking about at this meeting will require software changes. How long will it take the current process or the processes we are talking about to go through the FDA to get approved? Or, are there mechanisms to use them in the interim?

MS. GUSTAFSON: We are reviewing software right now, and we have been for some time.

DR. BOYLE: No, I am asking if the FDA passes something that says we have to quarantine plasma and I have to implement it, I need software to do that. Are we setting up a system here that we are going to pass regulations on blood bank and say they have to meet all these, and make an impossible situation to say that they have to do this and then make it so that it takes two years to get the software out?

MS. GUSTAFSON: We currently are regulating software to that extent. By taking advantage of the new paradigm, it should speed up the clearance process. By classifying, we are not really changing what we are doing now. We are removing it from having to make a case-by-case decision every time we look at a 510(k) to having the software in a classification structure so that it will be more automatic.

I guess I could say that of the software that we have seen, the stand-alone blood bank software, even the systems that do certain things as record keeping, as was mentioned earlier, we would view within the class II structure because, remember, you are integrating functions in a blood bank that affect donor suitability and product quality and safety, and are all part of the nation's blood supply. So, we really have not seen any blood establishment computer software that we would be willing to say is in class I and would be exempt from the design control requirements of the

quality system regulations.

DR. BUCHHOLZ: With respect to a change in a commercially available system, if that change goes through the FDA and receives the required clearance, does that do away with the obligation of individual blood centers to do any filing or make any establishment license change? Or, is there a whole separate regulatory process that would have to go through on an individual center basis to accommodate the change that the commercial manufacturer made in his program?

MS. GUSTAFSON: There is a separate regulatory process for blood establishments through licensure of the blood establishments. In the guidance that Mr. Fogle mentioned, guidance dating back to 1988 and 1989, we have allowed the changes to be reported to us in a way where we don't do a complete review again at the user side. We do expect site validation separate from the vendor design and testing of the software.

DR. BUCHHOLZ: I guess the concern goes back to the previous question that was asked relative to how this whole thing shakes out in terms of timing. Let us suppose there is a situation where there is just a plain computer glitch that somebody missed and we are using every hundredth unit. Now, that is something that presumably would be easy to fix. But, if I understand what is being proposed, this would have to involve some gathering of information, putting together

some sort of filing to FDA, sending that in, having a review process, however long that would take, the information comes back to the manufacturer and then FDA or the manufacturer would disseminate that information.

I guess, echoing the concern that was raised earlier, if you know that there is something that is wrong and you can fix it, how long do you want to continue having that wrongness in the system, and is there some way that you could have a really expedite review in situations like that, or some agreement that it would be implemented and then submit?

MS. GUSTAFSON: Yes, that is right. By policy in both the centers for devices and radiological health, and Biologics, if there is a need for a safety critical bug fix, we allow that bug fix to be done and then be followed up by a filing. But even in designing a safety critical bug fix, we expect the vendor or the software developer to go through a design process and document that process and include testing. But they can go ahead and do that and send out the safety critical bug fix without our clearance.

DR. BUCHHOLZ: Does that constitute a recall or something equivalent to that on the part of the manufacturers?

MS. GUSTAFSON: Well, it could.

DR. BUCHHOLZ: Do you anticipate that might be

something that might deter the rapid acquisition of that information?

MS. ROSECRANS: I might add one thing here too. We have a policy out on the Web -- I can't think of the exact title but about submitting a 510(k) when there is a recall, and there is a special policy where if it is a recall that requires a 510(k) -- there are a lot of recalls where something goes out of specs and needs to come back into specs, but if the actual device needs to be changed in such a way that a 510(k) is required, then our offices will be working with you and the 510(k) will be more or less a technicality. You know, it is going to be processed immediately and it is going to have a different title, special 510(k) changes being effected. You are going to have the okay from the field to implement that change right away. We are going to be reviewing it with you before it is submitted. We have a policy like that, but only when a recall involves a 510(k), which isn't always the case.

DR. MITCHELL: You stated that people will be required to resubmit the pre-amendment equivalence. What kind of process is that?

MS. ROSECRANS: If you were legally on the market before May 28, 1976, and we have criteria of what you need to be able to show pre-amendment status -- that is what we call it on the Web, then you are grandfather'd. Okay?

Now, if we classify a device into class III, a device that was on the market pre-amendment and we put it into class III, eventually we may call for PMAs on those devices or we may ourselves decide at that time that we have enough information to reclassify it. The most famous example we have probably are the silicone breast implants, where they were 510(k)'d in class III and then we called for PMAs.

So, if it is in class III it will go through the 510(k) process at some point in time and then either be a PMA or be reclassified.

DR. MITCHELL: If someone was equivalent to a pre-amendment, then they would presumably be equivalent to the new registered?

MS. ROSECRANS: With all the unclassified devices, the ones we missed in writing the classification regulation, someone would be comparing it to that device. Once it is classified, they all become that class unless they change the use in a significant way or the technology, or do something where we would find it not equivalent and place it in class III, requiring a PMA.

DR. MITCHELL: Okay, but they would not have to go through -- let me see, only one would have to go through the full 510(k) process?

MS. ROSECRANS: Each person who plans to market the device, a device in finished form for sale to an end-user,

each person would be required to have a 510(k). Those who were on the market before May 28, 1976 would be grandfather'd unless they make a change to their device that would trigger the need for a 510(k), if they modify the use of the technology. You know, we have that whole document.

DR. MITCHELL: I am sorry, you said they would be grandfather'd or they would not be?

MS. ROSECRANS: They are grandfather'd for the device they made before '76, but if they modify it in any way that could affect safety or effectiveness they would have to submit a new 510(k) for the modified device.

DR. HOLLINGER: How much software was on the market prior to May of 1976?

[Laughter]

We are talking here about blood banking software. I would say there was probably none that would be grandfather'd. Am I wrong in that?

MS. ROSECRANS: The only ones grandfather'd would be those themselves, not somebody who was like that but the actual, say, firm X who made it in 1974. They would be grandfather'd, not somebody who was like firm X after '76.

DR. BOYLE: Since time is an issue, we received in the HIMA statement that 50 software products were submitted to the FDA on or before March 31, 1996 and only 16 have been approved to date. The question I have is the other 34, are

they still sitting out there? Are they denials? Are they withdrawals? Do we have software products that have taken over two years?

MS. RAY: I am Molly Ray, from the Division of Blood Applications and I am a software reviewer, and I though would qualify what she said and provide a little more information.

Devices that were on the market prior to May 28, 1976 are considered pre-amendments devices or predicate devices to which substantial equivalence may be claimed for devices that are intended to be marketed. For blood banking, when we did get 510(k)s in, they were predicates that were on the market prior to that date. So, there were predicates available.

So, your current question is that we have had many iterations with the vendors. They have sent in their original 510(k). We have reviewed it. We have asked for clarification or additional information, enough information to determine that the device is safe and effective. We have had to have communication with them several times. So, the 510(k)s that have not been cleared are currently in the review process.

DR. BOYLE: So, if less than half have been approved in a two-year period, then you are talking about an average that is going to be, once you get through this process, of a

year and a half to two years.

MS. RAY: One of the reasons why we are here is to try to streamline this and to try to take advantage of the alternative positions or alternative procedures that are available to try to make this more streamlined for both us and for the submitters.

DR. BOYLE: But even the statement about whether it is a 30-day or 90-day process, that is the time it takes you to get back to them rather than the length of the approval. Correct?

MS. GUSTAFSON: That is right. I will clarify that, yes, we have some that were submitted initially that have not had clearance yet. Of those though, they have all had at least one or two rounds of reviews. We have cleared software in as little as 26 days but, depending on the complexity of the software, depending on the submissions that we receive, depending on compliance problems that have been noted -- I mean, they are not all the same and they don't take the same amount of time. We obviously would like to have some efficiency within the 510(k) paradigm to allow the vendors who have demonstrated their ability to ensure appropriate design, documentation and testing to utilize some of the new efficiencies because, quite frankly, some of the other pending submissions are the ones that are taking our time in terms of one-on-one contact in working with the

vendors.

DR. HOLMBERG: Have there been situations where the vendor has removed the 510(k) or pulled it?

MS. GUSTAFSON: We have had some withdrawals, yes.

DR. HOLMBERG: Is that a large number?

MS. GUSTAFSON: I don't have the numbers with me. I don't think it is a large number comparatively but we have had some withdrawals. Of course, that is not public information in terms of putting it on the Web. We can publish our cleared submissions; we can't acknowledge the ones that were withdrawn without prejudice.

DR. HOLMBERG: I have some other questions. The three questions that I asked earlier, I think you addressed some of those in your presentation but, if I understand correctly, all blood bank software -- if we recommend this, all blood bank software will be classified as class II?

MS. ROSECRANS: If the panel recommends class II and the agency goes through the classification process and they decide whether they agree with the panel or not, put a proposal in the Federal Register, there is an open public comment period, and then a final rule and the comments are addressed in that final rule.

So having said that, if they are placed into class II, then they will be submitted as class II devices, reviewed that way and if there is any reason that they do not meet,

say, the special controls, they are not going to be class II. If they have some -- I can't think of an example but some total different use that impacts safety and effectiveness to a significant degree that we think alters the diagnostic effect that could be not equivalent, requiring premarket approval, or if they change the fundamental technology so greatly in a way that it raises a brand-new type question, that would be not equivalent. In CDRH we have about 2% of 510(k)s that are not equivalent.

DR. HOLMBERG: Okay. That leads to my second question, and that was HIMA's concern about the classification time line as far as if we make the recommendation today, publishing in the Federal Register, receiving comments back, what are we looking for as a time line to be able to do this 510(k) paradigm shift?

MS. ROSECRANS: You can do the 510(k) paradigm right now. You don't have to be classified to use the paradigm but, for example, for specials you would have to voluntarily adhere to design controls.

DR. HOLMBERG: So, to the end-user it is going to be superficial.

MS. ROSECRANS: I wouldn't agree with that. But I think it could be very beneficial when we have guidance documents that you can declare conformity to and follow, and standards that we have recognized. I think that would make

it a much quicker process for FDA and a quicker process for the industry as well. Perhaps I should just let CBER say their opinion too, but we think it is a good thing. You know, we think the paradigm is a good thing.

DR. HOLMBERG: So, basically you are putting the developer on notice that these are the elements that you want in your design.

MS. ROSECRANS: Well, basically the guidance describes the kind of data we would like to see, labeling, we can put recognized standards in a guidance, whatever. It is helpful to the industry. We can have a guidance now for devices that haven't even been classified that we missed initially.

DR. HOLMBERG: Until this is decided on and the comments have been responded to -- you said people can use the 510(k) paradigm now, today --

MS. ROSECRANS: Right.

DR. HOLMBERG: Will the timetable to get something cleared be expedited also?

MS. ROSECRANS: Well, a special is going to be much quicker for us to review than a traditional 510(k) so it is going to be quicker than a traditional 510(k), and traditional 510(k)s have been required for this blood bank software. Just because it wasn't classified, it didn't mean 510(k)s weren't required. It just meant that we hadn't gone through the classification process.

DR. HOLMBERG: Okay, but as an end-user, will the product be cleared faster right away? I mean, are we talking 18 months from now before we can see a difference?

MS. GUSTAFSON: By end-user, do you mean the vendor or do you mean the blood bank?

DR. HOLMBERG: The establishment.

MS. GUSTAFSON: The establishment. In terms of using the 510(k) paradigm, it is available for, you know, when a 510(k) is required. By going through formal classification, it removes the case-by-case decision-making every time we get a 510(k) in. It is a more public process, and we then will, by definition, have blood establishment computer software classified as a class II device and there won't be case-by-case decision-making or questions about classification each time a 510(k) is submitted. Does that help?

DR. HOLLINGER: Have these guidelines been established already for the vendors as to what you expect at the very minimum for the establishments, and so on?

MS. GUSTAFSON: As Mr. Fogle mentioned, the general CDRH software guidance has been out since 1991. Our specific reviewer guide for computerized software was made available in April of 1996. It was published in the Federal Register for comment and for implementation.

DR. HOLMBERG: For clarification, I think what the

developer saw was that when the reviewer guideline came out there were additional things that they had to backtrack and incorporate into their 510(k) application. This is from my own personal experience, I think that the reviewer's guideline then became the standard. Is that a correct assumption?

MS. GUSTAFSON: Our reviewer's guidance built on the 1991 guidance. It is an official standard but it does include the review elements that we look for when reviewing a 510(k) submission for software.

DR. HOLLINGER: I would like to ask maybe Kay Gregory, speaking for the AABB as a large organization, are there a lot of different vendors out there for software that the blood banks are using? Are these all in-house type things that have been established, like in American Red Cross or perhaps, Celso, at your place? What are we talking about here in terms of vendors? If somebody comes and they have a blood bank and they say we are using this vendor, or what?

MS. GREGORY: My understanding is that there are 12 vendors. There are also some home-grown systems that people do themselves.

DR. BIANCO: That is correct, and all of these systems by now at all these institutions that have home-grown systems have submitted applications for 510(k)s. These are the statistics that we heard. There are a number of them

that seek approval. But it is an ongoing process.

DR. HOLLINGER: And this would cover plasma fractionation centers also --

DR. CELSO: That I don't know.

DR. HOLLINGER: -- or just blood bank establishments?

DR. BIANCO: You gave me the opportunity to ask a question --

DR. HOLLINGER: No, you can't do that!

[Laughter]

DR. BIANCO: I think that what is missing here, and I heard a little bit from Mary Gustafson, but what is really the difference that it makes from having the software now that is unclassified and making it class II? What is the real difference? I think that is what Dr. Holmberg was trying to ask. What is the difference for the user, for the manufacturer of this device? What is the difference?

DR. HOLLINGER: Well, you tell us. I suspect it has something to do with regulation, paperwork and so on, more than anything else.

DR. BIANCO: But I did not clearly understand the difference that it will make, and what happens in between because there was also a concern about the time to get there and what happens in between, and how different will it be when this is published as regulation in the Federal Register?

MS. RAY: The reason that we are classifying it is that the Federal Food, Drug and Cosmetic Act, Section 513 states that the Secretary shall classify medical devices into one of three classes. So, that is why we are here.

[Laughter]

MS. ROSECRANS: And I concur. That is the same for CDRH. You are supposed to go out with open public comment and rule-making with a recommendation from a panel to decide what class it is in.

MR. FOGLE: I think in a nutshell, it is fair to say that this is a regulatory housekeeping issue for the agency. In practical terms, Celso, probably it does not make a huge difference in the already established regulatory scheme. We have already established that 510(k)s are appropriate for commercially distributed software.

I would like to clarify -- and we can go back to a presentation that was made in 1996 where some of the lines were drawn -- that what we are talking about in terms of a 510(k) submission is for software that is made and developed and commercially distributed. A 510(k) would not be required for an in-house developed system that is used in blood establishments that is not commercially distributed. It is for a software package that is developed that goes to other users, not in-house use. That is not to say that the in-house software does not meet the definition of a device

and is subject to certain requirements for validation. But the threshold for 510(k) is interstate shipment of the software as a package.

DR. HOLLINGER: Thank you Boyd. Yes, Miss Knowles?

MS. KNOWLES: I see these guidelines in class II as providing specifications and technical assistance to the software companies so that they can conform to basic standards and establish some consistency throughout the industry.

I think the other thing that is important is that FDA continue to communicate with all of the software companies that are providing the software via official memos, fax or even conferences to help people understand what changes need to be made as new regulations are established.

DR. HOLLINGER: Thank you. That is a good summary of that. Yes, Boyd?

MR. FOGLE: Just to underscore that point, as Mary Gustafson mentioned, this is a process to be viewed as regulatory housekeeping, if you will, but also to level the playing field in terms of expectation up front, prospectively, going with out initiative being proactive, actively communicating to the industry the expectations and then there is not the case-by-case decision when a 510(k) is or is not submitted, or when a situation comes up during an establishment inspection.

DR. HOLLINGER: We are going to take a break until 10:30. Then we will come back and deal with presentation of the questions and a response. Thank you.

[Brief recess]

DR. SMALLWOOD: The presentation of the questions and committee discussion -- at this time I would like to allow the American Blood Resources Association to make a presentation. It was overlooked in the open public hearing. We apologize to ABRA, but at this time would you please come forward?

MR. HEALEY: Good morning. I am Chris Healey and I will be speaking on behalf of the Information Systems Committee of the American Blood Resources Association.

As you heard yesterday, ABRA represents the commercial source plasma industry, and ABRA members operate nearly 400 source plasma collection facilities across the nation. From those 400 facilities, we collect nearly 13 million donations annually, and that aggregates to roughly 11 million liters of plasma that supplies the U.S. market.

Most members of the industry currently are in various stages of design, development, implementation and upgrading of donor management systems. As such, the issue of the 510(k) process and blood bank software regulation is of paramount importance.

We believe that a more complete evaluation of how best

to manage the regulation of blood bank software or blood and blood component software is necessary. As we understand it, the status quo has been to attempt to utilize the 510(k) submission and review process. However, in practice we believe that these important products have been treated more like class III products in terms of the documentation required for these submissions. We understand that extensive validation, protocols, validation reports and other design documentation has bee mandated for these submissions and that this has resulted in slow review times and delayed implementation of important products and technologies.

The current regulatory structure simply hasn't kept pace with current technology. The software industry is one that undergoes exponential change virtually overnight. Current software permits more rapid, flexible and comprehensive modifications than was previously thought possible. Even more importantly, evolution of regulatory and operational environments demand more rapid development, approval and implementation of technology changes.

As such, we applaud the agency's efforts to formally classify these products, and we applaud the use of new tools such as the abbreviated 510(k) process and the special 510(k) process. We hope that these are merely administrative housekeeping changes and that they have a

significant impact on the review times and implementation times for these technologies.

However, these tools are new. As such, we think this provides an opportunity to bring industry, CDRH, CBER and the software industry together to talk about what changes should be implemented and what sorts of standards would be necessary to go forward with the abbreviated 510(k) process.

As we heard, CDRH is just now beginning to review the standards that are appropriate or may be appropriate for the abbreviated 510(k) process, and we think this is the critical point for the software industry in particular and the blood and blood components industry to be permitted to have an open dialogue with the agency and discuss what would be meaningful and important in terms of shortening the review times, while ensuring the safest possible products.

