

BLOOD PRODUCTS ADVISORY COMMITTEE
CENTER FOR BIOLOGICS AND EVALUATION

Meeting Of:

BLOOD PRODUCTS ADVISORY COMMITTEE

(DAY ONE)

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P R O C E E D I N G S

(9:06 a.m.)

Agenda Item: Statement of Conflict of Interest

DR. SMALLWOOD: Good morning. Welcome to the 55th meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary of the committee. At this time, I will read the conflict of interest statement. This announcement is made a part of the record to preclude even the appearance of conflict of interest at this meeting of the Blood Products Advisory Committee on June 19 and 20, 1997. Pursuant to the authority granted under the committee charter, the director of the FDA Center for Biologics Evaluation and Research has appointed Paul R. McCurdy, M.D., and the lead Deputy Commissioner of Foods and Drugs has appointed Carmelita Tuazon, M.D., as temporary voting members.

Based on the agenda made available and all reported financial interests as of this date, it has been determined that all interest in firms regulated by the Center for Biologics Evaluation and Research, which have been reported by the participating members, present no potential for a conflict of interest at this meeting.

The following disclosures are presented: Dr. Charles August has an unpaid association with the Medical Advisory Board of the American Red Cross, South Florida

Division. The agency approved a waiver on June 11, 1996, for his association.

Mr. Benjamin Cheng*s employer has received an educational grant from two different regulated firms. Both grants are unrelated to the committee discussions. Mr. Corey Dubin has an agency-approved appearance determination on December 11, 1996, regarding a class action suit. Dr. Blaine Hollinger will serve as the acting chairman at this advisory committee. He had served as the principal investigator on an unrelated grant awarded by a regulated firm which could be affected by the general discussions. This has been determined not to present a conflict of interest.

Dr. Jerry Holmberg has an agency-approved appearance determination regarding the use of test kits from regulated firms in relation to his official government duties. Dr. Carol Kasper, in her capacity as the medical vice president, World Federation of Hemophilia, is responsible for organizing the 1997 annual meeting which involves soliciting regulated firms for financial support.

Dr. Rima Khabbaz* employer, the Center for Disease Control, Division of Viral and Rickettsial Diseases, has unrelated CRADAs with two firms which could be affected by the general discussions. Dr. William Martone is a federal

government employee detailed to the National Foundation for Infectious Diseases, a non-profit organization. The foundation receives grants and/or donations from regulated firms. The grants and donations are unrelated to the committee's discussions, and Dr. Martone receives no personal remuneration from these grants and/or donations.

Dr. Paul McCurdy is employed by the National Heart, Blood and Lung Institute. As a part of his official government duties, he reviewed proposals submitted to the cord blood program for the collection, process, storage, and transplant of cord blood stem cells from two firms that could be affected by the committee discussions.

Ms. Beatrice Pierce has reported that she spoke at the National Hemophilia Association and the Kentucky chapter of NHF. The agency approved a waiver on June 11, 1996, regarding her association with the NHF. In addition, the agency approved an appearance determination on December 14, 1996, regarding a class action suit.

Copies of all waiver statements addressed in this announcement are available by written request under the Freedom of Information Act. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the

participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

I would just like to make a few announcements before we begin. First, I would like to announce that the chairman of the committee, Dr. Scott Swisher, will not be in attendance due to illness, and Dr. Blaine Hollinger will be the acting chairman for this meeting. We also will have joining us Dr. Carmelita Tuazon, who is a member of the Microbiology Device Panel. Dr. Tuazon, would you raise your hand, please? Thank you. As mentioned, we have Dr. Paul McCurdy as a temporary voting member with us, as always, with our meetings.

At this point I would just like to again introduce to you the members of the committee so you will recognize where they are seated. Dr. Hollinger, would you raise your hand, please? The acting chairman for the day. To Dr. Hollinger's right is Dr. Rima Khabbaz, Dr. Charles August, Dr. Jane Piliavin, Dr. Jerry Holmberg, Dr. Susan Leitman, Mr. Benjamin Cheng, Dr. Paul McCurdy again, Dr. Paul Ness, Reverend Violet Little.

Beginning at the top of the table are Dr. Jeanne Linden, Dr. Joel Verter, Dr. William Martone, Ms. Beatrice Pierce.

I have been informed that Mr. Corey Dubin will be late attending the meeting today, and Dr. Kenrad Nelson, I assume, will be attending. He is just walking in the door now.

[Laughter.]

I would also like to announce that for the remainder of the year, we have tentatively scheduled two additional advisory committee meetings. Those tentative dates are September 18 and 19, 1997, and December 11 and 12, 1997. Please read the Federal Register and contact my office to confirm these dates and places.

Thank you.

At this time, I will turn the proceedings of the committee over to the acting chairman, Dr. Blaine Hollinger.

Agenda Item: Welcome and Opening Remarks

DR. HOLLINGER: Thank you, Linda.

I am not going to pretend to do the fine job that Scott Swisher always does here, but this is an excellent committee, and I have been told really that a chairman is sort of like a madame in a brothel; you are really there to keep

things moving but not to participate in the action. So that is what I am going to try to remember to do as the acting chairman for today and tomorrow.

The session today really is going to be on reclassification of medical devices. Apparently this committee can serve as a medical device panel and be assembled as such to look at making changes in the classification of certain medical devices, and this is, I think, probably new for many of the committee members. So it is going to be important for us to understand what they mean by classifications and reclassifications and so on. So with that in mind, we will go ahead and get started then. I think Leonard Wilson is going to begin by giving us an introduction and background to this reclassification.

**Agenda Item: Reclassification of Medical Devices
Used in Blood Collection and Processing and Donor Screening -
Introduction and Background**

MR. WILSON: Could I have the first slide?

Today*s presentation is directed at providing the committee with, one, background regarding medical device classification and, two, seeking recommendations regarding reclassification of a number of medical devices used in the manufacture of blood and blood products. This effort was

prompted from three sources.

Next slide.

First was the need to reassess the level of risk specific to medical devices based on new information. Secondly, the 510K review reengineering program that is ongoing at our sister agency, the Center for Devices and Radiologic Health, which is essentially reexamining how 510(K)s are reviewed, and CBER, Center for Biologics Evaluation and Research, is a full-time and active participant in this effort, and, three, the need to better allocate FDA*s review activity to those products where increased regulatory controls are needed to assure safety and effectiveness.

Next slide.