In conclusion, we think that the classification of blood bank software as a class II medical device should provide improvement over the currently review and approval process. However, the software development process, the industry operating environments and constantly changing FDA regulation and compliance expectations demand that we go further to improve the level of communication regarding FDA's approach in this area. Thank you.

DR. HOLLINGER: Thank you, Mr. Healey. We are sorry we overlooked that.

We want to have a presentation of the question but I want to try and see if I can clarify some issues that were brought up. If I am wrong in my clarification, please clarify for me then.

It is important to understand that many vendors or in-house establishments already have a 510(k). My understanding is that if we classify this as II, that doesn't mean they have to go back through and do the 510(k) again. They already have it; it is fine, and it is just a paper chain basically. So, that is not going to change. So, we are not asking them to go back and do more paperwork. So, that is the first thing.

The second thing is that if there are changes in their software, the only thing they will have to do is get these modification for those changes only. They aren't going to have to resubmit the whole 510(k).

Finally, this classification not only deals with commercial vendors, or vendors of this but also in-house establishments that ship interstate. Obviously, if you are an intrastate establishment and you don't ship anywhere you don't have to have a 510(k). It would probably be smart if you did, or at least you looked through these things to make sure that it is consistent, and so on, but my understanding is that that is not a federal requirement if you are intrastate. Is that correct, or am I incorrect on that?

MR. FOGLE: I think as part of the clarification on the 510(k) requirement, when you look at software as a product, we are looking for an interstate nexus with respect to the software as a product. We distinguish that from interstate shipment of blood products. If, for example, there is an intrastate blood bank and they don't ship their products interstate that really has no bearing on whether the software is subject to a 510(k) or not.

DR. HOLLINGER: I guess I was talking about if you had in-house --

MR. FOGLE: I am getting to that. Does a 510(k) relate to my interstate movement of blood products? No. You focus on software as a product. Is there an interstate nexus either because that product moves interstate -- that can be out-of-house, if you will, to other organizations. It can also include a shipment to another facility. Even though it may be under the same organization, if you distribute that software to another facility within your organization, that no longer qualifies for the in-house exemption because it is no longer strictly in-house. So that is an interstate nexus because it is movement of product.

Also an interstate nexus is if the product itself does not move but we have interstate movement of safety critical data, and that data is used in blood safety decisions as far as donor suitability or product quality. We believe that

that interstate movement has an impact on interstate commerce, and we use that also as an interstate nexus for software regulation.

DR. HOLLINGER: Thank you very much, Boyd. Could we have a reading then of the question? I think there was one slide that had that on it.

The question for the BPAC is does the committee agree that blood establishment computer software be classified as a class II medical device?

We have had a lot of discussion already on this but I would like to see if there is any further discussion from the committee. Dr. Boyle?

Committee Discussion and Recommendations

DR. BOYLE: I would just like to comment that the types of defects or problems identified by the FDA are extraordinarily serious. From our standpoint, they are intolerable in terms of the risk to the patients. In point of fact, they seem to far out-shadow the types of concerns in terms of what could be missed with window periods that we were hearing about yesterday. So, I think this is so serious that something has to be done.

I also think that doing what we are doing may help to address the sort of issue that was raised by the speaker from the Committee of Ten Thousand. Eventually what we want is enough uniformity in the systems that we can get some

kind of uniform recall.

So, for all those reasons, I think we should move forward and approve this but, at the same time, since the FDA has asked for the authority, I hope the FDA is also willing to make the commitment to do this in such an expeditious fashion that delays in these types of approvals will not also cause risks to the blood system.

MR. DUBIN: I want to underline that. I think it is clear from our perspective that it does outweigh the need for some baseline regulation in terms of software. Obviously, we feel that any move towards standardization and software standards is good, not just in the specifics of in-house at the blood bank but towards the larger system and how that relates.

But I think it is important, it would be nice to see some streamlined coordination between the two sections of the FDA because there is overlap. I certainly want to be sensitive to what we hear and not create another layer of bureaucracy that slows down the process. I hear FDA saying that is not going to happen, and I support that. I think maybe some interaction in the right places could be very good, but I do think, as you said, John, that it is outweighed by the need to get some baseline regulation here. So, I would support the question.

DR. BUCHHOLZ: I would echo those comments in terms of

the safety aspects that are implicit in this issue. I guess the one concern I would have in this whole field which is rapidly changing -- and yesterday we discussed some things that could have a very substantial impact on how blood transfusions and product collection take place in terms of inventory hold periods or quarantines -- as I look at this in the future, I wonder if FDA can really guarantee that timeliness in terms of effecting changes, not only in terms of the vendor who supplies the material or supplies the information that allows the change to be supported, but the actual implementation of those changes at the blood center or plasma collection center facility.

I think it is nice to see some pictures that show 30 days or less, but my concern is that if things to continue to change as rapidly as they have the potential to do and have changed, then we need to be very careful that we don't create a system that actually hinders us in doing the right thing.

DR. HOLMBERG: I agree with that. Let me just say that I applaud the agency not only for the housekeeping, but also for trying to expedite and trying to shorten the time for clearing computer systems.

If I can address to you all some of the problems that most vendors -- and Dr. Hollinger was exactly right as far as home-grown systems versus commercial -- I can tell you

from our own experience with the Department of Defense that we were not considered a home-grown system even though it was only to be used in the Department of Defense. But the fact is that we distributed among the three services and around the world, and that made the difference there.

But if I can talk from experience as far as the time factor and the dollars that are involved -- I know we are not supposed to talk about dollars on this committee, but it does affect us. First of all, we have from time to time, as was already pointed out, new regulations that come out, new tests that are added, new lookbacks. For instance, I am sure we will be addressing HCV very soon and whatever disease comes down the road. But we have to be able to respond in a timely fashion.

In the Department of Defense system, we got clearance or equivalency on our version 1. Our version 2 has been developed for almost two years now. That is currently in the queue. Version 3 is going to be a Windows NT version that will, hopefully, be ready to go this summer. So, here we have a product that will almost be out the door; we are ready to push our version 3 but we are still back to version 1 and trying to respond in a timely fashion.

So you look at meeting the safety requirements, and the cost of just having something sit on the shelf, and the things that are taking place. If the agency can assure us

that the time line will be shortened, I applaud this. I think that there has to be some sanity that is brought to the table as far as what is required, and we have come a long way.

So, I applaud the action to do the classification. I still think that there is going to be some judgment calls that we have to make. I also encourage the agency to be speaking between the CDRH and CBER and open up the communications there, and also with the industry.

I just want to raise another issue as far as safety. I think that what was presented with, I believe, 16 recalls -- I don't want to minimize those 16 but in the scope of the numbers of errors that happen in blood agencies, I think that this may be a small number. We need to continually improve our safety but, you know, I think we have things in place there, for instance, the controls with Good Manufacturing Practices.

DR. MCCURDY: If I understood what was said before, these were system recalls, not product recalls. The system recalls has really affected considerably larger portions of products, or at least have had the potential for that.

DR. HOLLINGER: Yes, that seems to be correct. Well, not seeing any further discussion, I am going to call the question and we will vote on the question.

DR. SMALLWOOD: Before voting takes place, I just need

to clarify for the record that Dr. Holmberg is eligible to fully participate in this issue. He did make an appropriate declaration prior to this meeting and has been cleared. So, for the record, I would like that to stand. Thank you.

DR. HOLLINGER: Thank you. So, we are going to watch how you vote!

[Laughter]

All those in favor of the question, does the committee agree that blood establishment computer software be classified as a class II medical device, so signify by raising your hand.

[Show of hands]

All those opposed?

[No response]

Any abstaining?

[No response]

Consumer representative?

MS. KNOWLES: Yes.

DR. HOLLINGER: And industry?

DR. BUCHHOLZ: Yes, but with a proviso that there be some sort of very serious look at this timing issue from the implementation phase.

DR. HOLLINGER: That has been brought up several times. I think that is very key.

DR. SMALLWOOD: The result of voting is unanimous by

the voting members present. There are 12.

DR. HOLLINGER: Thank you. That concludes the morning issues. I am going to ask the committee to please be here five minutes before. We are going to take a break until noon, but I would like the committee to be here at least five minutes before because we really have a very busy afternoon potentially and I would like to get started right at 12:00. Thank you.

[Whereupon, at 10:45 a.m., the proceedings were recessed, to be resumed at 12:00 noon.]

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

DR. SMALLWOOD: A few of our committee members will need to leave. So, we are asking all the participants to, please, be prepared when called upon and to adhere to the times that have been allotted to you. Thank you. Dr. Hollinger?

DR. HOLLINGER: The first session this afternoon is on relative safety of solvent detergent-treated pooled plasma and fresh frozen plasma, donor retesting. We are going to have an introduction and background to this topic by Dr. Silverman, medical officer, Hematologic Products Branch, Division of Blood Applications. Dr. Silverman?

Relative Safety of Solvent Detergent-Treated Pooled Plasma and Fresh Frozen Plasma, Donor Retested

[Slide]

DR. SILVERMAN: I am going to talk this afternoon abut whether or not these two products represent alternatives for transfusion practice.

[Slide]

I would like to review the indications for fresh frozen plasma. These indications come out of the circular of information for the use of human blood and blood components fro the AABB. The indications for use of fresh frozen plasma are relatively limited, and for the most part are tailored for patients who would have chronic therapy. FFP

is indicated for the management of bleeding for preoperative patients who require replacement of plasma coagulation factors when specific corrective factors are not available; for patients with documented coagulation factor deficiencies for which other specific corrective factors are not available. FFP is indicated for reversal of coumarin affected patients who are bleeding or need to undergo an invasive procedure before vitamin K reversal of coumarin effect; patients with massive transfusion who have abnormal coagulation assays; and therapeutic plasma exchange for TTP, thrombotic thrombocytopenic purpura.

[Slide]

As part of the background, I would like to go over the 1997 GAO report to Congress with regard to viruses transmitted by blood and blood components. This is expressed as risk per unit of fresh frozen plasma, and also describes the window period.

For HIV, the risk per unit of FFP that I found in the document was approximately 1/700,000, with a window period of 22 days for the antibody test with a 95% confidence interval and a range of 6-38 days, and a 16-day window period when the p24 antigen test is used. For hepatitis B, 1/63,000 risk with a 59-day window period and a range of 37-87 days. For HCV, the risk per unit of FFP has been a very broad range, anywhere from 1/4100 or 1/100 or 125,000,

depending on the assumptions made about the specificity of the test. The widow period is approximately 82 days for the antibody test with a range of 54-182 days. The risk for HAV per unit of FFP is estimated to be about 1/1 million. HTLV-1 and 2 are not currently known to be transmitted by a cellular plasma products. The window period is 51 days with a range of 36-72.

[Slide]

Pooled plasma solvent detergent-treated is manufactured from AB group specific plasma. The plasma pools may contain plasma from up to 2500 donors. These are volunteer donors. The solvent detergent process involves incubation with TMVP and Triton X-100, removal of the chemical by chromatography, sterile filtration and the product is refrozen in unit sizes of 200 mL.

[Slide]

These are the indications for pooled plasma solvent detergent-treated: surgical prophylaxis in patients with congenital deficiency of fibrinogen, Factor V, Factor VII and Factor XI, surgical prophylaxis in patients with Factor XIII deficiency. The clinical trials showed that the product could be used for the treatment of active bleeding of patients with congenital deficiency of fibrinogen and Factors V, X and XIII.

[Slide]

Clinical trials further showed that the product could be used for the reversal of coumarin effect for the treatment of patients with multiple coagulation deficits, and for the treatment of acute and chronic thrombotic thrombocytopenic purpura.

There are some points that I would like to make about the clinical trials that were done. These were reviewed in the December, 1996 BPAC. The studies were small, and although in some studies patients were randomized to FFP and the solvent detergent plasma, the studies were under-powered to detect a difference between the two should such a difference have existed. Thus, strictly speaking statistically, equivalence of the two products has not been demonstrated. .

Secondly, while SD plasma lacks the largest von Willebrand factor multimers, clinical trials were not designed to and did not show a therapeutic advantage of solvent detergent-treated plasma over FFP in the treatment of either acute or chronic TTP.

[Slide]

This slide documents the <u>in vitro</u> reduction of viral infectivity by solvent detergent treatment for a variety of model viruses. I think it is clear that the solvent detergent technology is used to reduce the risk of

transmission from currently screened lipid enveloped viruses from donors in the infectious seronegative period, and lipid envelop viruses that are not currently recognized as transfusion risks. However, this process is not designed to inactivate non-enveloped viruses or agents associated with CJD or other transmissible spongiform encephalopathies.

[Slide]

What are the advantages and disadvantages of this particular product? One of the advantages of this product are that one has a consistent and reproducible level of coagulation factors. As I have shown you, there is a high efficiency inactivation of lipid-enveloped viruses.

What are the disadvantages? It is a pooled plasma product. As I have said, it is not designed to inactivate non-lipid envelope viruses or pathogens insensitive to the solvent detergent treatment. It is thought that the neutralizing activity of antibody in plasma pools, particularly for hepatitis A virus and parvovirus B19, will provide detection against some non-envelope viruses. However, in my opinion, it would seem prudent to vaccinate chronic recipients for hepatitis A virus. It would also seem prudent to consider the risk of parvovirus B19 in susceptible populations as for example pregnant women, patients with chronic hemolytic anemia and patients with chronic severe immunodeficiencies when choosing whether or

not to use this product. Finally, the ever-present risk of unknown, untested blood-borne pathogens not sensitive to the solvent detergent process.

[Slide]

Fresh frozen plasma donor retested is produced from single volunteer whole blood or apheresis donations. The product is subject to donor screening and donation unit screening. It is proposed that there be a true quarantine hold period beyond an estimated infectious seronegative window period for recognized tested blood-borne pathogens. What this means is that quarantine release occurs only after the donor returns after the quarantine period and is found to be seronegative for all required testing.

[Slide]

What are the advantages of this product? It is a single-donor product. This is a true quarantine hold for infectivity window period.

What are the disadvantages? Well, a long interdonation period is a risk here in that patients who do not return within the dating period for the product, the product will be discarded; the sensitivity and specificity of current screening methods; the logistics of storage, processing and release of quarantine units; and, again, the risk of unknown, untested blood-borne pathogens. It would appear that recruitment of dedicated, long-term, frequent volunteer

plasma donors would be the major logistical hurdle facing blood centers choosing to use this approach.

[Slide]

There are questions for the committee. I have thought long and hard about the order in which to present these questions and I have come to the conclusion that we will look at the second slide first.

The first question the FDA would like to ask, is does the committee concur in principle with a true quarantine hold for an infectivity window period? Subsequent to the discussion of that, what does the committee recommend as the minimum quarantine period for release of previously donated units of fresh frozen plasma?

[Slide]

Finally, does the committee agree that pooled plasma solvent detergent-treated and fresh frozen plasma, donor retested, are acceptable alternatives for those indications held in common, or to be held in common between the two products?

DR. HOLLINGER: Thank you, Dr. Silverman. The next presentation is going to be by Dr. Bernard Horowitz, who is with VI Technologies, which is a company that makes the solvent detergent-treated pooled plasma.

Presentation

[Slide]

DR. HOROWITZ: I am Bernard Horowitz, represent V.I. Technologies, or VITEX. Some of the data that I will present to you was developed when we were still part of the New York Blood Center.

Solvent detergent is the single most effective means I know of for eliminating envelope viruses from transfusion plasma. Let me repeat that because it is an important statement. Solvent detergent is the single most effective means I know of for eliminating envelope viruses from transfusion plasma. A large safety margin is suggested by the rapid and complete kill of envelop viruses observed in the laboratory.

Our findings have been confirmed repeatedly by groups worldwide, and proven by 13 years of routine clinical use. By contrast, the safety of single-donor plasma, donor retested, which I will refer to as quarantine for ease of language, is unproven. Moreover, because of the limitations inherent to all donor screening procedures, the safety of quarantine plasma cannot match that of solvent detergent-treated plasma. Thus, in my opinion, the solvent detergent-treated plasma, SD plasma, is the safer alternative.

Since the committee has previously seen evidence on viral safety of SD plasma, I will limit my discussion to only those few slides which serve to illustrate the points I am making.

[Slide]

As I have already mentioned, there is a 13-year history of solvent detergent treated use since first licensure by the FDA of solvent detergent-treated Factor VIII in 1985.

[Slide]

Quite a number of viruses have been studied with solvent detergent. The most remarkable aspect of this list is that kill is complete regardless of the titer of virus that is used in the challenge study.

[Slide]

There is ample evidence supporting the efficacy of solvent detergent. It starts with the laboratory viral studies which I have already indicated to you. Some of those are pathogens, not simply models of pathogens used in human studies, such as studies we have done in chimpanzees with hepatitis B and hepatitis C, as well as hepatitis delta virus. Others are models.

Clinical evaluations in closely monitored hemophiliacs have been performed through the years, as well as in other closely monitored patient groups. The outcome is always the same -- no transmission of envelope viruses to those patient groups.

Finally, at least through December of 1996, there are over 15 million doses, separate treatment episodes of solvent detergent-treated products on a worldwide basis.

This represents two-thirds of the world's coagulation factor concentrates today.

[Slide]

I would like to remind the committee that solvent detergent was first implemented prior to HIV screening. Thus, as a consequence, we know that safety can confer to products even without screening. Of course, today's screening procedures have gotten ever better and so the margin of safety has improved. The same statement can be made with respect to hepatitis C testing.

Finally, the last point on this slide is that we have prepared a hyperimmune gamma globulin to HIV from donors, all of whom were infected with HIV, and used that preparation as a treated plasma in chimpanzees to demonstrate safety, and safety was demonstrated both with respect to HIV as well as hepatitis viruses.

[Slide]

This is a slide which illustrates the breadth of solvent detergent treatment in terms of the variety of products that are made worldwide. They include coagulation factor concentrations, immune globulin concentrates, and even has extended into monoclonal antibodies and other preparations of biotechnology.

Perhaps the single most important number or impressive number is the number of doses of Factor VIII which have been

administered to hemophiliacs, which now represents over 100,000 man-years of usage of that particular product in that patient group.

[Slide]

So the simple summary over this period of history, from 1985 through the present, is that there are no cases of hepatitis B, hepatitis C or HIV transmission with solvent detergent-treated products.

[Slide]

As Dr. Silverman already described with respect to solvent detergent plasma, the methodology is designed to eliminate HIV, hepatitis B, hepatitis C and all other envelope viruses from transfusion plasma. The technology is well proven. The donor base is a volunteer donor base, as was emphasized with some importance yesterday.

It is a pooled product, but unlike most of the pooled products that the committee is used to hearing about, we have limited the pool to a maximum of 2500 donors. By contrast, in a normal fractionation setting, as this committee has heard in the past, that number can approach 80,000 donors or above. Antibodies are present to protect against hepatitis A and parvovirus, and I will speak more about that later. There is a consistent content of coagulation factors. The largest forms of von Willebrand factor are missing, and they are missing because in the

final sterile filtration they are removed by that process. Some people consider that that is an advantage in the treatment of thrombotic thrombocytopenic purpura, TTP. That is the reason why cryosupernatant is sometimes used in the treatment of that disorder.

[Slide]

So, the safety to SD plasma is conferred in two ways. Certainly solvent detergent protects against envelope virus. I think everyone in the audience appreciates the power that has been demonstrated. But, in addition, pooling guarantees the presence of antibodies to both hepatitis A and parvo B19. Single-donor products may or may not have the presence of those antibodies. Approximately 15% of donors have antibodies to hepatitis A and approximately 50% of donors have antibodies to parvo B19.

[Slide]

Specific viral kill studies which have been performed with solvent detergent-treated plasma are summarized on this slide. Again, I emphasize that this includes studies in chimpanzees with respect to hepatitis B and hepatitis C.

[Slide]

Perhaps even more impressive is the rate of kill we achieve of viruses that we add into the plasma or the treatment with solvent detergent. The normal incubation period is 4 hours. The first time point in these studies is

15 minutes. By 15 minutes all virus is gone. BVD, for those of you who are not familiar with it, is a model for hepatitis C, as is sindus virus and HIV, of course, is its own model.

[Slide]

With respect to antibodies, we know that both hepatitis A antibodies and B19 antibodies are neutralizing and protective. To illustrate this point, a standard dose of solvent detergent-treated plasma would contain 30-50 times more antibody than an intramuscular injection given to protect against hepatitis A. A standard dose of plasma, again, would deliver more than 24,000 units of antibody to parvo. Although not as well studied as hepatitis A, at least in the laboratory you only need 1-2 units to protect against parvo infections.

Antibody has three different ways of acting. In one case it can prevent infection, that is to say, neutralization of the virus. In the second case it can speed the clearance of the virus from the body. The third way that it can act is through prevention of cell-to-cell spread.

There have been a few reported cases of hepatitis A, as the committee has heard, from purified products. Let me emphasize that those purified products lacked antibody in the final preparation. Whereas, SD plasma, much like

intravenous immune globulin, continues to contain those antibodies.

[Slide]

With respect to viral safety studies in man, a number have been done. This slide demonstrates the ones that we performed at VITEX, as well as those performed in Europe with respect to product made in Europe by the three manufacturing sites that prepare a similar product there. The bottom line, over 2000 units, 81 lots tested -- no transmission of virus.

[Slide]

Speaking about Europe, solvent detergent-treated plasma was first introduced in Germany, in one of the stadts in Germany, in 1991, and came into more widespread use in 1993. It is selected as the exclusive form of transfusion plasma in two countries, Belgium and Norway. In addition, it is licensed in the other countries listed here, including France and Germany. From 1991 to 1997, over 3 million units and more than 3000 batches have been used in Europe, prepared, again, by three manufacturing sites, all without evidence of transmission of virus.

[Slide]

Let me then turn attention to some philosophic issues that affect the deliberation that is before the committee. There are numerous advantages confirmed by viral

inactivation, as summarized on this slide. Yesterday this committee expressed a desire to better understand the relative importance of the various measures taken to improve safety of the blood supply. In my opinion, viral inactivation is the single most important factor. It addresses the window period in a way that no testing can. It provides a large margin of safety. It attacks viruses which are mutants and perhaps not detected by current test methodology. It eliminates viruses for which we have no tests. Of course, it accommodates laboratory error.

[Slide]

Had viral inactivation been available in the 1970s, in the late 1970s, a whole generation of hemophiliacs, of course, would have been saved from the devastating impact of HIV infections. By contrast, had quarantine been available in the late 1970s, it would have done nothing to impact that transmission.

In 1985 to 1988, had quarantine been available with respect to transfusion plasma, it would have done nothing to stop hepatitis C transmission for there was no test.

In 1995 through 1996, had quarantine been available, it would have done nothing to stop the transmission of HIV type O had it entered the blood supply, as many of the tests were unable to pick it up.

Here, in 1998, quarantine does nothing for hepatitis G.

[Slide]

So, the deliberations that are before the committee -- and we heard expert testimony by probably the world's most leading expert on the window period is yesterday, Michael Busch -- we certainly need to understand what the basis of the window period estimate is. We need to understand the standard deviation that surrounds those estimates and what the likelihood of outliers is. I think we heard yesterday, with respect to HIV, in one study where there were 52 cases of transmission, 2 of those cases, or approximately 5%, had an incubation period of 6 months.

What is the length of the quarantine period proposed, and that is a question posed to the committee? And, an element which has not entered the discussions thus far is how will centers control inventory which is designated to go into quarantine? How will the product be labeled? What computer systems will be put into place and other logistical considerations?

[Slide]

I put up this slide in part to remind me that I probably need to make a new one. Dr. Busch delineated yesterday two window periods for us, one of which is the period between exposure and infectivity, and the second of which is the time between infectivity and marker virus positivity.

A more conservative view would be to sum these periods. Dr. Busch attempted to define or delineate through computer modeling what the first of those periods is but, as I say, I think a more conservative approach would be to sum those too. If I copied down the numbers correctly from his summary slide, if one summed the two, for HIV the window period is approximately 40 days with a 10-250 interval. Hepatitis C, and I know that was changed in the end but it went up to 135 days and I didn't catch the change. And hepatitis B up to 88 days.

So, those are parts of the deliberation that I think are before the committee, and certainly Dr. Busch is the single most knowledgeable person I know to address that issue.

[Slide]

Well, what are the other limitations besides the window period? Yesterday I also heard from Dr. Busch that there is a non-window period risk estimated at 20% for hepatitis C, 7% for HIV and 2% for hepatitis B. This risk in part comes from immunosilent infections, viral variant viruses we do not test for, as well as errors which are made in the laboratory.

[Slide]

To further illustrate that there are viral variants, the committee did hear at a previous meeting about HIV type

O and what manufacturers of screening tests were doing to bring their tests into conditions which could detect this particular variant. Hepatitis G, we now know is in approximately 1% of donated blood. And, just in last month's Transfusion, a new hepatitis B virus variant, which is not detected by some blood screening tests today, was described.

Also, we heard Dr. Tabor yesterday talk about two other viruses, HAV type 8 and HTLV type 1, which his committee has examined to determine whether or not there is risk. I note that both of these are envelope viruses.

[Slide]

So, in summary, if I were attempting to put a single table which would estimate risk, I would divide it into the following categories: with respect to the viruses that we know, HIV, hepatitis B, hepatitis C and the HTLVs; current fresh frozen plasma, a single dose and this is a dose which is approximately 5 units, not a single unit of fresh frozen plasma, has a risk more or less of 1/6600. For sure, quarantining plasma will reduce that risk. It may reduce the risk by as much as 90%. For SD plasma, I consider the risk to be zero.

For hepatitis G and other known viruses -- well, hepatitis G we know is in approximately 1% of donors. So, I have listed the risk as 1/20. Fortunately, as best we know

today, there is no pathology associated with that transmission. Quarantine does nothing to decrease the risk and, as has been shown by PCR studies by others, solvent detergent destroys that virus.

Hepatitis A and B19 -- transmission by FFP as well as quarantine is possible. Hepatitis A is rarely transmitted by blood, and that is because it is rarely in the blood supply, but it also has the possibility of a new neutralization even with single-donor products.

Similarly with parvo virus, which is frequently in the blood supply, we do not screen it today and, yet, we must be exposing a great number of patients even with single-donor products. With solvent detergent plasma we at least guarantee the presence of antibody.

Finally we reach this category or virus, which is the most difficult category to deal with and is, I think, the reason we are here today. What do we do about the unknown virus which is non-envelope? That is to say, a virus which we don't now believe is in the blood supply but perhaps it is there and perhaps it is insensitive to solvent detergent treatment. Of course, it is possible that pooling may increase that risk.

[Slide]

In summary, in answering the question posed to the committee, it is clear to me that the safety of quarantine

plasma cannot match that of solvent detergent-treated plasma since quarantining relies solely on screening tests and, thereby, suffers from all of the drawbacks that characterize such tests. Nonetheless, it is equally clear to me that the safety of solvent detergent-treated plasma, as well as quarantine plasma, is higher than that of fresh frozen plasma. With that, I thank you.

DR. HOLLINGER: Thank you. Any questions right now? If not, we will now move into the open public hearing. There are six individuals who have asked to speak. Wo, we will start the open public hearing with a presentation by Dr. Holland.

Open Public Hearing

DR. HOLLAND: Thank you. I am here on behalf of America's Blood Centers. I represent the Sacramento Blood Center also. I am here to discuss the relative safety of pooled solvent detergent plasma and something new you have just heard about, and you are going to hear more about, that is, single-donor fresh frozen plasma, donor retested.

In comparing these things, I don't think you can really compare one to the other. I think you should compare each of them to what we have now, which is single-donor fresh frozen plasma, which is really a very safe product but it still has measurable risk, as you have heard. So, in my presentation I want to contrast each of these new components

that you are talking about, pooled solvent detergent plasma and single-donor fresh frozen plasma, donor retested, which I will carefully define for you, with what we currently have.

Both of these new components are safer. They have less risk. They have different risks but they have minute risks. They are not zero. So, what I am going to try to do is build upon on what Dr. Horowitz just said. I am going to show you that I will respectfully disagree with some of the statements he made regarding the safety and regarding the simultaneous presence of antibody to hepatitis A and parvovirus in these preparations, which do not protect against infection. At best, they might modify it but they do not protect against infection.

Basically, I want to show you that I believe that having an alternative to pooled solvent detergent plasma would be a great idea. We have submitted for license for this, and I believe it would be very helpful for most blood centers to have this safer alternative so we have something else which is comparable but different.

[Slide]

Okay, what am I talking about? From the discussions yesterday, I want to make it clear what I am talking about. Basically, fresh frozen plasma, donor retested, you phlebotomize or pherese a donor with some fresh frozen

plasma. It comes from one donor.

You test it, of course. It has to meet all the requirements. You freeze it and store it for a minimum of 90 days. You then recall that donor. That donor must come back and be tested or preferably donate another unit which passes all of your tests. So, as opposed to inventory hold that you heard about yesterday, this donor must come back, must go through the screening process, must pass all the tests again.

If all of that testing is non-reactive, then you may release that stored unit. But also keep in mind that you had an interval history. In that 90-day period of time, if the donor had been exposed to hepatitis A or come down with parvovirus, or something like that, and it were clinical, you would know about it. So, you have that additional safety factor. You have an additional 3 months of history in that interim period of time even though we are concerned about the sample that was drawn 3 months before.

The follow-up testing of each subsequent unit permits the release of any which you have had more than 90 days in your freezer. I think this really gives you a minute, but certainly not zero, risk of viral transmission. And, it is all based largely upon the window periods that you have heard so much about, and I want to reiterate them too.

[Slide]

This is from a couple of years ago but, basically, this was before HIV antigen testing. The window period is estimated to be 22. I am using the total window period. Dr. Busch very carefully pointed out that there is an eclipse period when the donor could be infected or is infected but is not infectious, and then that second period which is the time when they are infectious but still pass our tests. I am going to lump them all together even though the total window period does not represent a total period of infectiousness.

HTLV-I is not a major problem. It is not really transmitted by plasma. This is a study from the Netherlands, which looks at a 98-day window period for hepatitis C. It is based upon only 9 patients, but it is based upon the right kind of patients, that is, patients who were transfused. These are the only people, say, for needle sticks, that we know the exact time they got infected. We follow them prospectively and we know when they develop evidence of hepatitis or other infections. I am going to show you three series that show you that in most cases for both C and certainly for hepatitis B that window period is covered most of the time. Yes, there are some longer incubation periods. This is why the 2.0 test, hepatitis B surface antigen test. which may be not covered, but the vast majority, well over 90%-plus are covered.

[Slide]

To give you one example, here is a series from Spain, which is only partially published, from Dr. Barrera in Barcelona, and this is 29 patients who developed hepatitis C post transfusions and were followed prospectively. Using the 2.0 version, the average day of reactivity was 72 days, the median was 71. All 7 of the patients, by 90 days, had evidence of antibody by this 2.0 test. However, 7, or 24%, did not. However, 5 additional ones had an elevated ALT, and we are virtually all using elevated ALTs, so all but 2 of these individuals would have been picked up by a screening process by the combination of the 2 tests, the elevated ALT and the second generation test. Using the 3.0, you shorten that window period somewhat. You pick up a couple of additional patients and, again, all but 2 of them with the combination of the 2 tests would have been picked up.

[Slide]

I am going to show you two slides that Mike Busch used yesterday from Harvey Alter. This looks at the interval from the initial ALT elevation to anti-HC seroconversion by the EIA-2. What it shows is that either simultaneous with the presence of the antibody, within a month by 79% of them and within 13 weeks by all of them, they had an elevated ALT. So, in this particular series, and there were 63

patients, every single one of them would have been identified by an elevated ALT or a positive serology for C within the 90-day period.

[Slide]

This looks at Harvey's slide in another way, where there is this sort of 3-week eclipse period before PCR becomes positive. There is evidence of nucleic acid for hepatitis C RNA. Then, with the third generation test, the 3.0 test, here is the ALT first and then you have the 3.0 and the 2.0. So, again, by 12 weeks, 13 weeks post transfusion all of these individuals were identified, and if they had been potential donors would have been picked up and their units would not be used within a 90-day hold.

[Slide]

So, this is really more true of today, that is, with the p24 antigen test in place we have a 16-day window period for HIV and even with the rare cases of prolonged seroconversion, remember, most of those healthcare workers were not infectious for that period of time, by the way. For the 3.0, 64. Again, a few would go beyond 90 days. For surface antigen for B, yes, a few would go beyond 90 days. But the vast majority are going to be picked up.

[Slide]

This is my summary of what solvent detergent-treatment plasma does. Yes, clearly, it is going to inactivate lipid

envelope viruses like B, HIV, hepatitis C, and probably HGV, presuming it is even important, as Dr. Horowitz said. However, it has minimal to no activity against non-envelope agents and non-lipid envelope viruses.

I want to focus on parvovirus B19, hepatitis A and a new non-envelope transfusion-transmitted virus which was just described by the Japanese, which they unfortunately call TTV, the initials of the patient. I am not going to talk about hepatitis E, but it is another non-envelope virus. It can be transmitted in Third World countries. It may be transmitted in our country in a version which is in pigs. It has a very high mortality rate when it occurs in pregnant women.

[Slide]

Parvovirus B19 antigen r genetic sequences in the plasma from volunteer donors -- there are two published studies and one unpublished study showing you the frequency with which our volunteer, healthy donors who pass all of our tests are carrying this agent at the time they donate blood. This study, 1/5000. This study found 1/20,000, from Scotland or 1/3300, and Sue Stramer did a study of 10,000 Red Cross donors last year, and 7/10,000 were positive for a rate of 1/1400.

So, if there are 2500 units in a pool of solvent detergent plasma, then using the smaller number there is at

least a 30% chance. Using these numbers, there is a higher chance that that pool will contain B19 and could infect hundreds of recipients of that pool of solvent detergent plasma.

A big issue was made about, well, there is antibody in there. Well, how did this group detect it? They used plasma pools of 500 and they are able to detect the DNA of B19 in a pool of 500, undoubtedly, where hundreds, if not thousands of those donors had antibody it clearly didn't neutralize B19 there. Not only that, they actually found one donor who had IgG antibody before and during the detection of this virus. So, the presence of antibody to this virus is not protective and will not help.

[Slide]

Most of the time this is a very mild disease in most children. It is called the "slap cheek" syndrome. But here is a patient who had thalassemia, a chronic hemolytic anemia, and here is what happened to this patient when he got parvovirus B19 infection from a transfusion.

He had an aplastic crisis. He went into heart failure. He had antibody. He showed seroconversion. He had virus in there. n fact, the virus was detectable for at least 4 months in this particular patient.

It was interesting, they went back and they found the donor that was implicated, and the donor had antibody and

virus simultaneously at the time of the donation, once again showing that the presence of antibody to this virus is not protective even if it is in the pool or even if it is in an individual donor.

[Slide]

This caption is hard to read. It says, "yes, it's pretty lonesome out here. All my family is in hospital with something called infectious hepatitis." My point is that I want to lead into some points about hepatitis A which could be transmitted by transfusions.

There are at least 10 case reports, or reports in the literature of hepatitis A being transmitted by transfusions. There are probably others, because I know we have a huge one which was never reported, which have not been reported. The transmission of hepatitis A to the patients is the least of the problems, i will show you by this group of patients, who were impacted at our center. This is a case we published.

The infant got some fresh frozen plasma we collected and clearly got infected with hepatitis A. More importantly, his mother got exposed to him when she was changing his diapers and 9 nurses in the intensive care unit that were taking care of this child also were infected. This was found out when these nurses started coming into the employee health service with clinical symptoms.

So, it isn't even so much the patient. The patient was

fine. He just seroconverted. But, in taking care of him, that patient infected with fresh frozen plasma which happened to be from a donor who was incubating hepatitis A, infected 10 other people. At our university hospital this was magnified even more because three children got exposed to the same components and dozens of healthcare workers and families ended up getting hepatitis A.

[Slide]

What about the effect of solvent detergent? This is a study from Italy, where there was transmission of hepatitis A to patients with hemophilia by Factor VIII concentrates treated by solvent and detergent. From this batch, 52 patients with hemophilia were infected. This has been passed up as, "well, it was the Italians; they didn't know what they were doing and it doesn't happen in America."

[Laughter]

[Slide]

This was published by our own Centers for Disease Control and Prevention. I have given you the MMWR reference and an update, presented at the ASH meeting. There were three cases after Factor VIII preparation and two cases after Factor IX preparation, solvent detergent from the same source plasma pools. To prove that that was the source of infection, the CDC found that the HAV in the plasma pools in the Factor VIII and two of the patients they tested was

identical by genetic sequence analysis. So they got infected by that product which had been solvent detergent and, certainly, in the pool there was a ton of antibody to begin with, and it didn't affect that virus.