Medical device amendments of 1976 to the Federal Food, Drug and Cosmetic Act established a comprehensive system for the regulation of medical devices intended for human use. Regulations promulgated from these amendments, 21 CFR 800, applied to all medical devices. In FDA, most medical devices are regulated by the Centers for Devices and Radiologic Health. Based on the 1991 inter-center agreement, which designates product jurisdiction among FDA centers, those medical devices used in the manufacture of blood and blood products and other biologics are regulated by CBER, and that

means that CBER reviews the product submissions and handles other regulatory activities employing the same medical device regulations as CDRH.

In 21 CFR 860, classification of medical devices subpart J, there is a section entitled - subpart J is entitled "Products Used in Establishments that Manufacture Blood and Blood Products." In this subpart, 23 products are listed, including automated blood-typing equipment, blood warming devices, automated cell separators, blood bank centrifuges, refrigerators and freezers, among others. Each one of these products is classified into one or more of three categories or classes, depending on the regulatory controls needed to provide a reasonable assurance of their safety and effectiveness.

The three categories are - next slide - class I, requiring only general controls; class II, requiring special controls in addition to general controls; and class III, pre-market approval, requiring a pre-market approval from FDA prior to commercial distribution. Medical devices used in blood establishments were classified initially in 1980, after FDA received a recommendation from a device classification panel, such as this panel is now a device classification panel. It published the panel*s recommendation for comment,

along with proposed regulation classifying the device, and then published a final regulation classifying the device after comments were considered.

The next slide gives a typical listing that one would find in the CFR, and this is an example, 864, which is subpart J, a heat sealing device. A heat sealing device is a device intended for medical purposes that uses heat to seal plastic bags containing blood or blood components. How is it classified? Class I, general controls, and you can see the Federal Register notice and the date of that notice, September 12, 1980, which formally classified the device. So there are 23 of those listed in the CFR that are similar.

Now in determining safety and effectiveness, the device panel took into consideration the persons for whose use the device is intended, its conditions for use, its probable benefit to health weighted against the risk of use, and the reliability of the device. I want to also mention that in the area of blood donation and transfusion, reliability of the device can be an important factor as the blood availability is always on a very, very narrow time-frame, and when equipment has problems, that can have a substantial effect on the availability of the blood and blood components.

Now I would like to move into what the classes

actually mean. Products classified as class I require only general controls to provide a reasonable assurance of their safety and effectiveness. Such general controls consist of manufacturer registration with FDA, that they list the products with FDA, a pre-market notification, otherwise known as a 510K, filed with FDA, records and reports of the product established and maintained to reasonably assure that the device is not adulterated or misbranded, and maintain compliance with the quality system regulation in the manufacture of the product. Quality system regulation has recently been adopted as a sequel to what was formerly known as GNPs, and I will talk about that a little bit later.

Next slide.

An advisory panel that recommends that a device be class I can also recommend that a device be exempted from one or more of the general controls.

Can we go back one slide?

For example, a class I device that has a reasonable assurance of safety and effectiveness without filing a 510(K) with FDA may be exempted from filing that 510(K) but would still be obligated to comply with the remaining general controls, and the firm would still be subject to routine FDA inspections. An example of a class I device would be a blood

grouping viewing box. An example of a class I exempt device would be a thromboplastin generation test.

Next slide.

Products that are 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. Thus, in addition to general controls, special controls may consist of performance standards for a product, postmarketing surveillance, patient registries, development and dissemination of guidelines, recommendations, or other appropriate action to provide a reasonable assurance of the device's safety and effectiveness, without the need to file, which is the next level of regulatory control, a premarket application.

An example of a class II device would be an automated blood grouping system. In the case of cardiac pacemakers - could you leave that slide back up? - in the case of cardiac pacemakers, a patient registry is a special control. For today's proposed class II devices, FDA is proposing the development of a reviewer guidance, which would fit under category four, there, guidelines, as a special control for each of the proposed class II products, similar to

that which was published in April 1996 for blood establishment computer software.

Now, to round out the system, but not to get into it, because it is not part of this discussion, I just want to describe briefly what a class III device is. Products that are classified as class III are those that insufficient information exists to determine that the application of general controls are sufficient to provide a reasonable assurance of safety and effectiveness, and it cannot be classified as class II, because insufficient information to determine that special controls would provide a reasonable assurance of safety and effectiveness. In addition, the device is purported or represented to be for use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health or prevents an unreasonable risk of illness or injury.

In this case, a premarket approval application, commonly referred to as a PMA, is submitted to FDA prior to marketing, and examples of class III devices would be an HIV RNA assay by PCR for prognosis or home collection device for HIV testing.

Next slide.

I want to drop back for just a second. It is

important to emphasize to the committee that the revision of the device GNP as one of the general controls is viewed by FDA as a strengthening of the manufacturing process, as there are new requirements for manufacturers. Document controls, additional purchasing controls, records servicing and management responsibility, and most importantly for class II products and several class I products that are under development or cleared after June 1, 1997, design controls. Design controls are a system to better ensure that product design requirements are properly established, translated into design specifications, and that the designs released to production meet approved specifications. Thus, in considering reclassification of the device, I would invite the committee to be aware that the GNP aspect of general controls is now significantly strengthened.

The initiation of a reclassification proceeding can begin by a petition or at the discretion of the commissioner. A device panel - in this case the Blood Products Advisory Committee sitting as a device panel - deliberates on factors affecting the safety and effectiveness of devices being evaluated, and we can just - next slide - it is just reminder of those elements. Those factors include persons for whose use the device is intended, conditions for use, its probable

benefit to health weighted against the risk of use, and the reliability of the device.

The panel then makes a recommendation for a classification in considering those elements, and it is published in the Federal Register along with the proposed rule. Following consideration of comments made on the proposed rule, FDA will then issue a final rule which is published in the Federal Register reclassifying the device. So to distill this, what we are doing is asking the committee for a recommendation, and then there is a regulatory process that we will be going through to take into consideration that recommendation and also other public comments prior to finalizing this reclassification. I might also add that the reviewer guidance that we would be proposing would follow the same basic pathway. There would be ample opportunity for public comment, as well as manufacturers* input.

Current reclassification issues allow for the reclassification of medical devices based on new information. This information can raise concerns or lower concerns regarding the safety and effectiveness and proper reclassification proposals from the manufacturer or FDA to raise the classification or lower the classification respectively.

For this panel, two groups of products are being considered. The first group are class I products proposed to be reclassified to class II. In this instance, we feel that general controls are insufficient to determine safety and effectiveness, and we would be proposing special controls. Automated test equipment used to test donor blood for blood-borne pathogens. These would be the equipment that is used to run enzyme immunoassays, radioassays, et cetera, for blood-borne pathogen detection in blood establishments. For example, these are the equipment that the licensed test kits are run off, HIV antibody tests, HB, SAG[?], et cetera.

I wanted to also note that while this equipment is currently classified as class I, automated blood grouping systems are already classified as class II.

The second is automated vacuum-assisted blood collection systems. This is a system where a blood bag would be inserted into a plastic cylinder, and vacuum is placed on the cylinder to accelerate the drawing of blood. This is not intended to address passive or manual vacuum-assisted systems where tubing is attached to a vacuum container and blood is drawn. It is our understanding that while these types of equipment are not commonly used these days, it is still on the books, and if a manufacturer were to come in with such a

device for clearance, we have some concerns about the automated aspects, and I will get to that in a moment.

The third product class that we are looking at is automated blood mixing devices and blood weighing devices. Again, this is not the manual standard drip balance type of product. This is an upgrade where there are automated aspects to it.

Now in each of these instances, FDA has concerns that safety and effectiveness of the devices cannot be reasonably assured by general controls alone, and special controls in the form of FDA reviewer guidance for each of these products would be proposed. FDA's concern centers largely on equipment automation, where operators will clearly place a great deal of reliance on the equipment to be alerted to equipment malfunctions and have an adequate safeguard in place to reduce or prevent injuries to both donors and recipients.

FDA would propose to prepare a 510(K) reviewer guidance which would be targeted at each of the three aforementioned specific devices and would include two basic parts: regulatory guidance, what FDA would expect to sponsor to submit to fulfill the regulatory requirements, such as the name of a device, registration number, classification if it

has been established, performance standards if they exist, proposed labeling, et cetera; and, two, information at a scientific level, at the appropriate level of detail, describing, for example, functional requirements of the device, design and manufacturing information as appropriate, an analysis of how hazards, medical, mechanical, or electrical, that may be associated with the device or its intended use of the device are mitigated, and what type of performance data are needed to support product claims.

For example, in the case of an automated pipettor, guidance would include the need for the equipment to alert an operator if a pipetting step had been compromised in, for example, an HIV assay. In the case of an automated vacuum-assisted blood collection device, the guidance would include the need for a safety valve to limit vacuum and an alarm to notify the operator if a vacuum regulator fails and vacuum increases to a dangerous level.

In the case of an automated blood mixing and weighing device that has an additional feature a bar code reader which records patient identification and drawing information, the guidance would include the need for adequate software design, product testing, as well, to ensure that the bar code reader accurately reads and records patient

information.

FDA views that guidance for such devices would benefit both FDA and the industry, as it will make manufacturers aware of FDA's current thinking on the appropriate safety and effectiveness concerns for these specific products; it would promote consistency among FDA product reviewers. It should also reduce 510(K) review time as the need for FDA to write the sponsor for more information in order to clear the 510(K) would be expected to be reduced. An example of how this has worked successfully recently for FDA is our reviewer guidance for blood establishment computer software enabled us to clear a manufacturer's 510(K) in a net total time of 22 days.

The issuance of the draft guidance again would be consistent with our good guidance practices and thus be published in the Federal Register for public comments. After all comments are considered, it would be published in the Federal Register as a final guidance.

The second group are class I products proposed to remain as class I, general controls, but are exempted from the 510(K) submission. Other general controls would still be retained. The first is the heat sealing device, and that was the listing that I had showed you earlier, and I want to

emphasize that this is not a sterile docking device. This is simply a heat device to crimp tubing. That is the extent of its basic use on a blood bag. We had originally proposed a copper sulfate solution for specific gravity determinations to be exempted; however, information that we came across in the last 4 to 5 days has prompted us to change our position on that, and I will be filling you in on that in just a moment.

The third product is a cell-freezing apparatus in reagents for in vitro diagnostic use. This is not a cell-freezing apparatus for blood for transfusion. This is a device which is used to - it is a droplet freezer into liquid nitrogen where cells are frozen for compatibility testing of rare cells so that they could be used as a reference for providing transfusions later on.

In each of these instances, these two instances, FDA feels that the safety and effectiveness of these devices should be adequately maintained without filing a 510(K) notification. The remaining controls would be sufficient.

Now I would like to take a step back and talk about the copper sulfate withdrawal, just so the committee is aware of where we are with that. We are withdrawing this from consideration by the committee to exempt copper sulfate from filing a 510(K). This decision is based on publication last

week of a letter in the June issue of transfusion citing four instances where donors who presumably passed the copper sulfate test to estimate hemoglobin donated a unit each when they were all, according to the report, very anemic at the time of the donation.

In formulating FDA*s original decision to recommend to the committee exempting copper sulfate, it took several elements into consideration. The product had been used since the mid-1950s. Its formulation is very simple, and formulation mistakes can easily be detected. The AABB technical manual had alerted users for many years of the possibility of false results using copper sulfate solution to estimate hemoglobin. A 510(K) review by FDA on a simple product such as this would be felt unnecessary, because it would largely consist of assuring that the manufacture of a simple salt solution was done properly. General controls were viewed as being able to cover for that, and only one medical device report was filed with FDA in the last 12 years. Now medical device reports are those reports to the FDA where death or serious injury has been encountered with a particular medical device, and it gets reported in.

The only report that was filed was a laboratory worker who, believe it or not, accidentally drank the copper

sulfate solution. The person was reaching for a glass of water and drank the copper sulfate. So based on this information, we felt that there was a reasonable reason to go ahead and propose an exemption. However, with this latest report of these potentially anemic individuals, FDA is going to reexamine the possibility of underreporting of donor problems with copper sulfate in donors.

Now I want to also make another change that we had provided to the committee. We also would propose to withdraw our secondary questions for the first three products that we are proposing to have reclassified to class II. They were originally posed to ask the committee if they concurred with the reviewer guidance to be a special control for each of the products that would be listed. In reflecting on this, the committee may be at somewhat of a disadvantage in recommending a guidance that they had not actually seen, and secondly, what we were trying to do is give some measure of exposure to get public input on such a guidance document, but with our new guidance practices, we will be proposing that guidance, and it will be published in the Federal Register and the public, manufacturers, are all welcome to put public comment in, and all of those would be considered. So from that point of view, we felt that the secondary questions need not be considered by

the committee, unless of course the committee feels otherwise and they would care to make comments, but we think that this is probably the simpler approach.

Thank you.

DR. HOLLINGER: Are there any questions of Mr. Wilson?

DR. HOLMBERG: Yes, I was just wondering if the reviewers guide would be available to us on the committee. Will we have an opportunity to comment on that as a committee?