[Slide]

Just to show you how important this can be, this is a study published this year in the New England Journal of Medicine. It looked at patients who had hepatitis C or hepatitis B or neither, who got superinfected who got, in addition, hepatitis A. And 6/17 hepatitis C-infected patients died when they got a hepatitis A superinfection; the 7th patient got fulminant hepatitis but, luckily, lived. Interestingly, none of the 10 with hepatitis B had this problem and none of the 191 others who just got hepatitis A alone.

So, hepatitis A on top of your hepatitis C can be very bad, so much so that I know in California the recommendation just came out, in January of this year, that if you are a recipient of clotting factor concentrates you should have the hepatitis B vaccine, and if you are a recipient of clotting factor concentrates you should receive the hepatitis A vaccine.

[Slide]

What about his new virus. The Japanese just described a novel DNA virus, called TTV, with elevated transaminase

levels in post-transfusion hepatitis of unknown etiology. They were looking for this. They looked at cases of non-B, C, D, E, G that had all the clinical findings of hepatitis post transfusion, and they wanted to find out if there was a new virus, and they found it.

[Slide]

I want to focus on only a couple of things. One, they could find it in some of the donors and, most importantly, it is a non-enveloped virus. So, this virus, if it is in a pool, will not be inactivated by the solvent detergent process. So we have at least one X virus, one more hepatitis virus, which could get in this pool and, if it did, it is going to be magnified by 2500 times.

[Slide]

Once again, solvent detergent plasma, yes, it is great. It has a wonderful benefit. It inactivates envelope viruses in the pool even if the pool tests negative.

But I want to focus on only two of the negatives. One is of the downsides is there is only going to be a single processing facility in the United States. If anything goes wrong, if anything happens to that facility we are out of business. We can go back to what we already have, of course, which I think is pretty good, which is fresh frozen plasma.

The second point is that there are new risks. You have

the large pool size. You have non-enveloped viruses, and whatever that risk of a single unit is, it is going to be magnified 2500 times.

In addition, as Dr. Epstein said yesterday, this thing has to work perfectly, and it has to work perfectly every time. That solvent, that detergent and the extraction process, they are all toxic materials and they all have to be removed otherwise that could have an impact on patients.

[Slide]

What am I proposing? It is something pretty simple. We have something called single donor, fresh frozen plasma donor retested. You should have received in your handout the elements needed for an FDA license submission, and we have actually submitted for a license.

You set up your criteria, and the main criterion is it is fresh frozen plasma, except we are saying it has to be held for at least 90 days and the donor has to be retested.

We have modified the package insert to say here is another product. It has all the same attributes of fresh frozen plasma; it is used the same way; everything is the same, except that it has been retested. The attributes I have given you, the description for its use are the same. You have to set up some kind of a computer software or other control mechanism to make sure that you get those donors back and you don't release it, and you don't label it as

donor retested until you have gotten the donor back at least 90 days later. We have developed in the label a new bar code.

[Slide]

Finally, I want you to know I believe that both these components are very safe. Believe me. But I want you to know that both single donor, fresh frozen plasma donor retested and pooled solvent detergent frozen plasma, I believe, are really only temporary components. As soon as we have nucleic acid genome amplification testing in place for all of our components and/or we have more effective panmicrobial inactivation processes in place, which can be applied to all of our components, including the cellular ones -- and an example I can give you is psoralen ultraviolet treated -- we won't need either of these because between this and/or this we should have essentially -- it will probably never be 100% safe but we will have essentially 100% safety for all blood components as possible. Thank you very much for your attention.

DR. HOLLINGER: Thank you.

DR. HOLLAND: I believe Dr. Katz is now going to do the second part of this as far as a narrative, but I am happy to answer any questions first.

DR. TABOR: I think it is important to say that the TTV virus reported by the Japanese in VBRC, in late 1997 and at

a meeting in California, in January, has not been shown to be transmitted by transfusion so far. It is true that they did find it in a number of patients with non-A to G hepatitis, but they also found it in such a large number of normal in Japan that there is a very good possibility that it will turn out to be a virus that is just present i plasma throughout the population. Other investigators have not found it in American blood donors. So, while it is a concern and bears watching, it is not a cause for alarm immediately.

DR. HOLLAND: I wouldn't disagree with you. I think we need to know more about it. My point is that it is a non-envelope virus. It appears to be in patients with fulminant hepatitis and in patients with non-A, C, B, E hepatitis, and I don't think we can disregard it.

DR. TABOR: I just think that for the record we ought to recognize that this is not yet clearly a hepatitis virus, and it has not been shown to be transmitted through transfusion so far.

DR. HOLLAND: Not so far, I agree.

DR. HOLLINGER: Paul, on the co-infection, weren't most of those patients who died of fulminant hepatitis ones that had significant hepatitis C infection?

DR. HOLLAND: I am not quite so clear. The article was published in January, in the New England Journal of

Medicine. It really just looked at all of their patients and then looked at how many had, in addition, superinfection hepatitis A. I don't think they exactly split it out.

The point is that even if it is so, if you have hepatitis C and you have hepatitis C, and you get hepatitis A on top of it, then your chances are 1/3 of dying. That is important.

DR. HOLLINGER: Yes, but I think in reality the issue would be that that patient would have to get that very low level of hepatitis A in the plasma.

The other question is, I think it is fair to say that DNA is not necessarily synonymous with infection. The finding of parvovirus B19 DNA does not necessarily mean that the product is infectious. Would you agree with that or not agree with that?

DR. HOLLAND: I would agree. Again, there is always the same question. When you have nucleic acid there, does it mean infection or not, and it isn't always clear. Certainly, in some of the case reports they have been able to demonstrate that nucleic acid was there and was infectious, but it is not really clear. I would agree.

DR. HOLLINGER: But if the virus is there and it is neutralized, still the nucleic acid is going to come up to be positive.

DR. HOLLAND: Right, but I think it is interesting, as

I have shown you from at least one and I am sure there are additional examples, you can have the virus there and the antibody and it is infectious. It is neutralizing antibody that we are apparently measuring.

DR. HOLLINGER: Thank you. Dr. Katz?

Presentation

DR. KATZ: Thanks for doing all the hard work, Paul. I am here,, in fact, representing ABC and reading a statement, that the committee has been provided with, that represents the position of our organization.

I want to thank the committee for the opportunity to present ABC's views today. ABC, as some of you know, is a voluntary association of now apparently 71 independent community blood centers --

[Laughter]

Our members draw, process and distribute almost half of the volunteer blood supply in this country, and we are committed to improving transfusion safety by any measures required.

Solvent detergent plasma represents an advance for preventing the transmission of enveloped viruses to recipients of FFP. However, its aggregate benefits may be more apparent than real and, accordingly, we believe that innovative alternatives are highly desirable.

The large majority of plasma recipients receive other

cellular blood products, red cells and platelets, that cannot be subjected to viral inactivation procedures at this time. The potential value of SDP, therefore, is mitigated in proportion to the number of other products transfused. In a study presented at the 1997 AABB annual meeting, Dr. Shimits and Yomtovian, from the University Hospitals in Cleveland, demonstrated that in their institution 97% of FFP recipients, potential candidates for SDP, received a mean of 19.5 other components. Conversely, only 3% of patients received FFP exclusively. These patients received only approximately 5.5% of the FFP transfused.

SDP, solvent detergent plasma, is a pooled product that will be manufactured from approximately 2500 pooled individual donations. The SD process is unarguably highly active against the lipid-enveloped viruses of recognized significance for transfusion medicine today. It does not, however, as you have heard, inactivate non-enveloped viruses like HAV and perhaps parvovirus B19.

SD-treated Factor VIII concentrates in Europe have transmitted hepatitis A, a non-envelope virus, to hemophilia A patients and, while HAV is thought of as a low virulence pathogen, the recent report of high mortality from acute hepatic necrosis with high mortality during acute HAV superinfection of patients with chronic HCV should give us all pause. HAV may be a model for novel agents not

currently recognized as transfusable pathogens. Trepidation about pooling must be particularly acute when a pooled product, SDP, is advocated as a replacement for a single donor product, FFP, which we all agree represents a fairly safe product in 1998.

With some trepidation, I will quote Dr. Harvey Alter, at the AABB annual meeting: "The risk of pooling is greater than the risk of the infection solvent detergent technology aims to prevent. Viral inactivation has great potential, but it should not be at the expense of converting single units to pooled products." It is an important perspective that today the FDA has not suggested that the potential advantages of SD plasma are sufficient to warrant removal of standard FFP from distribution.

The ABC and others are actively pursuing technologies to allow viral inactivation of single donor products, obviating the need for pooling. These include photodynamic inactivation using methylene blue and psoralens with UV radiation. In addition, as donor testing with gene amplification technology is brought on-line in blood centers during the next one to two years, the advantages afforded by SDP for preventing transmission of enveloped viruses will further erode.

Arguments based on cost-benefit calculations have not been afforded high priority in the discussion of blood

safety initiatives in this forum, and certainly should not influence decisions by FDA regarding licensure of individual products, like SDP or fresh frozen plasma, donor retested. They can, however, provide a very informative frame of reference. Aubuchon and Birkmeyer, in 1994, published an analysis of the use of SD plasma, suggesting that the marginal cost-benefit of the use of this product was $289,000 per quality adjusted life year saved. Most medically accepted interventions fall in the $50,000 range or below. The critical parts of any cost-benefit analysis are the baseline assumptions. In the cited article the assumed rates of HCV and HIV transmission were roughly 10- and 3-fold higher respectively than current estimates from the NHLBI Retrovirus Epidemiology in Donors Study, the REDS study. The assumed marginal cost of SDP over FFP was $20, while in Europe SDP is currently sold for 1.5 to 2 ties the price of FFP in this country, for example, $92 per unit in Austria. Accordingly, the $289,000 estimate is undoubtedly a several fold underestimate of the actual cost per QALY in the use of SDP over FFP in 19998.

Finally, the cost-benefit analysis concluded that at a risk of 1 in 71 million for a hypothetical non-enveloped pathogen, with 50% infectivity and a 50% reduction in life expectancy, contamination a 4000 unit donor pool, any benefits of SDP over FFP for preventing HCV, HBV and HIV

would be lost.

An alternative to SDP is fresh frozen plasma, donor retested, which Dr. Holland has so nicely described. The concept is simple. A volunteer donor presents, donates, and is made from that donation. This component enters frozen quarantine for a minimum period exceeding the infectious seronegative window period for relevant transfusable viruses, and until the donor returns, is fully qualified and retested for incident infection. The initial unit of FFP-DR is released only when repeat testing and screening beyond the window estimates is negative, minimizing the risk of recognized transfusion transmissible infections.

Another advantage of FFP-DR that is obvious is that it is unpooled product which can expose only a single recipient to an unrecognized transfusion pathogen.

In addition, the cost of FFP-DR should be substantially lower since it needs no further manufacture, and need not leave the center where it is produced, incurring transportation costs. ABC member centers have been developing standard operating procedures and data management programs to support the production of FFP-DR as an alternative to SDP with its potential disadvantages. One such center's application for its licensure, in part, leads to your deliberations today.

With REDS estimates of infectious, seronegative window

durations for HIV -- let's see if that makes it easier for me to read.

DR. HOLLINGER: Yes. While we are waiting, let me ask the presenters, we have heard a lot of these numbers time and time again here. Let's not go over this again --

DR. HOLLAND: Yes, I am going to skip the numbers.

DR. HOLLINGER: -- so we can move forward because we have a lot of things still to do and a lot of things to talk about. So, keep is succinct. Let's hear the points and go from there.

DR. HOLLAND: You have heard the REDS estimates of the window period donation, and in light of the estimates that you have been provided, ABC would support a minimum quarantine duration of greater than or equal to 90 days for FFP-DR. Logistic considerations and the outdate for FFP at one year suggest that quarantine durations beyond 120 days would be difficult to implement. This is based on initial modeling by Dr. Jane Manitol at the Community Blood Center of Kansas City.

You have heard REDS data documenting current window period estimates, and the profound impact of repeat conation on the incidence of new infection of blood donors with known transfusion transmissible virus. Production of FFP-DR from necessarily repeat donors is an important assurance that it safe. One can argue from the REDS data that merely

producing FFP without a quarantine period, from greater than or equal to 3 time donors, will provide a substantial margin of safety to balance the viral inactivation process used for SDP when the risk of pooling is considered. My center and others are actually investigating this second alternative to SDP.

I am very excited that SD plasma is only the beginning of an era of increasing safety for plasma products. It starts with a virally inactivated but pooled product. It should be accompanied by the single donor alternative, FFP-DR, and by other creative approaches like the pedigreed donor, plasma screened for infectious agents by molecular technologies, and single unit viral inactivation technologies which are further in the future. Thank you for your attention.

DR. HOLLINGER: The next presenter is Michael Busch. I can take one more window period, Mike!

[Laughter]

Presentation

DR. BUSCH: We have a window for TTV! Just one quick comment on Dr. Horowitz's presentation. He added these two window periods, and that is incorrect. The overall exposure to seroconversion window period is inclusive of the latter portion of that, which is the infectious window period. So, it was inappropriate to add those two window periods.

[Slide]

I thin what we have heard in the last couple of days is that the risk of blood is exceedingly low, and what we are dealing with now is people, I think, pushing the envelope of risk to a level that obviously is measurement, and perhaps is beyond reason when we are dealing with the potential downside of some of these measures, not to mention the extraordinary cost ineffectiveness of these measures.

The pending licensure of SD FFP has led to the concern that there will be widespread pressure, for various reasons, to implement SD FFP and potentially replace available standard FFP with SD FFP. That concern, and a variety of industry issues, has led to the concept of collecting FFP and requiring that a donor return over a period of time and test negative at a subsequent time point, this so-called donor retested.

That is extraordinarily logistically difficult to do, and it is going to be extraordinarily expensive. It won't be money that the blood centers pay per se to the vendor, but it will be money that will be required to put into place the freezer inventory systems, the computer programs to monitor this, etc., and considering this, I don't think, personally, any of this is worthwhile.

One alternative approach that we considered was the potential that FFP -- again, one point I think was made is

that virtually all people exposed to FFP are concurrently getting cellular components which carry with them the risk estimates that we have been discussing, and reducing the fractional risk of one component that is often a minor subset of the total exposure is debatably useful. But one alternative to try to make this frozen component a safer component that the current standard FFP, rather than trying to inactivate the virus or, in essence, eliminate the window period through interdiction of seroconverting donor prior donations through inventory hold or quarantine, would be to selectively make FFP from a safer subset of our donors.

There is a variety of characteristics that we know identify safer donors, demographic characteristics, etc., but one that is feasible and could be implemented, I think, with fairly minimal effort is to selectively prepare fresh frozen plasma components from multiple time repeat donors. I think included in your materials that were distributed there is a brief analysis of this, with fairly extensive tables. I am just going to show three tables that summarize the bottom line of this analysis.

[Slide]

What we looked at in the REDS study data set was the distribution of donations by frequency of donations among donors, and then the relative incidence for the various infections, given a history of donation patterns.

We looked at three different breakouts of the donor base. We looked at the cumulative number of donations that donors had given; the period of time that a donor had been donating, two years or less than two years; and the rate of blood donations, 3 or more donations per year, 1-3 or 1 or less per year.

Important from the practical perspective here is how far down the line of frequency of donations could we set a standard that would still allow us to obtain enough plasma to support the needs of our donors.

I will present only the data on number of donations because as the analysis that you received summarizes, there is lower risk associated with donors who have been giving for longer periods of time and with donors who give more frequently. But in a multivariate analysis the absolute cumulative number of donations is the only independent predictor of lower incidence, and it is also practically a much simpler parameter to track.

The bottom line here is that although only 23% of our donors, for example, give 6 or more donations, those donors, by virtue of giving regularly, account for approximately 50% of all blood. The group that gives 4-5 units account for 21%. So just drawing a line here, requiring a history of greater than 3 donations, allows us to actually capture 80%, of the that are donations, to meet that criterion. As we

will see, if we draw a line here we are really at an extremely low incidence level.

[Slide]

So on this slide we will look at the incidence rates for the various viruses relative to these number of donations. The bottom line here is that for each virus, HCV, HIV and HTLV -- HBsAg is a little complex here because you are dealing with a marker that is transient, and the more frequently you give, actually, the more likely you are to pick up a person in the transient antigenemic window. So, I won't focus on that, although I am sure the risk issues bear true.

If you simply look at this column, here, which is the incidence rate, among repeat donors, if they have given only 2 donations, the incidence for HIV is 13.6 per 100,000. It drops to 3.6 with 3, and then drops and stabilizes with 1.6 beyond 4 donations. HIV, 9 to 3.5, to 2.1 and essentially again reaches an asymptotic level beyond 4, and HTLV drops from about 4 to a little less than 2. Each of these are highly significant correlations of lower incidence with more frequent history of donations.

[Slide]

What I have done on this slide is to actually calculate out what the comparison would be were we to exclusively collect FFP from greater than 4 time donors, versus an

estimated current composite donor incidence rate for these viruses. We know the incidence rate among our repeat donors overall and, actually, it is not as high as those numbers that were shown for the 2 time donors because a high proportion from the donations from repeat donors are coming from these very frequent donors. So, the overall incidence among repeat donors is shown here for each virus.

What we did, as Sue Stramer showed yesterday, was we used the relate incidence rate among first-time to repeat donors for HIV, which is measured using the "detuned" assay as a 2.4-fold increased risk to estimate the incidence among first-time donors to repeat donors, and then just basically represented the appropriate proportion of first-time to repeat donations to derive an estimated composite incidence for each virus, and then compare with that -- this is, in essence, the current incidence rate that applies to our standard FFP products. This would be the reduction in incidence rate that would be achieved if we were to exclusively collect FFP from multiple time repeat donors, in essence reducing the risk to about a third of the current level.

Clearly, none of these measures are absolute. This is one approach that I think would be extremely simple to implement, essentially zero cost, and in my opinion would take us to a safer product. I think the real concern here,

and my personal concern, is that FDA, or through industry competitive issues, moves to exclusively allow these safer, much more expensive products to be available, i.e., that they will delicense or disallow distribution of standard FFP, which is an extraordinarily safe and cost effective product. I think this approach would give us safer, but obviously probably not to the level of those others, but one that is practical. Thank you.

DR. HOLLINGER: Thank you, Michael. Girish Vyas has asked to present some information on hepatitis B immune globulin.

Presentation

DR. VYAS: Girish Vyas, from University of California, San Francisco. I will be very brief. Can I have the first slide, please?

[Slide]

Liver transplants are done on 4000 patients per year in the United States, and 5-10% of them are transplanted for hepatitis B virus infection. The graph gets infected almost 100% of the time, and one-year survival without any intervention is only 50%. Each liver transplant costs about $260,000. So, loss of the graph and the patients, both are major concerns.

[Slide]

A group in Europe has actually done a study to show

that hepatitis B immune globulin, or HBIG, which is not licensed for intravenous administration but is an intramuscular product, and is actually diluted and given intravenously in a large dose, 40 mL. Administering 10,000 IU per dose, the patients get 8 doses in the first week of liver transplant and then every month for an indefinite period of time. For as long as five years, hepatitis B immune globulin has been shown to be effective and the patient survival, as opposed to no treatment -- I am sorry, 19% patients die despite therapy, and without therapy or no treatment virtually 80% of the patients would die. The cost of hepatitis B immune globulin, the intramuscular product as it is being used today is $30,000 per year per patient.

What we are proposing to do is to have single donor FFP, donor retested product, prepared uniquely from a group of no more than 50 donors who are regularly coming to the blood bank for donation of their platelets. So, plasma would be derived from these individuals after they have been vaccinated with hepatitis B surface antigen. Hyperimmunized donors are screened, and then ascertain that they have high enough antibody titer to qualify at a set level of 10,000 IU per 80-90 mL unit of plasma for transfusion. This is a study that we are planning to do over the next five-year period.

The pilot study that has been done, and the study that

is done in Geneva, show that the product is safe, effective, and the failure rate in the Geneva study has been 8%, 1/12 patients was lost in a 3.5-year follow up.

So, we are proposing to undertake a study for which we have an IND from FDA for donor retested plasma from a small group of donors who are pre-immunized, and these immunized donors, whose platelets are being transfused every month so we have clinical safety already built into the algorithm of donor selection. Let me make it clear. These donors are monthly donating their platelets. Plasma is coincidentally derived in the machine, 400 mL, in addition to the platelets. Every month these donors' fresh frozen plasma is stacked away in the freezer in small units of 80-90 mL so that 10,000 IU can be given to liver transplant patients. This plasma is quarantined for 3 months until the donor is retested and ascertained to be negative for all markers.

We believe that this product will be very safe and very effective for management of liver transplant patients. This is a very small group of patients at a very high risk and, therefore, this unique management has been proposed as a research project.

DR. HOLLINGER: Mr. Lamb, from American Red Cross.

Presentation

MR. LAMB: Thank you, Mr. Chairman. My name is Christopher Lamb. I am the Vice-President of Plasma

Operations with the American Red Cross.

The American Red Cross recognizes that both delayed release plasma and solvent detergent-treated plasma offer incremental increases in product safety for existing FFP. Pro and con arguments for both delayed and SD plasma have been articulated, but the issue should not be one versus the other but, rather, that both options, if licensed by the FDA, should be considered appropriate alternatives, and clinicians should make a decision based on their assessment of which product offers superior safety benefits.

There are a number of issues that have been discussed today. I will just quickly review five of them. One is the issue of new agents that may emerge. Obviously, if there is a new non-envelope virus for which there are inadequate neutralizing antibodies, a case under certain circumstances could be made for the delayed release product. If, however, there is an emerging envelope virus, such as HIV in the early '80s which would be inactivated by SD, this would be a preferred product.

Yesterday you heard a lot of discussion about window periods for HCV, HIV and HBV, with a 90-day retest period delayed plasma reduces the potential for window period donations. With solvent detergent window period donations should not be an issue, assuming a well validated manufacturing process operating under cGMPs.

There is the issue of product quality. Delayed plasma is essentially the same as FFP with presumed levels of plasma proteins and normal coagulation factors. SD is a sterile filtered product with defined product specs for plasma proteins and coagulation factors. In addition, solvent detergent plasma contains no red blood cells, red blood cell fragments, white cells, white cell fragments, bacteria or parasites.

Fourthly, there is the issue relating to HAV or parvovirus. Concern has been expressed about the pool size for solvent detergent-treated plasma and the risk of HAV in parvovirus B19 infection for that product. Dr. Horowitz has reviewed the presence of neutralizing antibodies to both hepatitis A and parvovirus B19, and that a patient receiving 50 mL/kg of SD plasma could receive approximately 30 times more anti-HAV antibody than would be received for HAV prophylaxis.

Finally the issue of logistics, as you heard yesterday we discussed about the logistics of quarantining or retesting plasma for fractionation. The logistics associated with retesting recovered plasma are extremely difficult, not only in terms when a donor might return, but in terms of tracking systems and other mechanisms needed to ensure an adequately controlled product. The logistics for SD plasma require pooling a maximum of 2500 units by blood

type from plasma collected less than 15 hours after phlebotomy.

The current U.S. market for FFP is approximately 2.4 million units. Processing 2.4 million units of SD plasma is a manufacturing scale-up issue. Processing 2.4 million units of delayed plasma is much more challenging.

The American Red Cross recognizes the advantages of both single donor plasma, donor retested and solvent detergent-treated plasma, and what we would suggest is that both are considered superior to FFP.

I would note parenthetically that in many Western European countries the policy is to use either quarantined plasma or delayed release plasma or a viral inactivated product, such as methylene blue or solvent detergent. The United States should consider following a similar model.

Finally, let me add in closing that the American Red Cross has an agreement with VITEX, the manufacturer of SD plasma, to provide volunteer plasma to VITEX, and we will provide universal access to patients, all blood centers and hospitals for distribution throughout the United States and Canada. This is consistent with our mission to ensure the delivery of the safest plasma products to meet patient needs. Thank you, Mr. Chairman.

DR. HOLLINGER: Thank you. The final presenter is Dr. Kleinman, for the AABB.

Presentation

DR. KLEINMAN: Steve Kleinman, Chairman of the Transfusion-Transmitted Diseases Committee for AABB.

As you heard yesterday, the AABB is the professional association for approximately 2200 institutions engaged in the collection and transfusion of blood and blood components. The AABB has as its highest priority the safety and adequacy of the blood supply.

One mechanism by which the AABB continuously monitors new developments related to the safety of the blood supply is through our committee, the Transfusion-Transmitted Diseases Committee. This committee includes specially selected experts in blood-borne transmission of infectious diseases, as well as liaisons from other sectors of the blood banking community, such as ABC, ABRA, Department of Defense, Red Cross, and also has an FDA representative. The committee is charged with reviewing all facets of disease that may be transmitted through transfusion and transplantation, and in preparing reports for the membership on developments and issues in these areas.

This committee is currently reviewing the relative safety of the two products that we heard about today, SD plasma and donor retested plasma, as well as modifications to FFP production. One of the goals of this review is to publish the information so that it is available for hospital

transfusion services and other association members.

Just to review where AABB has been on this issue, there was an ad hoc committee formed to comment on solvent detergent-treated plasma, and the report from this committee, entitled current status of solvent detergent-treated frozen plasma, was published in Transfusion in January of this year, volume XXXVIII. This article is, I guess, a scientific reference article that includes a thorough discussion of issues related to safety and availability, and a reprint of the article has been supplied for BPAC.

So, at the current time, AABB does not have a position on the relative safety of solvent detergent plasma versus single donor plasma, donor retested. We would like to remind the committee that plasma for transfusion as currently produced, that is, single donor FFP, is already a very safe biologic. The risk of transfusion-transmitted viral infection by standardly produced FFP is no higher than that for other routinely transfused single donor components, such as red cells and platelets, and because it is virtually cell free, FFP is not associated with the transmission of agents exclusive to white cells, such as HTLV-1 or 2, or cytomegalovirus.

So the AABB is committed to reviewing these issues, trying to compare the products and submitting its findings

to BPAC in the future.

DR. HOLLINGER: Thank you, Steve. Before we close the public hearing, is there anyone that would like to make any statements? If not, then I would like to have the questions presented to the committee, and then we will open it up for discussion and recommendations.

Presentation of Questions

DR. SILVERMAN: Again, I have reversed the order of the questions. It strikes me that this is a more logical order.

Does the committee concur in principle with a true quarantine hold period for an infectivity window period?

The second question falling out of that, what does the committee recommend, if anything at this time, as the minimum quarantine period for the release of previously donated units of fresh frozen plasma?

Once you have discussed this, then the next question, does the committee agree or does the committee think that pooled plasma, solvent detergent treated, and fresh frozen plasma, donor retested, are acceptable alternatives for those indications held in common, or to be held in common upon licensure between the two products?

Open Committee Discussion and Recommendations

DR. HOLLINGER: We will open it up for discussion by the committee members at this point. You can ask for clarifications from people who have presented before. Paul?

DR. MCCURDY: It is my recollection that yesterday a quarantine with retesting was suggested as the death knell of recovered plasma. Yet, today we are being told that essentially fresh frozen plasma, donor retested, which sounds to me like a quarantine hold retest, is something that is very desirable. I wonder if the difference between those two views might be reconciled by the proponents of the fresh frozen plasma retested.

DR. HOLLINGER: Does anyone want to respond that talked about this yesterday, particularly from perhaps the American Red Cross or one of the other organizations as to why there might be this perception of discrepancy?

DR. HOLLAND: Paul, there are two different things. What we are proposing is a single donor, fresh frozen plasma, donor retested which is to be used as it is. We believe for the needs of our community -- and we actually did this two years ago -- we could supply the community with this product.

Now, the recovered plasma issue is totally different. That material will go into some kind of further processing, microbial, viral inactivation. So I think they are really two different things. The fresh frozen plasma we are talking about is being used as it is, except after the quarantine period. It is not going to undergo any further inactivation. But recovered plasma, which goes into

derivatives, is going to undergo one or more viral or other microbial inactivation procedures. So, they really are different, and you have that safeguard on the ladder of these additional processes to kill any viruses that are in there.

DR. MCCURDY: It seems to me, however, that the logistics of the two are somewhat similar.

DR. KLEINMAN: Well, I think one difference is that FFP for transfusion probably constitutes only about 20% of the plasma collected by blood centers. The other 80% goes into recovered plasma. So, it may be possible to get 20% of the donors to come back and to have follow-up testing at 90 days. I think it would be clearly impossible to get 100% of the donors to come back -- we know it is impossible, and be able to release the product. So, I think what you might see is whereas you could meet the supply of transfusable product through this proposal of donor retested, much of the plasma that goes into the recovered plasma market would have to be not utilized, and so you would have a real decrease in the amount of derivative available. So, I think it is just a question of the percentage of donors that you need to meet this market versus the recovered plasma derivative market. But the procedures are the same. I mean, the computer systems you have to have in place, etc., would be the same whether you applied it to 20% of the donors or 100%.

DR. KATZ: Just to make it a little bit more graphic, to do FFP-DR at my blood center, we need approximately a 50% increase in our freezer space. To do recovered plasma quarantine, we need 5 or 6 times as much, at 5 or 6 times the expense, with a substantial plurality at least of the product that goes into storage for the recovered quarantine being discarded because the donor didn't come back in that time frame.

MR. LAMB: As I mentioned in my remarks, I think it would be very challenging and unrealistic to assume that you could supply 2.4 million units of delayed release plasma to meet the U.S. market. So, while I think this can provide an option, I think it is something that is relatively limited in what it can do. That is why, from the American Red Cross perspective, we have opted to work with VITEX. We think this is logistically much easier to scale up and provide universal availability of this product to meet the U.S. need.

DR. HOLLINGER: Thank you. Any thoughts on the committee on the question about quarantine hold? Can there be in principle a true quarantine hold based on the window period that one is seeing and the ranges? There is concern right now that there is not any genomic amplification technology being used. Yes, Dr. Buchholz?

DR. BUCHHOLZ: Since the question, as I understand it

is really out of order, would it be appropriate to modify the question somewhat to identify what product we are talking about?

DR. HOLLINGER: We are talking about fresh frozen plasma.

DR. BUCHHOLZ: For consistency's sake?

DR. HOLLINGER: Yes, I think here they are talking about fresh frozen plasma.

DR. BUCHHOLZ: I understand that, but if the questions are presented in the transcript in this order, that may not be totally clear.

DR. SILVERMAN: I would like to clarify. This is with regard to fresh frozen plasma, donor retested.

DR. HOLLINGER: Who else would like to comment? Anyone? You don't have any comments? Let's then put it up for a vote. Does the committee concur in principle with a true quarantine hold for an infectivity window period? If you answer yes to this, then the question, I presume, would be, what would they recommend as a minimum quarantine period for release of previously donated units of fresh frozen plasma? So, the first part of it then has to do with does the committee concern in principle with a true quarantine hold for an infectivity window period?

All those that are in agreement with the question, raise your hand.

[Show of hands]

All those opposed?

[No response]

Abstaining?

[No response]

Dr. Buchholz?

DR. BUCHHOLZ: Concur.

DR. SMALLWOOD: The results of voting for the first part of the question, does the committee concur in principle with the true quarantine hold for the infectivity window period, and this is for fresh frozen plasma, donor retested --

DR. HOLLINGER: Delayed release.

DR. SMALLWOOD: The results of the voting, 12 yes votes. There were no no votes; no abstentions. The industry representative agreed with the yes votes.

DR. HOLLINGER: The second part of the question has to do with the minimum quarantine period for release of previously donated units of fresh frozen plasma. Comments? We have to have some time -- 90 days. This is not a yes or no question.

DR. BUCHHOLZ: Could I just be clear that this is being presented as an option, and not as this will be mandated, which I think might be an important distinction to make.

DR. HOLLINGER: So, some discussion. I think we

recognize that on several window periods we have seen there is a certain percentage of window period samples that will be beyond that period of time, a small percentage, perhaps 5%, less than that, but a certain small percentage. Yes, Dr. Mitchell?

DR. MITCHELL: Yes, I would agree with the 90-day proposal. Although there is a small percentage of samples that would convert past the 90-day period, I think that from the presentations yesterday about the shorter window period or the period to infectivity, it appears to be much shorter, and even those that become positive, test positive later, it appears that the period of infectivity is closer to the time of testing positive. So, therefore, the window period would, in fact, be shorter. So, I would feel very comfortable in supporting a 90-day period.

DR. KOERPER: Let e be sure I am clear on this. This is a minimum hold of 90 days. So, if the donor returns in 60 days, that doesn't count. If a donor returns any time after 90 days and is retested, then his unit could be released. He may not return until 240 days, in which case the plasma could potentially be held that long and then be tested and released. So, we are talking about a minimum hold of 90 days, not a maximum hold. So, I would concur with the 90 days.

DR. MCCURDY: I wonder if you might want to phrase it

as some confidence limit of the best estimate of the window period as of the present time. Right now, I think 90 days is reasonably close to that but I think within a year perhaps there will be pooled testing for hepatitis C RNA, which is the longest of the bunch, and the 90% confidence limits might go down, and at some time after that there is likely to be single donor unit testing using automated systems of one sort or another, and that might further drop the window period. If you put it in terms of confidence limits of the best current estimate, I think the FDA and their biostatisticians probably can look at the data and come up with an acceptable change if, indeed, it seems right.

MR. DUBIN: I agree with Dr. McCurdy. It builds in flexibility. It is the best estimate that we have seen and heard over recent days, and it also gives FDA staff the opportunity to be flexible with it. My kind of last comment is echoing your comment about we have seen enough windows. It is interesting to see the plasma wars play our right here.

DR. HOLLINGER: Do we have any information about the samples that had a delayed -- I mean, often a delayed seroconversion is related to the volume or the concentration of the virus the person gets in the first place, but there could be other things in other units that might make a

difference to that. But do we have any information about the concentration of virus that is reached in those individuals who have a delayed onset? Some had occurred after 90 days. What has been the pattern in those two patients particularly? What was the pattern of HCV RNA that developed? Was it slowly developed or rapidly developed? Did it go to the same levels, or what?

DR. BUSCH: Well, there is HCV and there is HIV. With HCV, the evidence, interestingly, is quite consistence relative to whether a person acquired HCV from blood transfusion or community acquired sources. In talking to Dr. Prince, at New York Blood Center, apparently animal data showed that the inoculum size has nothing to do with the incubation period. In other words, the seroconverting plasma donors who were probably infected by standard community routes, as well as transfusion recipients, we had virtually an identical period of high titer viremia. So, with HCV it seems to be much more consistent. It was about a week or two weeks post exposure. There was nasty, high level viremia that persisted at very high levels throughout that one-month-plus, probably 40-day high titer viremia phase prior to antibody. Also, the distribution from time to exposure to seroconversion was much more consistent for HCV than for HIV.

It was HIV where we had this delay tail in those two

delayed cases of seroconversion in the healthcare workers. Again, in those cases there were not samples available prior to test back and determine how long these people were viremic at previous time points. Both those people did develop acute syndrome in the week before they were tested and seroconverted. In other studies the acute syndrome is associated with this burst of viremia. In two published cases of similar delayed seroconversion, where they did have samples available, the individuals were only viremic immediately prior to seroconversion. So the delay seems to be not associated with persistent viremia.

DR. HOLLINGER: So, again, the patients that had a longer window period, the people who had window periods after the 90 days -- say, we were going to choose that -- were there samples that were collected at the beginning in order to get that time, were they PCR positive --

DR. BUSCH: In the CDC study there are not samples. There are published reports of similar delayed seroconversions where samples were available, and all of the samples were negative by PCR until a several week period prior to seroconversion.

DR. HOLLINGER: So, these could actually be infections later on.

DR. BUSCH: Well, again, they were linked genetically to the source. It was a discrete needle stick. So, these

clearly were attributable to the exposure, but the suspicion is that they were not viremic until immediately prior to seroconversion. So, the virus was somehow being maintained in a very low level replication in the inoculation site or the draining lymphoid tissue, and they were almost certainly not infectious.

DR. HOLLINGER: But, of course, with sequences it depends on the genotype and other things.

DR. BUSCH: This is pretty rigorous. This is HIV envelope sequence --

DR. HOLLINGER: Okay. Thank you. That is helpful. Other questions regarding time periods?

DR. EPSTEIN: Blaine, if I could be permitted a comment? First, on this question we have chosen our words carefully. We said a quarantine hold for infectivity window period to address precisely the point that you are asking of Mike Busch, namely that the concern ought to be the time from infectivity to a marker.