MR. WILSON: Certainly. We have not developed these reviewer guidances yet, and I think we can provide the committee copies of that, as well as anyone else who would care to comment. Such a reviewer guidance would be publicly available once it is developed, and comments could be made by a variety of -

DR. HOLLINGER: I am confused a little bit about this notification, this 510(K) premarket notification. I mean, what does it entail? What is the problem? Why are there exemptions looked for? Is this a lot of work? Are there some reasons that it should be exempted? It was not clear to me.

MR. WILSON: Medical devices class I, class II, and class III are categorized based on increasing risk, and in

consideration of some of the FDA reform efforts, in consideration of new information that we have, we have taken a step back and looked at the current review workload as well as what the concerns relative to these risks are as we look at it in 1997. These products were classified in 1980. We know a lot more about these types of products. The Center for Devices, our sister agency, has taken a very strong lead in reengineering the 510(K) review, and they are again looking at it as a risk-based approach, and we as full participating members are essentially participating at that same level and looking now at those areas where we should be concentrating our efforts at greater risk and exempting those products where we feel that the general controls are sufficient to ensure safety and effectiveness. That is why, for example, with copper sulfate we essentially did our homework and felt that the general controls were in place. We checked our MDRs, there was only this one, and then just recently we saw this relatively potentially serious situation that was published in Transfusion. So we are pulling back from that. Does that answer your question?

DR. PILIAVIN: It did not answer the question for me. Could you just tell us what the 510(K) review involves? I believe that was what the question asked. How onerous is

it? How many person-days does it take and so on, just roughly?

MR. WILSON: Okay, here goes, 510(K) 101. The 510(K) is a premarket notification. Such products are class I or class II. They are not approved by FDA. They are cleared by FDA. That clearance allows a manufacturer to market the product. The content of a 510(K) to be submitted to FDA is articulated in the CFR, and it has regulatory aspects and scientific aspects, and the bottom line on the content is that a manufacturer is attempting to demonstrate to the Food and Drug Administration that this product is substantially equivalent to cleared products already on the market. The determination of substantial equivalency is the issue with class I and class II, and for regulatory purposes there are what is the name of the device, labeling, what is its intended use, a truth and accuracy statement, et cetera.

On the scientific side, the manufacturer describes, oftentimes in summary format, other times in detailed, detailed scientific data, sometimes with clinical studies, the defense of the products claims. Manufacturers file these, and according to regulations there is a 90-day statutory turn-around time. If a manufacturer files a 510(K) and in the course of the review FDA determines that there is insufficient

information to determine substantial equivalence, a letter is sent back to the manufacturer describing that concern, and the manufacturer by statute has 30 days to respond. We oftentimes allow more time, but 30 days to respond with that information to allow the product to be cleared. If the manufacturer takes longer than - the ball is then in the manufacturer*s court. Some manufacturers respond immediately. Some manufacturers respond a year and a half later. That is completely beyond FDA*s capacity to regulate.

At the point at which the manufacturer provides adequate information for determination of substantial equivalency, a letter is written to the manufacturer declaring that, and the manufacturer is then allowed to market the product. Does that help?

DR. PILIAVIN: That is terrific, thank you.

DR. HOLMBERG: But that still raises a question about the reviewers guide. If you look in the CFR, I believe that the CFR is really not clear with all that is required in the 510(K), and what I am concerned about with the reviewers guide that you are proposing right now is that these reviewer guides really become the guidelines, and in the case we have learned here about a year ago, a lot of software developers had already submitted their 510(K) months before the reviewers

guide came out. So I am concerned about that, and I just think we need some clarification here as far as definitely making sure that everybody has clear understanding of what the guidelines are, because by default these reviewer guides actually become the regulation or the parameters in which they are evaluated.

I am also concerned, in class I, they still are required to have a 510(K). Now you made the stipulation there about cleared versus approved. There is still a review process that goes on; is that correct?

MR. WILSON: Yes, that is correct. If a manufacturer can demonstrate substantial equivalence to a product already on the market, then that manufacturer's 510(K) is cleared.

DR. HOLMBERG: For another clarification, if something is a class I but is exempt, then there is no 510(K).

MR. WILSON: Exemption can apply to any one of the general controls. It is typically applied to the 510(K) review process, but any or all of the general controls can be considered for exemption. Again, the point of this is that with a view of lower risk fewer controls would be needed to ensure proper intended use and safety, use of the device.

I would like to backtrack just a moment and address

the issue of the reviewer guidance relative to software. One of the things that is important to consider is that the reviewer guidance which was developed was considered to be an overlay of the CDRH 1991 guidance on software. I can confidently say overwhelmingly that those manufacturers who are experiencing difficulty in getting a 510(K) cleared had not really considered the guidance that was available five, six, seven years before we published our reviewer guidance. Our reviewer guidance was an overlay specific to those areas of the manufacture of blood and donor management, unit management, et cetera.

In the case of this guidance, it was felt to be an additional supplement. In most instances, what we have found in 510(K) reviews for blood establishment computer software are fundamental problems that were not addressed based on the 1991 guidance, documentation problems with software design, hazard analyses, et cetera. Things that we felt are genuinely important in the safety of such products, as well as what the public would demand relative to that safety.

So from that point of view, it is FDA*s view that while we had added an additional guidance, it was viewed that it was fine-tuning what was already there rather than generating new issues for manufacturers to deal with. We have

also - I just want to also mention that we recognize that since there are so many problems with getting many of these 510(K)s cleared, our software team has had in excess of accumulation of 100 either meetings or lengthy telephone conversations with virtually all the manufacturers in order to help them walk through some of these concerns. In addition, the public presentation this time last year at BPAC articulated in a series of slides by Nancy Jensen[?] in our group precisely those areas where we felt that the manufacturers were having difficulty, again, to walk through some of these problems.

So reviewer guidance is never going to be perfect, but the effort was to assist the manufacturers, and as I said, we did clear one in 22 days about two months ago.

DR. HOLLINGER: Thank you, Mr. Wilson.

We are going to ask Mr. Balick then to start on this identification of the proposed medical devices for reclassification.

**Agenda Item: Reclassification of Medical Devices
Used in Blood Collection and Processing and Donor Screening -
Identification of Proposed Medical Devices for
Reclassification**

MR. BALICK: I will now present a proposal for the

reclassification of medical devices used to test donor blood and blood components for blood-borne pathogens. The following regulation gives the Center for Biologics Evaluation and Research the authority to consider regulating these devices under greater scrutiny when they are used to screen donors of blood and blood components for blood-borne pathogens. Under Title 21 CFR part 606 current good manufacturing practice for blood and blood components under subpart D equipment section 606.65e states supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer. The gold standard is running one patient*s specimen manually, because the operator can ensure that all assay steps have been completed according to the package insert.

Next I will present some significant procedural steps that must be accurately performed by an operator of a typical manual microplate enzyme immunoassay, or EIA, when following a manufacturer*s package insert instructions. Then I will present comparable procedural steps which must be accurately incorporated into the process and monitoring functions of a typical fully automated microplate EIA procedure or a procedure which utilizes automated subsystems, which I will define later.

My use of the microplate EIA procedure as an example

is not meant to exclude other EIA procedures such as those employing beads or other solid supports, nor, furthermore, specific donor assays for blood-borne pathogens such as Western blots or IFAs. In this slide, you get a typical manual microplate EIA. First, preparation of patient specimens and controls. In many assays, the patient specimens and controls are run undiluted, but in some assays the patient specimens and controls will need to be diluted. The operator must ensure that the appropriate volumes of specimen and specimen diluent are mixed. The operator must ensure sufficient mixing without foaming of the specimen due to excessive mixing.

Second, pipetting of specimens or controls and then reagents. This applies for specimen, conjugate, conjugate substrate, and stop solution application. The operator uses a single or multi-channel hand-pipettor. This pipettor must be calibrated on a regular basis. The operator visually inspects the specimen for clots and air bubbles, thus preventing low volume or no specimen being dispensed. Care is also taken to prevent cross-contamination of the microplate wells.

Next slide.

Third, dispensing and aspiration of wash buffer

solution. The operator takes care not to cross-contaminate the wells in the process of multiple cycles of aspiration and dispensing. Complete aspiration must occur in each cycle without scraping the bottom or sides of the wells. After the last aspiration, the wells must be free of all wash buffer before the next reagent is added.

Fourth, incubation of the microtiter plate for each assay reaction phase. The incubator must hold a constant temperature, typically plus or minus 1 degree Celsius, and there must be a record of the incubation.

Fifth, after the reaction is stopped by the addition of acid, the optical densities are read. The operator manually reads the optical densities of the controls and specimens in the spectrophotometer. Finally, the operator manually calculates the cutoff and identifies the donor specimens that are reactive based on the cutoff.

EIA procedures such as the one I presented or other in vitro diagnostic procedures used to screen blood and blood components for blood-borne pathogens for all practical purposes are not performed in their purest manual forms. Instead, automated subsystems or fully automated systems are utilized. The primary reason for this is simply due to the sheer volume of blood that needs to be processed in a

relatively short period of time.

Most equipment that employs software that controls process steps would be considered an automated subsystem. Equipment in this category includes automated pipettor dilutors, automated spectrophotometers, and automated solid phase ligand assay washers and incubators. A system which contains computers used to control the assay procedure and interpret assay results, along with the equipment they control, is an example of a fully-automated system.

Based on the 1991 inter-center agreement between the Center for Devices and the Center for Biologics, all submissions for devices intended to be used in blood donor screening should be submitted to the Center for Biologics. However, as of this date, all fully automated equipment systems and automated subsystem equipment that have been and are currently being used for blood donor screening have been 510(K) cleared as class I devices. Because these equipment have not been specifically labeled for blood donor testing, the 510(K)s submitted to the FDA for these equipment have been cleared by the Center for Devices and not by the Center for Biologics.

Now I will reiterate the procedural steps I presented in the manual EIA procedure, but this time I will

present them in the context of steps which must be accurately incorporated into the process and monitoring functions of a typical microplate procedure utilizing a fully automated system or automated subsystem, and of course, since equipment in a fully automated system and automated subsystem equipment will be minimally monitored, the following steps will be performed without operator verification.

The first process is the preparation of patient specimens and controls. Again, in certain assays, patient specimens and controls will need to be diluted. The automated pipettor dilutor must ensure that appropriate volumes of specimen and specimen diluent are mixed. The automated pipettor dilutor must also ensure sufficient mixing without foaming of the specimen due to excessive mixing.

The second process is the pipetting of specimen or controls and then reagents. Again, this applies for specimen, conjugate, conjugate substrate, and stop solution application. The automated pipettor equipment must be designed to identify specimens drawn with clots and/or bubbles and if these specimens are pipetted and the run continues, the operator must be notified at the time of detection of the problem and at the time of report generation at the end of the run.

Next slide.

The third process is the dispensing and aspiration of wash buffer solution. The equipment must be properly adjusted so dispense and aspiration needles do not scrape the bottom or sides of the wells, thus preventing sporadic and/or reduced optical density signals. The dispense pressure must be appropriate in order to deliver sufficient volume of wash buffer. Not enough, and the sides of the wells will retain some unbalanced specimen or reagent which will interfere with the next reagent reaction; too much and there may be cross-contamination of adjoining wells.

The fourth process is the incubation of the microtiter plate for each assay reaction phase. The incubator must have an alarm capability to notify the operator of any aberration from the set temperature. Again, typically of aberrations more than plus or minus 1 degree Celsius. There must also be a record of the extent and duration of the aberration.

Finally, the automated spectrophotometer with a resident or interfaced data reduction capabilities reads the optical densities of specimens and controls, accepts or rejects the controls, calculates the cutoff if the controls are valids, and interprets specimen results as positive or negative.

All equipment used in fully automated systems and automated subsystems must be inherently reliable due to the crucial timing of availability of blood. In other words, from a design point of view, equipment reliability on a day-to-day basis has a direct impact on blood availability. Equipment malfunctions can cause two types of deleterious effects on the blood supply. First, equipment breakdowns can cause a decrease in the overall output of available units; second, equipment malfunctions without specific and timely error flags may cause positive results, false positive results, thereby decreasing overall output of available units, or, most importantly, false negative results, thereby endangering the safety of the blood supply.

The following three overheads list a series of equipment malfunctions which have occurred over the last five years while the equipment was in use in a blood establishment or clinical laboratory. FDA became knowledgeable of these events through medical device reports, MDRs, submitted to the agency by the manufacturers themselves or by their customers and/or upon biannual or directed inspection of the equipment manufacturer.

For automated pipettor dilutors, malfunctions included too much specimen dispensed, unequal volumes of

diluent dispensed, conjugate delivered to half of a plate, keeps getting clogged, will not pick up tips, and the following malfunctions occurred without an associated error flag being generated: no specimen dispensed, insufficient specimen dispensed, no diluent was dispensed, skipped a row, no reagent added, positioning problem with bubbles, last digit of bar code dropped, and bar code scanner missing a row of twos.

Next slide.