Secondly, I think what would be helpful to the FDA is a sense from the committee whether it is enough to address a mean or a median window period as a basis for the quarantine, or whether we should be concerning ourselves with the upper confidence limits. If it is the upper confidence limits, is it 90% or 95% or 99%? Because, very clearly, there is a tradeoff here between approval criteria

which will make it practical to have these products linked to fairly short holds as opposed as a lack of practicality for very long holds. What we are playing with is a one-year dating, and that could be changed based on storage temperatures. But there fundamentally is this issue of longer periods providing increased confidence, but that these are marginal returns given the shape of the window period curve.

So, I think what we are really looking for is a sense of the committee, is a mean enough, or should we be looking at an upper confidence limit? And, if it is an upper confidence limit, where do we want to set ourselves? Is 90% adequate? And, that is against the background of what we feel is a reasonably safe product, namely FFP without a hold, and recognizing that no amount of hold is going to be perfect intervention. So, I think that is the framework in which Dr. Silverman presented. I think that is the context in which your remarks would be most helpful. You don't have to nail a date; you must have to give us a sense for what we are trying to achieve.

DR. MITCHELL: I believe, first of all, that this type of an approach, a quarantine and also selective donor, is the kind of thing to reduce the risk through selection of individuals who are at lower risk for having an infection in the first place. It is the type of an approach that should

be preferable.

I believe that the quarantine period should be an upper limit, probably in the range of 95-99% of the upper limit. I say that because I think it is important that we provide as much protection as possible. I don't think that 95-99% is unreasonable because it seemed to me from the presentations yesterday that most of the infectivity window period tends to be less than 60 days even for hepatitis C. So, I think that it would be reasonable for the 95-99%.

DR. STRONCEK: I think that if we are going to have a confidence interval that we will only catch half of the products it is probably not worth the trouble to do the quarantine. I think though that 90% would be adequate. I guess I heard Paul Holland -- I am not sure if I remember this right but I think Paul said that the 90-day quarantine that they are using in Sacramento would catch at least 90% of all window unit products, and I think it would be adequate.

I would be careful about arbitrarily saying 95 to 99. I would like to see that, but if that is going to create a situation where we have to hold plasma for 6 months and we only have 6 months to use it, we are not going to be able to have a practical system. So, I think 90% would be okay. But it might be nice if the FDA would come back with some modeling next time to show what each interval would mean as

far as a confidence interval hold on the plasma that would have to be held and what implication that would have for the supply.

DR. HOLLINGER: Do we have a confidence interval for HCV, not just the 90% you would capture but a confidence interval for that? Is Paul here? Well, anybody that would like to respond.

DR. HOLLAND: It depends on the virus, of course, and it depends upon the study. I think for HIV you have heard, at least for most of the cases except for the needle stick exposure, there were 2/50. So that exceeds your 95% confidence interval there.

For HCV, for the one series I showed you it was 94% for that series of 29. For Harvey Alter's series it would have been all of them when combined with ALT. So, that was 100%.

So it really depends upon the virus and what your criteria are. That is why I used the number of greater than 90%, and, again to emphasize, we are saying a minimum of 90 days. The odds are you are not going to get the donor back on the 90th day. The odds are you are going to start calling the donor on the 90th day and you will get him on the 100th day or the 120th day, or something like that. So, I really believe that it is sufficient to have the minimum 90 days.

DR. MITCHELL: Could I ask a question? Is that the

infectivity period?

DR. HOLLAND: I based my whole thing on the total window. I believe the actual infectivity period is really less. So, I am taking a very conservative approach. I am saying the total window period, which includes that eclipse period which for hepatitis C is at least 2 or 3 weeks, for HIV even a greater proportion of the total window. So I think it is a very conservative way to look at that with the 90 days.

DR. MITCHELL: Right, and that is why I am saying that if we have information about the 95% confidence interval for the infectivity period, I think that would be helpful.

DR. KLEINMAN: Just to echo what Paul has just said, it does depend on the virus. I guess Mike is going to show some HCV data which I think probably has the largest number of data points. But I would just like to mention HIV and hepatitis B. For HIV, the data on blood donors was derived in a way in which 95% confidence -- there are a number of statistical manipulations. I am not sure that you can directly calculate 95% confidence intervals, but clearly there are a lot of data points and the range is relatively narrow and, certainly, we know the infectivity period is not very long. So, i am sure 95% confidence would not exceed a matter of 30 or 40 days for infectivity.

But for hepatitis B there just isn't very much data. I

mean, the window period estimate of 56 days is based on 7 cases. I think a 95% confidence interval is worthless there. So, I think you just have to be careful. If you attach for each virus confidence intervals, you have to recognize that there are some limitations for B.

DR. HOLLINGER: Thank you. Yes, Dr. Busch?

DR. BUSCH: I think with both HIV and HBV we have antigen assays, and the viremia prior to antigenemia is really quite brief, as we discussed yesterday. If you look not at the exposure data but at the extensive accruing work on duration of detectable viremia prior to antigenemia, it is really very consistent, very brief and diminishing in levels. With HCV, for which we don't have an antigen test, we have this very prolonged viremia.

[Slide]

This slide summarizes the distribution of time from transfusion to elevated ALT. We talked yesterday about the problem to seroconversion but we do ALT testing still. So, perhaps this is appropriate. This does include the exposure to seroconversion. So, you could probably subtract a couple of weeks from this because it takes a couple of weeks from exposure to viremia, and this is 113 cases so it is a pretty good population distribution.

You can see that at 90 days you are probably catching 95% of these cases from exposure to elevated ALT. If you

were to back a couple of weeks from that for viremia, really I think you would be very safe.

DR. HOLLINGER: Thank you, Mike. Could you put up the question again, please? So, I suspect we could ask the question or at least take a vote on whether the committee recommends as a minimum quarantine period a level that exceeds 95% confidence intervals for the window period for a particular agent. We could start with something and have a vote on it, and see where we go. Does anybody want to make a comment first? Yes, Paul?

DR. MCCURDY: I still think that on the basis of those available data for hepatitis C, which has almost certainly the longest incubation period, you could say 95% confidence limits, if that is what the committee believes, and then let additional data with new tests come along that show that it is shorter and safer to do it for a shorter period, and we don't have to have this discussion again in a year.

[Laughter]

DR. HOLLINGER: All those in favor of that modification of the question, raise your hand.

[Show of hands]

All those opposed?

[No response]

Abstaining?

[No response]

Dr. Buchholz?

DR. BUCHHOLZ: Concur.

DR. SMALLWOOD: The question has been modified to identify a 95% confidence interval. The committee has voted unanimously to agree with this modification. There were 12 yes votes; none no votes and no abstentions. The industry representative agreed with the yes votes.

DR. HOLLINGER: Okay, we will go to the next question, please. Does the committee agree that pooled plasma solvent detergent-treated and fresh frozen plasma, donor retested, are acceptable alternatives for those indications held in common, or to be held in common between the two products? I would like to open this up for discussion. Yes, Dr. Holmberg?

DR. HOLMBERG: Doe the VITEX people have any comments about the toxicity in pediatric patients?

DR. GROSSBERG: Howard Grossberg, with VITEX. In our clinical trials we have had about 20 kids treated -- I think there were 21 pediatric patients and 2 neonates -- no signs of toxicity; many of these patients were transfused multiple times. If we look at the European experience, in Norway, where solvent detergent is the only plasma available for transfusion. They have used in the pediatric cardiology service and there has been no evidence of any undue toxicity. We don't think there is any toxicity in

pediatrics or in massively transfused patients, which is the other 7 patients that we looked at. Of those patients getting more than 2 plasma volumes in exchange, there were 100 such patients looked at in France, with no evidence of any toxicity. So, we are quite comfortable with the toxicity profile.

DR. MITCHELL: I also have a question, and you may have answered it. My question was how much of the solvent plasma remains in the solution after it has been treated?

DR. HOROWITZ: In anticipation of that question, I called our quality control people this morning. To date, 19 lots have been made, fully passing all QC specifications. Our QC specifications for TMBP is 3 ppm and for and for TRITON N-100 is 3 ppm. The use concentration is 10,000 ppm. So it is well below the use concentration. Seventeen of the 19 lots were undetectable with respect to both TMBP and TRITON. That means less than 2 ppm for TMBP and 1 ppm for TRITON, and 2 of the lots had 1 more ppm than that. So, 17/19 were undetectable and each of 1 lots had 1 more ppm, just barely detectable.

DR. VYAS: On reflecting on the opinion of Stanley Prusiner that any pooled product has higher risk than single donor product, and when you prepare 2500 donor products, the risk is tremendously amplified for advantageous agents and well as for CJD, and I am quoting Stanley Prusiner.

DR. HOLLINGER: I guess the question from that would be whether there is a risk for CJD.

DR. VYAS: I think the risk is unknown. The rationale for withdrawal of the intravenous immune globulins or immune globulins in general will hold true for this product as well. That is my concern.

DR. HOLLINGER: I would like to get a feeling of the committee a little bit about Dr. Horowitz's single line which said that solvent detergent was safer than fresh frozen plasma, delayed release, which is safer than fresh frozen plasma. What does the group think? What is the feeling? Do you have thoughts about it, taking all the things into account that you have looked at? Is there a feeling among the group or do you think that they are comparable? Yes, Dr. Koerper?

DR. KOERPER: Well, I don't dispute Dr. Horowitz's data on the lipid envelope viruses, and I agree with it completely. It has been shown in hemophiliacs and other groups that solvent detergent does kill those viruses. But it doesn't kill other viruses, and it doesn't kill other agents that we don't even know about yet.

I feel like we are looking at HIV revisited. Hemophiliacs who were treated with cryoprecipitated in the early 1980s, even in San Francisco where we had a high rate of HIV infections, the rate of HIV in those patients in

those patients treated with single donor units of cryo was 50% compared with the hemophiliacs who were treated with pooled plasma products of 95%. Therefore, I don't feel comfortable with going to a pooled product when we have a product like FFP that is a single donor product, and that is exceedingly safe at this time.

DR. HOLLINGER: Thank you.

DR. STRONCEK: Well, I share the concern about the pooled product. On the other hand, I think the solvent detergent FFP is safer than single donor FFP. I feel uncomfortable just offering plain FFP, the way we offer it, if solvent detergent pooled product is available. I think though that the quarantined or even the repeat donor FFP would be a reasonable alternative, and we just don't know at this time, in the long run, which of these three alternatives will be better.

DR. HOLLINGER: Could I get some information from someone in the audience? Most of the data that we are dealing with here in terms of risk has to do with people who have gotten whole blood. That is where most of the risk is. Now we are talking about fresh frozen plasma. That is a different group of people, and they may be sicker; they may not live as long. Some of the numbers that we have to put together may be less important. What is the denominator of people that receive fresh frozen plasma in this country? I

mean, if we look at whole blood, it has been reported -- what? -- four million people receive whole blood, and perhaps around 3.5 units or so, 4 units a person? Those numbers may not be totally accurate, but some number like that. Can somebody give me some feeling about fresh frozen plasma? The ones where I use fresh frozen plasma are really sick people that are probably not going to live very long. They are people with liver disease, people with DIC and other things. That impacts a little bit about the potential of worrying about somebody getting a disease that is going to take 15, 20 years to cause a problem. I am now talking mostly about HCV. There are a lot of factors there. We have to take into account the percent that are going to become chronically infected. Then you have to take into account the ones that are actually going to get cirrhoses. Even with whole blood, these numbers can get down to maybe two or six a year -- small numbers at the present time. I need to sort of get a feeling for fresh frozen plasma. Paul?

DR. HOLLAND: Yes, I will make two points. One, you have heard from data that most patients who get fresh frozen plasma, at least from one study at a large university hospital, 97% or people who got fresh frozen plasma also got other blood units. They got blood; they got packed cells. So, relatively few patients get only fresh frozen plasma.

There is, however, one group that gets a lot and they get it almost exclusively, and these are patients that undergo plasma exchanges for thrombotic thrombocytopenic purpura or the childhood equivalent, hemolytic uremic syndrome, or the combination of the two. These patients will get liters and liters of this material for days and days, and weeks, and sometimes months. They get exposed to a huge amount of this material, and they get it almost exclusively. So, I actually think a lot of the plasma, the 2.4 million units we are using a year, actually go to relatively few patients. They go to heavily transfused patients who either get many other cellular components or heavily plasma infused patients who get almost exclusively, if not only fresh frozen plasma.

DR. HOLLINGER: But do we know the numbers?

DR. HOLLAND: We don't know the numbers. Maybe somebody behind me has the numbers; I don't know the numbers.

DR. HOLLINGER: We are trying to make some decisions here about risk, and risk has to do not just -- I mean, who cares if you get hepatitis B if you don't become chronically infected, and the rate of fulminant hepatitis is extremely low. The rate of chronicity in immunocompetent patients is extremely low. So, sometimes we sort of forget a little bit about these things and worry about getting a disease that may not have any relevance whatsoever. So, I think we need

some numbers. Steve, do you want to comment?

DR. KLEINMAN: Back to your previous issue about the risk of the two products, and I want to express my personal view now, and that is that you are betting on an unknown event. If that unknown event is lipid envelope virus that enters the blood supply in the future, it would have been better to get solvent detergent plasma at that point because that lipid envelope virus would be destroyed and your risk would be zero. If you got the non-treated plasma, donor retested, that new lipid envelope virus could infect the recipient of that plasma.

On the other hand, if it is a non-lipid envelope virus or a prion, if those turn out to be transmissible, that enters the blood supply, then if you give donor retested plasma one recipient gets expose. If you get the pooled product, 2500 units going in and 2500 units going out may be transfused to 500 patients I don't know -- an average of 5 units per patient, then 500 patients get exposed.

So, they are both theoretical risks with theoretical outcomes. To me, I guess, the decision goes on weighting those two possibilities in the future. It may be that the new agent has less than 100% transmissibility because of protective antibody we don't know. So, if there are no new agents entering the blood supply, then clearly solvent detergent plasma is safer than any other alternative. But

if there are new or unrecognized agents, then I think the framework is to think of those two possibilities and decide which one represents the situation you want to avoid.

DR. HOLLINGER: Thank you. Dr. Alter, do you want to tell us if you were misquoted or quoted correctly, or do you want to make another quote?

DR. ALTER: First, I don't want to go to a meeting without saying anything.

[Laughter]

Secondly, Steve gave me the option of going ahead of him and I said no, but he just said everything I was going to say.

[Laughter]

But I don't remember saying what I was quoted as saying but I probably said it.

[Laughter]

And I agree with myself --

[Laughter]

-- but Bernie made a very potent point today. Although I have been very fearful going from an almost safe product into a pooled product which has a theoretical scary point, the same point that Steve just made, I have a great fear of doing that should a new agent emerge and we are suddenly faced with the same fear that the hemophilia people have had. On the other hand, Bernie made a very potent point in

that if we look at our history, our history is that the deferred testing would have had no benefit for HIV because we had no test. It would have had no benefit for HCV where solvent detergent basically would have prevented all those cases. So, given our history, solvent detergent is a better method than the deferred testing process, but what we don't know is the future. That is the point that Steve Kleinman made. We are betting whether the next agent is going to be inactivatable or not. If it is not, we have hit a disaster; if it is, we are safe. So, that is the argument and nobody knows that answer. So, I think people have to make their own judgments and I think it is good to have both options available.

DR. HOLLINGER: Thank you, Harvey. Yes, please?

DR. TANKERSLY: Dr. Tankersly. I just want to make one quick comment.

DR. HOLLINGER: Yes, Don?

DR. TANKERSLY: That is, the fear of pooling -- it really is immaterial if the product is pooled in a tank and virally inactivated or whether it is pooled in a patient, and if, for example, a TTP patient receives many, many units of individual fresh frozen plasma, unless they are from a dedicated donor, that donor is also going to have this increased risk of exposure as well. So, the factor is probably much less than 1 in 2500, if that is the pool size.

DR. KOERPER: Another group of patients that receives FFP repeatedly -- speaking from a pediatric perspective -- is children with clotting factor deficiencies for which we don't have a treated product, such as Factor V deficiency, etc. Those children receive plasma products once or twice a week, depending on their factor level and how much it takes to prophylax them. If each time they are treated it is with a pooled product of 2500 donors, and then 4 days later they get another pool of 2500 different donors, and 4 days later another pool of 2500 different donors, the donor exposure increases exponentially. That is why I just cannot support this. Also, we don't know that the next agent is going to be a lipid enveloped virus that would be eliminated by solvent detergent treatment. So, again, I am fearful of this issue or this notion that pooling is not increasing the exposure risk.

MR. DUBIN: Well, I appreciate your comments, and that is part of what I wanted to say next because in response to what you asked, Blaine, these are young patients who have a fairly good outlook for a fairly lengthy existence and HCV is a serious issue for them.

I also appreciated your comments, in the 1980s, had we all been warned earlier, many of us would have chosen cryoprecipitate. Some of us had big enough families to choose donors -- there was a whole series of options that

could have been presented which would have greatly changed the equation.

And a side bar to Dr. Horowitz, had you guys been subjected to product liability, solvent detergent would have come on-line earlier, Bernie, and that is our opinion. But that is a side bar to a comment you made up there.

But more important than that, what I want to say is I sit here sometimes and I am awed by the level that we have attained. I mean, when Dr. Busch gets up there and demonstrates what we know about HCV, this is incredible stuff. You know, for someone who is not trained like a lot of you, and in a medical school environment, constantly surrounded by people who have that level, I am struck by how incredible it is that we have made this progress.

But I think there is another side to this that comes from us. I think we accept this wonderful progress but we kind of focus, and we keep celebrating the fact that HIV, HCV, HBV -- we have made all these grounds but I see on most of the issues we talk about, that is what we are focused on, and we got hit once before by something nobody saw coming. It feels like Murphy's law in some way, from our perspective, we are going to get hit again, meaning us i the bigger "us". If that hit is a non-lipid envelope virus we have a real problem on our hands. We are talking about having to damage control so we don't end up with another

10,000 casualties.