For automated microplate washers, malfunctions included not dispensing adequate volume of wash buffer, washer does not complete all cycles, fluid sensor not working, will not aspirate evenly, and the following malfunctions again occurred without an associated error flag being generated, which included not aspirating at all and an aspiration problem due to clot. For incubators, malfunctions included desired temperature not reached and temperature fluctuates.

Finally, a malfunction in a fully automated system: the assay run failed because a positive control was invalid; however, a positive or negative determination for each patient specimen was still recorded along with a specimen optical density value. In this case, a programming error resulted in this ambiguous printout.

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The Center for Biologics Evaluation and Research proposes a reviewer guidance for a premarket notification submission for automated testing equipment used in blood establishments. The use of this guidance would constitute the special control requirement of a class II device. These equipment should be classified as class II devices subject to special controls in order to ensure that the equipment follows the manufacturers* package insert instructions, and when it does not, the operator is appropriately informed by the equipment of the aberration.

Therefore, FDA proposes the implementation of the following classification: the classification name automated test equipment used to test donor blood for blood-borne pathogens should be included in 21 CFR part 864 hematology and pathology devices, subpart J, products used in establishments that manufacture blood and blood products. The classification would be class II, subject to special controls, and the following are examples of automated equipment that would fall under this classification name: automated pipettor dilutors, automated spectrophotometers, automated solid phase ligand assay washers and incubators, and computers used to control the assay procedure and/or interpret assay results.

Thank you.

DR. HOLLINGER: Thank you. Let*s go on to the second presentation by Ms. Hwangbo.

MS. HWANGBO: We have two more products. The first one is - these are under CFR part 864 subpart J, devices used in establishments that manufacture blood and blood products. The first one is vacuum-assisted blood collection system, the second one blood mixing and blood weighing devices.

The first device, vacuum-assisted blood collection system. This device is an automated blood collection system that assists drawing blood by creating negative pressure within a cylinder that contains a blood bag, thereby rendering a vacuum within the blood bag. Creating vacuum and shutoff may be operated by microprocessors.

It uses a vacuum to draw blood for subsequent reinfusion.

Justification for the proposal to up-classify. If the donor is left unattended and vacuum controls are lost, possible vaso-vagal accident can occur from increased vacuum, or recipient injury can occur from cell lysis and activation. We deem it necessary to require special controls beyond general controls for donor safety.

We are proposing a reviewer guidance to address

issues in microprocessor control system to ensure that the control system be appropriate, present, and functioning.

The second device, blood mixing and weighing devices. The devices are blood scales that are used during blood collection. They may electronically monitor bleeding and automatically shut off upon completion of the draw. It mixes blood with the anticoagulation with a constant agitation for increased blood quality and weigh the content during collection.

Our justification is this. The blood scales may fail to trip at the designated weight, and overcollection of blood may occur. Automated devices should be reviewed as a class II device. Reliance will be placed on donor identification, drawing information, as well as alerts and alarms. We propose a review guidance similar to that for vacuum-assisted blood collection system.

Now, this is for down-classification, reclassify from class I to class I exempt. This is also under 21 CFR part 864 subpart J, devices used in establishments that manufacture blood and blood products. The first device is heat sealing devices, second, cell-freezing apparatus and reagents for in vitro use. As Len mentioned, we dropped copper sulfate solution here.

Heat sealing devices. This is not a sterile docking device. This is only for a one-clamp close. These devices are open hand-held battery-operated devices that are used in blood banks or donor sites, commonly used as a companion to apheresis machines. They seal plastic tubings containing blood and blood components, often determine the thickness of the plastic tubing and automatically adjust itself to ensure that each seal be made properly.

Our justification is this. Users easily - quality control, improper sealing. The quality system regulations and other general controls will provide reasonable assurance of safety and effectiveness. Second down-classification. This is for cell-freezing apparatus and reagent for in vitro use. These are cell-freezing apparatus that are used to freeze reagent regular cells of known phenotypes. They freeze human red blood cells for in vitro reagent preparations for blood grouping and typing, as well as antibody identification.

Our justifications. Users easily quality control leaks, improper freezing, et cetera. Suspensions of reagent red blood cells can be inspected visually for evidence of deterioration, such as hemolysis. Quality system regulation and other general controls will provide reasonable assurance of safety and effectiveness.

DR. HOLLINGER: Thank you.

Are there any specific questions of the committee? There is going to be an open committee discussion of the charges later on, but of the last two presentations?

Yes, Dr. Holmberg?

DR. HOLMBERG: I guess I am still unclear as far as the difference between a cleared and an approved 510(K).

MR. WILSON: 510(K)s, either class I or class II, are never approved by FDA. There is a distinct difference between an approval and a clearance. The difficulty here, which can be confusing, is that medical device regulations essentially state that a class I and class II product may be marketed if manufacturers demonstrate substantial equivalence to a product already on the market. A premarket application, a PMA, a class III, does get a discreet FDA approval. Licensed test kits used to screen donor blood get a discreet FDA approval.

DR. HOLMBERG: In the last presentation, it said that the users* QC for the heat sealer - the users* QC would monitor the effectiveness. Is that an observational review?

MS. HWANGBO: I think so.

DR. HOLMBERG: And would the agency then require in their inspections that the user check off that they have

observed the seal, a documentation?

MS. HWANGBO: Yes, we think so.

DR. AUGUST: In the previous presentation, a list of equipment malfunctions in the field was given to us, but we really were not informed how frequently some of these things occur and what the FDA*s - whether there are acceptable limits, whether the equipment has to be 100 percent effective, whether a .1 percent failure rate is acceptable. What are the ranges of acceptability I suppose I am asking about. Then the same questions can occur - I am asking the same questions with respect to the number of times these errors failed to be picked up by the monitoring devices, which I think is also important. What are the limits of tolerance and how frequently are these things occurring?

MR. BALICK: Hi, this is Howard Balick again. The time frame I mentioned, I think, was five years, approximately five years, of some of the examples that I gave for malfunctions that I summarized extracted from MDRs over a period of time, and your question about frequency certainly is germane to the topic, and I do not have an exact number for a particular period of time in a year. We have extensive MDR reports, and we can certainly provide that information at a later time.

The significance, I think, for a lot of these MDRs is simply that their occurrence at all is quite disturbing, and I actually have just brought with me some actual MDR reports, which if you care to, I would read a few of them specifically as far as summaries, of course neutering them and not giving specific information, because I do not want to disclose a particular manufacturer or a particular instrument, but just sort of to hit home what we are dealing with here, let*s see if I can pull up a couple here.

Okay, here was an MDR for essentially a pipettor dilutor. The MDR was April 4, 1996. The summary of the event stated that the instrument threw a sample tube while running an HIV assay. No one was injured by the ejected tube. The company*s field service engineer was dispatched to account or verify instrument performance or review techniques.

Here is another one. This was April 17, 1996. So, you see this is a week later. They are coming in on at least a weekly basis of this type of sort. Again, a sample, essentially pipettor dilutor. During pipetting of a hepatitis service antigen assay, using a sample handler, large droplets were observed at the end of the tips, indicating that the full amount of sample was not pipetted. No error message was given.

Now it did state that the company service engineer was dispatched to evaluate this event and that no death or serious injury was associated with this event, and I do not have a statement here as to what the disposition of the unit that was affected, but certainly there can be significant ramifications of that type of situation.

I will just read one more for the purposes of this. This is June 6, 1996. Again, a sample handling system. While running an HIV I/II assay, the sample handler failed to pipette reagent in two rows and did not generate an error message. So we are concerned that these kinds of events happen at all, and it is certainly relevant, but I think secondarily to the fact that they do occur at all, and they do appear to be occurring approximately on a weekly basis. Now they are not all going to be on an instrument for a blood donor screening assay. Some of the items I have - and I did note that the MDRs were not just reported in blood establishments, but also in clinical laboratories, because all of the equipment systems have been cleared, as I mentioned, under class I 510(K)s by CDRH, because up to this point it has not made a difference where they have been used. So some of the MDRs will occur in other venues, but certainly ones I picked out are significant and did occur at blood

establishments.

MR. WILSON: This is Len Wilson. I would just like to add to that that the concern that we have here on raising all of these products to class II is the automated issue. It is the walk away, the machine is going to do what it is supposed to do - you know, in most people*s minds, automated equipment means that you can walk away from it. There is something there that will tell you when something is wrong. In situations where we have blood testing equipment, while the frequency is certainly a component of concern, the degree of error can be an overriding - the degree of one error can be an overriding consideration. For example, we had one instance where a manufacturer*s spectrophotometer had been reprogrammed as an upgrade, and there was a programming error where it not only did not read the one row in a microwell plate - one row, I forget whether it was 8 or 12 - correctly, it read them all as negative, all the time, and that manufacturer recalled the product immediately and steps were taken, but we had a situation where a blood establishment did not get on board with the recall that fast and had used it substantially. So the point here is then that the degree of error can be not only a discrete one day event, it can last for quite a long time, because these machines operate in a sense silently.

They are chugging along, and individuals use them on a full reliance basis.

The other thing I would like to add is that the Center for Biologics conducts inspections of manufacturers of these test kits, and oftentimes many of them have equipment that they sell along with it. So we have been monitoring the rates of complaints. Now complaints on equipment have to be balanced when one looks at them. One is that no piece of equipment ever works perfectly all the time. There is always going to be a failure rate, and sometimes those are hard to estimate.

Secondly, the type of complaints that are filed oftentimes have to be combed through carefully, because sometimes you will have operator error and it will get inadvertently reported as a machine malfunction. So you have to sort those things out.

What is our greatest concern are those ones that we have picked out as examples where flags were either not operating when they should have been operating, alerts, alarms, et cetera, or in fact they were not well-designed into the product itself up front. An alarm was not there. So to an extreme, one would have to sit and watch the automated instrument to see that it pipetted every sample accurately,

and in today*s society it is typically not considered to be an appropriate thing to do to watch an automated piece of equipment for that type of a level of control. So that is why we approach this more from a specific type of problem at a specific frequency, and our approach again to this would be to work with the manufacturers to essentially put these flags in place so that the products can be run confidently consistent with the 606 reg which says that the package insert of the test kit must be followed, and if the automated instrument is going to do that for you, at the very least, if it does not do it, a flag should go up so that action can be taken.

DR. NESS: I guess I am confused. Could you explain specifically how reclassifying something from class I to class II allows you to ensure the safety of that device? That seems to be missing in this discussion.

MR. WILSON: This is Len Wilson again. The products that we are talking about for specifically the viral marker testing equipment, but the others - well, let*s talk about viral marker testing equipment specifically. These are being reviewed by CDRH, and these products are classified as class I, and the reason for that is back when they were originally classified, it was felt that there was intervention capable at a medical level, as there is with many other devices, that if

an error was to occur, that remedial action could be taken by a physician in a medical testing atmosphere.

The problem that we have in blood establishment testing for blood-borne pathogens is simply that we are testing for silent diseases in presumably well donors, and one of the terms that has been recently used is that these become determinant tests. There is almost no way to accurately diagnose an HIV infection that is asymptomatic without the test. So the reliance on the equipment is somewhat greater than what the Center for Biologics views in terms of risk involved. So that is why we were proposing to elevate these to class II, and in our reviewer guidance essentially we would be proposing to put all these flags in place in terms of design.

In terms of the other products, our sense is that the vacuum-assisted device and the blood mixing and weighing device, it is the same essential concern. There is automated - lots of things have become automated in the last 10 to 15 years, and again, these were classified in 1980, and we know a lot more about them, and the point is simply that if they are going to be automated where reliance is placed on it by the operators that will essentially walk away from them, we feel that it is at least minimally important to have the

proper flags in place so that either donors do not get injured or recipients do not get injured.

REV. LITTLE: This is for either of the presenters. I found it striking that based on very recent information within the last few days that you were reconsidering what to do with the copper sulfate and the exemption. Doesn't this raise any concerns about the other products that you are naming to be exempt? Do you have any concern that new information could come up at any time, and if that is the case, then what do you do then? Do you propose another reclassification?

MR. WILSON: More or less, yes. In terms of the vacuum-assisted blood collection devices, this is a product that was on the market prior to the 1976 medical device amendments and as far as we can tell is rarely used if at all right now. However, with increased technology and everything getting automated, there may be a situation where this product design gets essentially revived and submitted to the agency. What we would like to do is simply be prepared, that if such a product were to be submitted to the agency, now we know better about concerns regarding automation and computer programming, et cetera, and what we would like to do is provide to the manufacturers our current thinking in the form

of reviewer guidance so that if there are flags absent or safety controls absent, we would say we feel strongly that that is inappropriate to clear without having these types of attributes added to the product.

In terms of the automated blood mixing and weighing devices, those are newer in the marketplace - I am sorry, I get them mixed up. What was the other one? The cell-freezing apparatus, I am sorry. The cell-freezing apparatus is one large step removed from laboratory medicine in the mainstream. This is simply an archiving system. If anyone has ever seen one of these things, you wash some blood in a freezing solution, add it to a droplet freezer, it simply freezes it. So the control is in place by the users. They can largely tell when something goes wrong with that type of piece of equipment.