I think that is what the Institute of Medicine report pointed out; that is the changes we have tried to make in the committee, and what FDA is really trying to move towards. And, I don't want to forget that in this kind of enjoyment of the progress, and I don't want to downplay the progress for a moment because it is really phenomenal what we are able to put on the screen and understand about hepatitis and HIV. But I don't want to lose that focus, and I am very concerned. Those are the patients I was going to identify because they do have a potential good life, and we are at 95% in severe hemophilia for HCV. In fact, I think once the AIDS epidemic plays out more you will see HCV again be the lead killer of people with severe hemophilia, which we approached in the mid-1970s. I think it is important that we understand that there are still things that even in all of our advanced knowledge that can hit us up the side of the head. So, I share your concerns especially about those patients being put on a pooled product.

DR. LINDEN: Actually, I have a question for Dr. Alter. I am also very nervous about the whole concept of using a pooled product when it isn't necessary, and I heard some conflicting statements by the speakers. I am concerned about hepatitis A, since we know there has been transmission from solvent detergent products, and Dr. Horowitz sort of

said there is going to be protective antibodies, and Dr. Holland said, no, these antibodies aren't really going to be protective. What is your opinion on the hepatitis A question?

DR. ALTER: I am not sure I have one. I mean, we use immunoglobulin for hepatitis A. We have used it for many years, knowing, however, that it attenuated infection; it doesn't prevent infection. So, in that sense, Paul's data is not totally surprising, that even though you can demonstrate large amounts of antibody it might not be totally neutralizing. Therefore, one could get infected. You would expect infection to be mild and very transient, but it looks like there have been some cases where it was more than that.

DR. LINDEN: Thank you.

DR. PEHTA: I am Joan Pehta, from VITEX. Just a comment on the recipients who would receive a product from 2500 donors and then the next day product from a different 2500 donors, it is a lot released product. So, the likelihood of different lots being infused into the patient on different days decreases because it is a lot released product.

DR. KOERPER: But when you factor that over a lifetime, it is 2500 to whatever X.

DR. HOLLINGER: Yes, Dr. Busch?

DR. BUSCH: Just one comment, coming back to my suggestion of collecting FFP from multiple repeat donors, I think we have seen historically that as new agents have become appreciated, their prevalence, when we are dealing with a new agent that hasn't been screened for, is much higher in the same groups who have always been infected. If we can focus our collections on safer donors, I think that will have an impact on unknown agents downstream as well as the known agents through reduction in the window period.

DR. HOLLINGER: When you look at people who are seroconverting even in the plasma group, you wonder. I mean, here are people who are coming frequently and, yet, we are finding that they are seroconverting to HIV, HCV or something. So, there is something missing in those individuals who are being asked questions presumably each time they come in and donate. The ones who are getting the disease are, clearly, high risk --

DR. BUSCH: Right, they are getting infected through risk exposure --

DR. HOLLINGER: Sure.

DR. BUSCH: What we haven't seen in the plasma sector is the rates among first-time donors --

DR. HOLLINGER: Yes.

DR. BUSCH: In the blood sector we can clearly show the drop in risk factors as well as incidence associated with

conversion from a first time to a repeat and serially in repeat donations.

DR. HOLLINGER: Thank you. Steve?

DR. KLEINMAN: Just to follow up on Mike's comment and point out to the committee again the difference between what we might be able to accomplish for FFP versus red cell or platelet transfusion, FFP really is made from approximately 20% of the units we collect right now to support the transfusion support. Therefore, within the range of acceptable donors because we obviously do screen everyone, and if you don't meet the acceptability criteria you can't donate whole blood. So, there is no red cell, platelet of plasma. But within the range of acceptable donors, the strategy is to pick up people who have characteristics that suggest they are less likely to get window period infection than the general blood donor population. Since we are only trying to pick out a fraction of those people, maybe 30%, 40%, 50%, to be the pool from which to make the 20% FFP, I think it is doable. I don't know how logistically difficult it would be, but we can gain an additional margin of safety by donor selection criteria within the realm of donors who have already gone through the eligibility criteria and passed.

MR. GILSHER: Ron Gilsher, Oklahoma Blood Institute. First a question to Dr. Horowitz and then a comment. The

first question relates to a statement that was made to me recently by a physician in France, who told me that the pool size for the SD plasma is significantly smaller than the 2500 pool size here, in the United States. Is that true? I was told that it was 500.

DR. HOROWITZ: There are three manufacturing sites in Europe, and the determination of pool size differs among those three sites. You are correct, the pool size in France is smaller. They limit themselves to pheresis plasma and approximately 100 donors. With respect to both Germany and Austria for the other two sites, they are essentially the same as we are.

MR. GILSHER: Thank you. That could reflect on some of the rates of infections, either positively or negatively.

The second comment that I wanted to make is, in fact, with respect to having a different kind of FFP. Our blood center, as I think some in this room are aware, has utilized fresh frozen plasma by apheresis technology for over 10 years. What I want to point out, especially to Mr. Lamb, is that when we look at the amount of FFP required, we can reduce that by a factor of 1/3 because the product that we collect for transfusion purposes is equal to 3 of the whole blood derived. So, in fact, it is doable and we are, in fact, doing it.

The donor pool happens also to be a pedigree donor

pool, that is, only donors who are frequent repeat. So, when you look at prevalent infections which would be first-time donor against incidence infections which would be seroconversion, the rate in that pool is less than 1/100th of what we see in our first-time donors. We have looked at that, and that would be a donor who is out at 6 donations or longer, really fitting very nicely with the data that Dr. Busch reported.

DR. HOLLINGER: Thank you. I am going to bring this question then to the committee to vote on. The question, again, is does the committee agree that pooled plasma, solvent detergent treated, and fresh frozen plasma, donor retested, are acceptable alternatives for those indications that are held in common, or to be held in common between the two products? Yes, please, Dr. Mitchell.

DR. MITCHELL: I guess another question is whether we want to talk about fresh frozen plasma as a viable alternative. Do we want to add that as part of the question?

DR. HOLLINGER: I think we will hold it back for right now. Yes?

DR. HOLMBERG: Also, we have heard a lot about the repeat donor. So, here we are only talking about the two products. I also look at this question and, you know, acceptable alternatives for the indications, I mean, are we

talking about the indication of use? It still is a clinician's decision what product he or she uses. So, you know, competition may be good and a clinician may choose not to use the solvent detergent because of the pool effect here. I am uneasy about the way it is worded.

DR. HOLLINGER: Help me out a little bit here, Jay. My understanding is that the solvent detergent is a licensed product -- it is not licensed yet? Okay. Well, then that is an issue. But if it will be, then it can be used. So the issue then is whether one feels that the fresh frozen plasma, donor retested, is an acceptable alternative. I think that is the way I sort of viewed this as a question here, whether either one could be used, and they both have their advantages and disadvantages as has been discussed here today. Many of the questions and concerns are theoretical but potential, and one should not downplay those in any way. But that is sort of the way I see the question. Right now we just don't have enough information yet in this country, although there is some information from outside. Yes, Paul?

DR. MCCURDY: I would like to make a couple of comments. I almost decided not to, but one of them is that 2500 donors in a pool is considerably different than 60,000 or 100,000 or 400,000 which are some of the larger pools we have heard about from one source or another. This is a

significant improvement, I think, in those areas. It should not be too difficult for the user that is going to be using this over a relatively short period of time to watch lots and be sure that they get the same lot. Unfortunately perhaps, these products are dispensed from pharmacies who are apparently not used to keeping track of lots the way blood banks are. Each unit, of course, is a separate lot.

None of these products we are talking about have absolute safety. They all have problems. My own feeling is that they are alternatives. They are alternatives don't solve all of our problems, but I think they do provide some improvement in safety over simple fresh frozen plasma the way it has been done for four years, or whatever.

DR. HOLLINGER: And I would clearly agree with that last statement, yes. You have the question posed, all those that are in favor, in agreement with the question, raise your hand.

DR. KOERPER: Excuse me, can I point out that you are asking us to vote all or nothing? You are asking us to vote on both of these products or none of these products. There are some of us who could vote in favor of one of the two products, and I would like to propose that you separate the vote.

DR. HOLLINGER: Jay?

DR. EPSTEIN: I think the confusion that is arising

here is we are not asking you whether each of these products is licensable. FFP is, after all, licensed and the addition of a quarantine could only be seen as extending an existing product label. Furthermore, with respect to the solvent detergent plasma, the question whether we should ever consider it for licensure was dealt with, I think, more than a year ago through extensive scientific workshops and a meeting of the BPAC, and there was closure reached that it was licensable.

What we are now asking is whether FDA, as a regulatory agency, should be taking a position on relative indications or preference in use. We are suggesting that the FDA, in looking at this issue, has decided that it should remain neutral on that point, and by approving each of its products with its label for similar indications, simply leave it up to treaters to decide which they prefer based on their knowledge of the relative risks and benefits. So, we are really asking do you agree with FDA that FDA should stay out of the arena of superiority claims with respect to these products, and that we should stay out of the arena of deciding that either of them is not licensable. Should we simply make them available for clinicians to choose based on accurate labeling? That is what we are asking you.

DR. HOLLINGER: So, I would like to go ahead and vote on the question as it is stated right now. If the question

doesn't pass, then we will go to another vote. So, the question is does the committee agree, as Jay has said, that these are alternatives that could be accepted by physicians out in practice at the present time, with our present knowledge, for the indications that are held in common, or to be held in common between the two products? All those that agree with that, raise your hand.

[Show of hands]

All those opposed?

[Show of hands]

Abstaining?

[No response]

DR. HOLLINGER: Dr. Buchholz?

DR. BUCHHOLZ: I have to disqualify myself from voting since I am actively involved in clinical trial testing of various agents that are single unit viral inactivation. So, I will abstain.

DR. HOLLINGER: If you would like to, I think you need to put in something about your feelings at this time because I think that should be registered in the minutes.

DR. BUCHHOLZ: I wouldn't want to.

DR. KOERPER: As I stated before, my concern is with the donor exposure with the pooled product. I think there are other methodologies that are being developed that will allow for viral attenuation of individual donated units of

plasma. My concern, when someone stated that the clinician can choose, is that there is no guarantee that my local blood bank, for instance, is going to make all three products available. My blood bank may say, okay, we are going to ship all of our plasma off and it is all going to come back as solvent detergent treated and, therefore, I don't have a choice. The choice is out there but it may not be at my particular hospital.

DR. HOLLINGER: That is a good point. Anybody have a thought on that, of how this might play out? Are blood banks going to have available various products or not?

MR. LAMB: The current plan for distribution -- the American Red Cross has an agreement with VITEX where it will be providing the plasma to VITEX and the product will be returned back to us. We have a commitment to make it available to all blood centers, and the presumption is that they will decide and what volume they would like, over what period of time, and so we are not in any way trying to restrict choice, but it would be available to all blood banks in the United States.

DR. HOLLINGER: Okay. Dr. Katz?

DR. KATZ: I will tell you what I am doing at my blood center, and I think some of my friends in the audience would agree I am not too far out on the edge so I suspect it is pretty similar to what other centers are going to do, at

least among the independents. We are talking to our hospitals. We are talking to the heavy plasma users and asking them what they want. Here are the two alternatives, actually three products that will be available. Tell us what you are going to use under what circumstances so we can plan inventory, and it is our intention to have what the clinicians ask for.

DR. HOLLINGER: Thank you.

DR. HOLMBERG: I would just add I think that is the beauty of this country, that we have a pluristic blood approach.

DR. HOLLINGER: Yes, final comment.

MR. DUBIN: I want to ditto what you were saying. I don't want to be repetitive but I do want to say that we were subjected in the '80s many times to various treatment centers saying this is our product right now; this is what you are going to use.

I think what you said, Jay, presupposes that clinicians are well educated always about the products. That is certainly not our history, and we see clinicians at varying degrees of understanding. When you are talking about pooled products and risk, we see a lot of clinicians that don't understand all that still in small communities, treating people with hemophilia, individual doctors.

So, I think what I want to close with is that there is

an awful lot of assumptions on the table about how this will play out that I want to raise serious questions about because I don't think those assumptions are necessarily correct, and I think that is the important thing that I want to leave it with.

DR. HOLLINGER: Thank you. Please, Linda?

DR. SMALLWOOD: The results of voting on the question, and I will just read it so it will be clear in the record, the question reads: does the committee agree that pooled plasma, solvent detergent treated, and fresh frozen plasma, donor retested, are acceptable alternatives for those indications held, or to be held in common between the two products? The results of voting were 9 yes votes, 3 no votes, no abstentions and the industry representative excused himself from comment.

DR. HOLLINGER: Thank you. The final presentations are on the FDA proposal for donor deferrals related to xenotransplantation. The presentation of information will be by Dr. Dayton.

FDA Proposal for Donor Deferrals

Related to Xenotransplantation

DR. DAYTON: I am Andrew Dayton, Division of Transfusion-Transmitted Diseases.

The topic of this talk is the deferral of xenotransplant recipients and their close contacts. This

talk is a summary of the December 17, 1997 meeting of the FDA subcommittee on xenotransplantation, and it is also a summary of a two-day HHS-sponsored workshop on developing U.S. public health policy in xenotransplantation, which was held in January of this year.

[Slide]

Let me start with a definition of xenotransplantation. It includes the transplantation of living cells or whole organs between species. It is important to point out that xenotransplantation includes materials that are encapsulated and/or used n ex vivo perfusion. I will go into what that means in a little while. Xenotransplantation does not include transplantation of non-living, processed biological products or materials from animals, such as porcine heart valves which are fixed with glutaraldehyde, for instance.

[Slide]

I have brought a couple of slides fro Kathy Zoon's presentation at the HHS workshop. This is to give you an idea of how xenotransplantation is basically regulated. Animal cells, tissues, and all organs intended for therapeutic use in humans are subject to regulation by the FDA under the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. Therefore, xenografts must be used under an IND application, and sponsors are encouraged to meet with the FDA staff in the pre-IND phase.

[Slide]

A notice and comment is being developed this year for the regulation of all xenotransplants as biologics. There are certain additional regulatory requirements of note which are going to focus on procurement and screening of animals which are used as donors. It is going to include discussing of issues post-transplant infectious disease monitoring of patients. It is also going to involve recommendations for archiving of biological specimens. This is going to be very important if something does happen and we have to go back and figure out what has happened. Also, it will involve participation in a national registry so that, again, if there should be a newly emerged pathogen which becomes a problem we should be well poised to do the epidemiology on it.

[Slide]

Let me give you a little idea of some of the current clinical trials in xenotransplantation, just the areas they basically cover. The donor species are mostly pig in a lot of the recent trials. Liver failure is being treated with hepatocytes, with whole liver transplants, with transgenic liver transplants. These are what is being planned.

Diabetes can be treated with implants of pancreatic islet cells. Neuronal cells are hoped to be transplanted successfully for Parkinson's and Huntington's chorea.

There are baboon bone marrow trials for HIV, and for refractory pain in terminal cancer, some cow cells are being encapsulated and implanted intrathecally. Not mentioned on this slide, but there have been maybe 150 pig skin grafts for burn victims.

[Slide]

Just to summarize some of the ethical considerations which are peculiar to xenotransplantation, xenotransplants have an obvious potential benefit to the recipients. The benefits are unproven for xenotransplantation but there is a severe shortage of donors for allotransplantations.

The risks to the recipient, though largely unknown, can be reasonably assumed by the recipient. This is the way traditionally play out in medicine but with xenotransplantation the risks to society and close contacts of the recipient are also unknown, but aren't readily assumable by the recipient under the standard practice of informed consent. So if I need a baboon heart transplant, sure, I can sign myself up for all of the consequences, but can I sign my spouse up or my children or co-workers?

So, as a corollary to this, informed consent will probably have to take a somewhat different form for xenotransplantation, and it may resemble a lifetime contract involving monitoring and possible quarantine.

[Slide]

It is useful, when addressing issues of xenotransplantation, to consider some notable categories of xenotransplants, and these, of course, are not mutually exclusive. They can be considered as either permanent, long term, which is what we would think of as a transplant heart that we hope will stay there for ever, or temporary, as a bridge pending allograft donation.

Another set of categories is to look at xenotransplants as being internal or external, and a typical example of external would be an ex vivo perfusion device. For example, Circe is a company that has an external perfusion device for liver failure and it consists of hepatocytes on the opposite side of a membrane barrier from the perfused blood. It can perfuse the blood through the equipment. It acts like a liver. So, that is an example of an external xenotransplant.

Finally, unencapsulated or encapsulated are the important categorizations. The unencapsulated, of course, we typically think of where you just stick cells or an organ right into a human. But the encapsulated ones maintain some kind of physical barrier between the graft and the host. Again, you can have an external encapsulated version such as the perfusion equipment I just described, or you can have internal encapsulated cells, such as the intrathecal implants I mentioned earlier, and those were cells used for

pain. A couple of companies have different encapsulation methodologies for pancreatic islet cells.

[Slide]

There are some particular differences between allotransplantation and xenotransplantation which, again, are worthy of note. As far as the transmission of infectious agents, the human spectrum of agents in allotransplantation is fairly well known at this point. That is not to say there are not new emerging agents, as we have all seen, but compared to the xenograft spectrum -- the human spectrum is fairly well understood but the xenograft spectrum is largely unknown. There are agents that are known to infect both species but much less is known about this situation.

In terms of supply and demand, the human demand vastly exceeds the supply. So, the allocation of human organs is really an allocation of a rare national resources. The xenograft supply may greatly exceed the demand. Presumably if we choose the donor correctly, we will have a very large source and supply won't be limiting.

Finally, in terms of effectiveness, it is known that human organ transplantation, allotransplantation works. It is not known if xenograft transplantation works.

[Slide]

There are theoretical issues which help illuminate the

general risks involved in xenotransplantation. Viral zoonoses may be more likely to occur in xenotransplantation of transgenic material than xenotransplantation or unmodified material. What I am referring to here is that there is a large body of work on making pigs, for instance, safer donors by transgenic methods.

If I can give you a little digression and give you an idea of the kinds of problems we could get into, the first problem you run into with a xenotransplant is hyperacute rejection. This is largely directed by complement fixing natural antibodies which are directed to a sugar on the surface of pig plasma membranes, alpha-gal, which is not present on human plasma membranes. Now, alpha-gal is absent in humans, as I said, and is present in pigs and most other non-primates. So, it depends on whether you are a New World or Old World monkey. Alpha-gal also is a target of retroviruses of other species. Our natural antibodies against alpha-gal gives a natural immunity to such retroviruses which bring the alpha-gal components with them. This natural immunity is a significant barrier, and there are retroviruses which can replicate in human cells but could never get past that barrier.

Now, pigs are being genetically modified to eliminate alpha-gal, or to reduce it by various methods, with the idea of eliminating hyperacute rejection. That is great for

inhibiting hyperacute rejection, but that is not good for inhibiting retroviruses.

To give you a related example, transgenic pigs express human complement regulators. As I mentioned, hyperacute rejection involves complement fixation. Transgenic pigs expressing human complement regulators, such as CD55, CD46 and CD59, are being designed to inhibit the hyperacute rejection, but you should note that CD46 is a human measles virus receptor, and human CD55 is the receptor for Echo and Coxsackie B viruses. So, if you are putting a graft into a human, well, you may be just begging for a new form of virus to emerge which can utilize these receptors in the pig and may be brought in by the graft and that could be devastating. So, there are a lot of very dangerous biology going on here.

Another major theoretical concern is that recipients of xenografts are immunosuppressed. So this is another phenomenon which begs the development of dangerous pathogens or new pathogens, if nothing else.

Finally, tissues in a xenograft situation are in prolonged and intimate contact. This is not necessarily true for the encapsulated versions of xenografts but we should remember that encapsulation systems can and do break down.

[Slide]

Again to address zenosoonoses of concern at a conceptual level, we should realize that there are agents that normally affect both organisms. I am particularly thinking of pigs and humans but basically humans and any other possible donor.

First, there is toxoplasmosis, and known agents can be readily detected by screening. You have to also worry about agents that are sufficiently similar to normal viruses that they can cross species barriers under favorable conditions. The perfect example of this would be pig endogenous retroviruses, the discovery of which really precipitated this discussion that we are having today. I will discuss that in a little bit more detail in a moment.

We also have to worry about opportunistic infections arising from immunosuppression, and the immunosuppression is likely to be severe for xenotransplantation and this can foster infection by normally non-pathogenic agents.

We have to be very worried about agents that can recombine with host agents, and I will mention a few examples of that in a minute. Finally, we have to worry about reactivation of latent agents in the graft that may lead to graft failure.

In fact, along these lines, I would like to point out a very interesting finding, presented by David Onions at the workshop, in January. At the end of this talk he showed an

electron micrograph of a dog tissue sample, and it was heavily infected with a virus that looked by electron microscopy to be very similar to African swine fever virus. It should be pointed out that the source of this, this dog, came from a veterinarian-monitored herd that had been closed for 20 years, and this agent had never been seen before in these dogs. It is still being researched as to what it is. And, it only appears when the dogs are treated with a particular anti-inflammatory agent. He didn't happen to mention which one. But this is a very stellar example of the dangers you can get into going into the unknown, as we are with xenotransplantation.

[Slide]

To give you some examples of cross species viruses, DNA viruses, for instance, canine parvovirus. Originally this was non-infectious in cats but since its original finding it has become mutated for greater infectivity in both dogs and cats.

Other cross species examples -- the herpesviruses are CMV, SA8, herpes B. In RNA viruses, influenza and here the reservoir is in wild birds. And, human and avian viruses can infect pigs and lead to gene reassortment. You have Ebola and Marburg if you really want to get paranoid.

[Slide]

Now, for retroviruses you have xenotropic murine

leukemia viruses, largely an experimental finding but they will infect human cells in tissue culture. Simian foamy virus is another retrovirus that can infect humans. SIV is a very good example of the kinds of problems you can get into. SIV has been introduced at least six times from Sooty Mangaby populations to humans to give you HIV-2.

In fact, this is a rather interesting case and what may be happening here is that SIV from Sooty Mangaby is fairly frequently infecting the human populations. In these regions of Africa many monkeys are kept as pets, much as we keep cats and dogs as house pets, and some of these strains of SIV that have been found in certain regions are very closely related to non-pathogenic strains of HIV-2 found in the same regions. It would seem that what happens in HIV-2 is that the normal introduction of SIV into the human populations is an HIV-2 which is non-pathogenic, and possibly by dirty needle practices these non-pathogenic HIV-2s have been transmitted from human to human, to human, and have subsequently become pathogenic.

On the other hand, HIV-1, which presumably comes from chimpanzees, it would seem that all of the direct transmissions there are probably pathogenic.

Finally, with pig endogenous retroviruses, it has been documented that they can infect human cells in tissue culture.

[Slide]

To briefly, in a sentence or two, summarize retrovirology, retroviral elements are present in all vertebrates. Recent proviruses, recent on an evolutionary time scale, which are not defective or at least for which there are non-defective members, and which still make virus have an erratic species distribution. They are absent in humans but they are present in many other vertebrates. A particular concern here are pigs, mice, cats -- I don't think we are thinking of pheasants as donors -- but baboons and others. And, it is not unusual for these recent proviruses to be able to infect cells of other species.

[Slide]

Now, the PERVs, or pig endogenous retroviruses, are probably recently introduced. There are about 20-30 copies of these in the pig genome. At least 4 different viruses have been described. I believe at least 2 of those are known to have replicative ability in human cells. Yes, these 2 subgroups can infect human cells in tissue culture. Generally, however, these experiments require prolonged intimate exposure of the tissues. Basically, it has to be done by co-culture. The pig viruses that get into the human cells are slowly replicating. They are not likely to be pathogenic via horizontal transmission, either via normal horizontal transmission, which is in everyday interactions,

or even in parenteral horizontal transmission.

[Slide]

In reference to the summary in the xenotransplantation advisory subcommittee meeting in December of last year, reports of PERV replication in human cells had caused a hold to be placed on xenotransplant trials until assays were instituted.

A major question is what assays are appropriate. The most advanced assays -- this is all being worked out as we speak and nothing is finalized, but the most advanced assays are RNA PCR and DNA PCR. Co-culture assays are also being devised.

Probably somewhat fewer than 200 patients have been exposed to pig xenotransplants. This would include about 150 pig skin transplants for burn victims. As of December, approximately 20% of these 200 have been tested for PERV and all those tested are so far negative. But, again, this is an emerging story. We haven't validated all the assays. We don't know how well they are working. They look good to begin with but we are still collecting data and figuring out what is going on.

[Slide]

To summarize, again, the same xenotransplantation advisory subcommittee meeting, there are many potential risks to recipients. The risks from PERV are probably

minimal to zero, almost certainly minimal to zero for both the patient and even less, if you can get less than zero, for the population.

There was a lack of a clear consensus on the correct course to take, but the general feeling was that trials should now proceed with caution, using careful monitoring. So, the numbers of patients which are soon going to be introduced into the population are not going to be huge, presumably, in the next couple of years.

Despite minimal risks, however, xenograft recipients and their close contacts should be deferred from giving blood, according to the committee. The logic was that if problems should develop -- it is unlikely they will develop but if they should develop, this is where it is going to be a disaster if you let it into the blood supply.

Current policy would be relevant and covers the small numbers of people in limited preliminary trials, and we should remember that the policy can certainly be modified or relaxed, if need be, at a future date if clinical practice advances to the point where large numbers of xenorecipients are represented in the potential donor population. I think it was clear that the xenograft transplant subcommittee recommended that we err on the side of caution.

So, that concludes what I have to say. What do we do? Do we have a reading of the questions?

DR. HOLLINGER: Yes, I would like to have the questions read and then we can open it up. There are two questions we have to deal with, one and two. We are going to ignore number three.

Presentation of Questions

DR. DAYTON: Number one, should the definition of close contacts of xenograft recipients include sexual partners and others with whom a participant participates in activities that result in intimate exchange of bodily fluids?

The second question is, should the definition of close contacts of xenograft recipients include household members not otherwise identified as participating in activities that result in intimate exchange of bodily fluids?

Committee Discussion and Recommendations

DR. STRONCEK: First of all, the first thing you said is theoretical, and I think based on that theory, we should defer recipients of xenotransplants. On the other hand, you know, speaking for donors, I have had a lot of contact with donors, not only blood but bone marrow donors, and donors feel like it is their right to donate. They like to donate. They gain satisfaction from donating. When I have arbitrarily had to tell them that either the FDA or the National Bone Marrow Program says that you can't donate, but it is for an arbitrary reason and there is no scientific data, people get upset and they feel that their life has

been affected for the worse.

So, I think it is wrong for us just to be arbitrary and say for just purely theoretical reasons contacts of xenograft transplant recipients can['t donate.

DR. MITCHELL: First of all, I have a question of the speaker about the number of people involved and the rate of increase in the number of people who have xenografts. Can you give me some sense of, for example, during last year about how many of these 200 people got xenografts?

DR. DAYTON: I don't know the exact history on the timing. I know that in the last couple of years there have been 200, and there are many different types. I would assume that in the upcoming clinical trials we are talking about the low hundreds. Maybe there is somebody else here who has that information.

DR. MITCHELL: Are you talking about maybe 100 a year, 200 a year, or something like that?

DR. DAYTON: I would think something like that in the next couple of years. I wouldn't expect to see it in the thousands.

DR. HOLLINGER: As you know, there is a real need. For example, I can tell you on the liver side the interest is growing for attempting to insert human genes into the eggs of pigs. Usually about 5/1000 times these are successful. Then they would be placed in the sow. The pigs, as they

would go on, there would be less problems of rejection in those particular pigs and, therefore, they could be used for liver transplants, for example. That is because in last year there were some 7,800 people who were on the transplant list. Only 3400 or 3500 transplants were done. Half the people on the transplant list died without receiving a liver. That is not going to get better. The supply is certainly not going to exceed the demand, and those numbers are just sort of escalating like that, the numbers of donors that we have and the numbers that are required. So, there is going to be real pressure, at least from that one standpoint alone, and that is part of the issue that one has to deal with here.

DR. LINDEN: I have a question about the implications of this. If we say yes, does that mean that the donor questionnaire is going to have to be amended so that you have to affirmatively ask have you ever had sex or lives with, whatever, with someone who has had something from an animal?

[Laughter]

That is my concern about what it is going to necessitate the blood banks doing in terms of donor questioning.

DR. DAYTON: Well, yes, there is going to have to be a question to that effect. Of course, that opens up all sorts

of issues about are you going to track down everything you want, and the answer is, no, you are not going to track down everything you want but you are going to have your best shot at it. The alternative would be not to ask the question.

DR. STRONCEK: Has FDA taken a position on household and sexual contacts of people who have gotten human gene therapy using retroviral vectors?

DR. DAYTON: I couldn't hear the question.

DR. STRONCEK: Have you thought about deferring people that have had contacts with people that have had gene therapy with retroviral vectors?

DR. DAYTON: I don't think we do. Again, with retroviral vectors, they are highly purified. You have to worry about the source. I don't actually know the answer to that.

DR. EPSTEIN: Well, the human retroviral vectors are designed so that they are not replication competent. In the studies that have been done, as you know, there has been monitoring to look for any reversions or recombinations but so far there have been none. So, it is not quite the same situation. We are dealing there with a very well defined agent in the transfection. Here what we are worried about are agents whose behavior we may not know, and we may not know what agent we are dealing with until some time later.

DR. DAYTON: You might have another mad cow disease or

something -- I mean, things can get so bizarre.

DR. KHABBAZ: I think it is not fair to compare it to the situation in the UK with variant CGD because your slide three here, actually, outlined very nicely the approach that is going to be taken and that xenotransplants in the next few years are going to be under IND, and there are some pretty well defined regulatory requirements. There is going to be a national registry for recipients, monitoring of patients -- yes, it is the unknown but we know quite a bit about viral and other infections of animals. So, there is going to be some close monitoring, and also the screening of animals, etc.

I think the question is not whether xenotransplant recipients can be donors. My understanding was that that is going to be deferred. It is the contact, and then how do we define contact? Do we want to go beyond the recipient to sexual contacts or more broadly? Isn't that the question?

DR. DAYTON: Yes. Certainly, that is in question two -- well, in both questions.

DR. HOLLINGER: Realizing that sexual transmission of hepatitis C is extremely low, at least in my opinion, are the blood banks excluding sexual contacts of patients with hepatitis C? And the answer is no. So, there we are dealing with at least a known potential risk, albeit low. That is an issue that was brought up last time. I think it

will obviously be up for discussion again in the future, but now we are talking about something much more potentially theoretical.

DR. KHABBAZ: And my comment regarding the U.K. situation, it was uncontrolled -- you know, it just happened, whereas, here it is being done quite a bit of regulatory scrutiny, appropriately so.

DR. DAYTON: I only referred to that as an example of how bizarre and unusual biological systems can be.

DR. HOLLINGER: Yes, Dr. Bianco?

DR. BIANCO: I would like to say something, but first I would like to request from FDA when such proposals come, if there was a little bit of notice we would have prepared some data and some statements about them that would be more sophisticated than what I am going to say now. So, we would love to have some advance notice.

I think there are two issues that I would like to consider. One, the donor questionnaire has about 35 questions, or something. In New York, actually, to make it easier we have combined them into about 20. But we ask the same things, we combine them in the same questions. We have 4 questions about CJD. Ultimately, when we look at the results that were published last February, a year ago February, from the REDS study on surveys of donors, that study showed that 1.9% of the people who responded would

have been deferred at the site of donation by the questions that they put in the survey. In part, this was interpreted because they were not comfortable, but in part I think they get confused. They have a lot of questions. We ask them, and there was discussion here, about behavior that they had 21 years ago when, really, the window that we are trying to focus on is a few weeks for certain behaviors that are high risk.

So, I would suggest that we don't make the questionnaire more complicated than it is. I think there is another approach that could achieve the same thing. It is very exciting for somebody to have a xenotransplant. It is something very important for the patient, for the family. What if it was part of informed consent, part of the whole discussion? The donor, his family, everybody should know that they should donate blood, that they should not do certain things because of the risks.

Your presentation was very illuminating. I learned a lot. But if we could focus on that instead of on a population focus that is very hard to achieve with the sensitivity and specificity that we desire in terms of the questionnaire. That is food for thought.

DR. DAYTON: If I could answer that, it is part of the informed consent.

DR. DODD: Roger Dodd, American Red Cross. I am sorry,

I wasn't really paying full attention to your presentation, but are recipients of xenotransplants advised to protect their sexual partners? Because, I mean, we are one step away from this --

DR. DAYTON: As far as I know, they are not told to, say, use condoms etc. But I may be wrong on that. Does somebody really have an answer to that? I know part of the informed consent is being careful about this sort of thing, but I don't know how far it goes actually.

DR. DODD: My point is that the sexual partner is far more at risk than the recipient is going to be, and we need to do this logically. I don['t think we should jump to blood recipients of sexual partners of somebody -- a further sexual partner and has a pig liver implanted. You know, if that really is a risk to the sexual partners and the sexual partners need to be protected --

DR. DAYTON: The regs on that are still being revised, I believe.

DR. DODD: Okay, thank you.

MR. DUBIN: It seems to me there are a couple of things out there. First of all, it sounded like they really didn't have a chance to prepare but Celso said something interesting and I would sure like to see what the informed consent looks like. Then Roger added something that I also think is important. If we see the informed consent we would

know if we are getting in front of ourselves. It doesn't seem like we are prepared to do this at this point.

DR. HOLLINGER: Any other comments?

MS. GREGORY: Kay Gregory, from AABB. I really just want to endorse Celso's comments as well. First of all, if we had a little advance warning we might have something more valuable to say and, secondly, we are concerned about the donor questionnaire and how complicated that is getting, and that needs careful attention.

DR. HOLLINGER: Thank you. Yes, Dr. Koerper?

DR. KOERPER: Given that we are feeling that we don't have complete information here, I would like to move that we table this discussion until the next meeting.

MR. DUBIN: I certainly second that motion.

DR. HOLLINGER: It has been moved and seconded that we table. Do we have questions? Yes, Dr. Mitchell?

DR. MITCHELL: The question is whether we will have more information at the next meeting. I am not sure that we will have much more information at the next meeting.

The other issue that I have is what is under consideration for xenotransplantation? Are the heart valves from pigs part of xenotransplantation? Should they be, or should they not be? It is a very complex issue but, again, I am not sure --

DR. DAYTON: Was there a question?

DR. MITCHELL: Well, there are two questions. One, are they considering having heart valve transplants from other animals considered under this xenotransplantation?

DR. DAYTON: If they are like the porcine heart valves, they are fixed in glutaraldehyde and they don't have any infectious agents -- they are dead.

DR. HOLLINGER: Is CJD destroyed by glutaraldehyde?

DR. DAYTON: I don't know. Do we have a CJD expert here? You can say theoretically it should be, but it doesn't mean anything until you actually have the data.

Xenograft recipients are clearly counseled not to donate blood or semen, or anything like that. That is clear.

DR. HOLLINGER: But I think the point that Dr. Bianco is making is, is the spouse counseled also not to have sex perhaps or that there is a potential risk of transmission?

DR. DAYTON: The spouses are counseled that there is a potential risk. I don't know if they are counseled to specifically have safe sex.

DR. HOLLINGER: Well, we have a motion to table for now for lack of information, and it was seconded. If there is no further discussion among the committee, I would like to put it to a vote. All those in favor of tabling this at this time, raise your hand.

[Show of hands]

All those opposed?

[One hand raised]

Would you like to make a comment?

DR. MITCHELL: Yes, I believe that this is a potentially serious issue. I believe that if we delay it -- let me see, I think that we should take precautions now. I believe if we delay it there is not going to be much information that we are going to be able to receive with which to make the decision, and so I think it should be made as soon as possible.

DR. HOLLINGER: I didn't ask Dr. Buchholz. Dr. Buchholz?

DR. BUCHHOLZ: Concur.

DR. SMALLWOOD: The results of voting to table response to these questions, there were 10 yes votes, 1 no vote and the industry rep agreed with the yes votes.

DR. HOLLINGER: Okay. I want to thank again the FDA, and the committee members for putting in a lot of time, and the people in the audience for this meeting. Dr. Epstein has a comment first.

DR. EPSTEIN: I would just like to draw the attention of the members to the fact that there was a draft guidance document placed in your mailer. Although we will commit to bring the issue back, I think it might be helpful if members had comments on the draft document, FDA would appreciate

receiving those.

DR. HOLLINGER: On the xenotransplantation?

DR. EPSTEIN: Right, on xenotransplant recipients and partner deferral. To address Dr. Bianco, as part of our good guidance practice, we will be making a proposal available for public comment.

DR. HOLLINGER: Thank you very much. The meeting is adjourned.

[Whereupon, at 3:17 p.m., the proceedings were concluded.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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