The heat-sealing device is the same thing. It is visually inspectable and verifiable that the seal is made. So that is why we feel that we have a comfort level with exempting. In both of the instances, with the heat-sealing device and the cell-freezing apparatus, in the last 12 years we do not have any MDR reports. Again, with the copper sulfate solution, we did not have but one, and it did not seem to be related to a donor threat. Now, we will be going back

to look at that, but this is what we are able to work with at the moment.

DR. PILIAVIN: This goes back to some of my questions about procedure before. With these automated testing devices that seem to have what strike me as an alarming amount of problems, do you then have - I am sorry, I am not being very articulate - my understanding is that this 510(K) procedure is for new products. If you change this classification from I to II, do you then go back to all the manufacturers of the existing products and say that they have to change things and you have to get them reviewed again?

MR. WILSON: There is a mechanism, yes, to do that, and I would like to reflect on that for just a moment. About two years ago, maybe three years ago, manufacturers of test kits that screen for infectious diseases such as CMV or tests that were screening for syphilis based on a treponemal antigen, as well as blood establishments, received a letter that basically stated that if you are going to be using these products in the manufacture of a blood product that they needed to have that specific intended use added to the labeling for use in screening donors. As such, based on our inter-center agreement, those products would be submitted to the Center for Biologics for review. There was a time frame

that was allowed for those manufacturers to in fact file those new 510(K)s for that new intended use. The rules are if you are going to change the intended use - and there are a number of other times that slip my mind at the moment - but if there is a new intended use of the product, that makes it eligible to file a new 510(K).

We anticipate that manufacturers that are developing such products now to test equipment, et cetera, that are at the beginning of their development process versus those at the end of their development process or in distribution, we would have to consider a time frame in which to integrate this into the blood screening scenario. So we would have to establish a time frame in which to do this, and that is a consideration, because many of these pieces of equipment can take a year or two to retrofit or to redesign. It is the development pipeline.

DR. HOLLINGER: Dr. Nelson?

DR. NELSON: I remember reading a paper a couple of years ago - I think it was in Transfusion, published in Transfusion - and it was really quite interesting and striking. It was a review of all of the blood banks in New York State, and they looked at instances in which false negative blood was used, or it slipped through the system, and

as I recall, very few, hardly any, were in the window period. Most of them were clerical or administrative problems. I thought it was an interesting review of a problem that everybody suspects occurs, but there was no real good data on the frequency. But I wondered in that paper if anybody remembers it, Susan or Paul or anybody, what were the proportions that were due to automated device problems as opposed to somebody just writing down or mistaking the result. In other words, how much was equipment failures as opposed to personal failure, if anybody remembers that paper?

DR. LINDEN: I sort of remember. In those particular instances where there were truly infectious units that went out, my recollection is that those were virtually all cases of transcription errors, human error of one sort or another, and were not equipment failure, but we certainly have observed in the facilities that we look at the same types of errors and problems that Mr. Wilson described, which is in fact one reason that we so strongly promote the idea of using additional external controls to attempt to discover some of these types of problems.

DR. NELSON: So maybe we should increase automation as opposed to decreasing.

[Laughter.]

Replace the person who writes down -

DR. HOLLINGER: Any other comment from the committee before we open it up for public -

Yes, Dr. Linden?

DR. LINDEN: I am still not completely clear on what exactly this additional review is going to consist of and how exactly you are going to prevent these types of problems, which I think a lot of the times these types of equipment failures are not preventable. Are you going to be looking at your existing MDRs for similar type of equipment in order to try to anticipate what the problems might be and see whether these types of equipment could be subject to those and whether it can be prevented or whether it can be flagged if it does occur, and what if there is other types of equipment that could have other problems that you do not know about yet?

MR. WILSON: There is no perfect piece of equipment. We realize that. But we also believe that if we use a test kit*s package insert as the backbone for steps to conduct an assay that is expected to give an accurate answer, then, as Mr. Balick walked through those manual steps, they would be the backbone, and we would simply ask how does the operator know if the operator is in the next room not watching it that that did not happen?

Now, I want to also say that one of the other elements of this is basic standard laboratory quality control procedures, too, relative to the CLEA controls, that would be helpful, but also maybe there needs to be some new thinking as to how control strategies, control reagent strategies, are applied to large runs using automated equipment. No single control reagent can prevent every possible error. There may need to be controls that are designed to detect particular errors and therefore would need to be run with the instrument, and then, of course, presumably, if it is an automated instrument, the automated instrument could be programmed to make sure that it is reading the low control as opposed to mixing it up with the high control and miscalculating some of these results.

So while we realize that equipment will always break down, equipment will always have problems, we also are of the belief that many of these types of flags and sensors, which many were available many, many years ago, and in light of the concern that a small error with a piece of equipment can translate into a large number of units being placed at risk, we feel that these types of flags should be in place.

One thing that does work for us is the frequency of the disease in the donor population. It is very, very low.

So oftentimes when these errors occur, many times units do not get released. So we have that on our side. However, we do have situations, as I said earlier, where a whole row was not being read, and a blood manufacturer had used it for a lengthy period of time and accumulated a very large number of units. So that did not - the low frequency of the disease in the population was not mitigating in that scenario. So that is what we are trying to get to, and we do not think that these types of sensors are something new and extraordinary. They were state of the art a while ago. They just need to be employed for better detecting silent disease screening errors.

DR. HOLLINGER: I think, obviously, as you said, this is an imperfect world, and machines will break down. I guess why some of the questions come up is that you are trying to reduce the risk as much as possible, the errors as much as possible, in the design or otherwise, and what are the guarantees that these are going to be reasonable suggestions to the manufacturers or vice versa. I presume you work very closely, obviously, with the manufacturer, and there is some give and take about what is reasonable, whether this is really going to be something that will prevent the errors that you really want to prevent. Some errors are intermittent with the computers and hardware. They are not there every time. They

occur periodically until they finally become constant, and of course these are the things we are always concerned about. Well, all of us who drive cars understand that. Machines always have problems, and things obviously happen with equipment. I guess is one of the questions I would want to pose to you.

MR. WILSON: In fairness, I do not think it is an easy answer. We are running the breadth of progress versus perfection, and it is very, very hard to make that cut. Also, equipment, because of its nature, intermittent problems, et cetera, can only really be improved with integrity by design, and that is what I had alluded to earlier in the new quality system regulations. In fact, this new GNP applies to the design of the product, not just simply the repetitive manufacturing, and where that came from was a study that was conducted by CDRH, I believe in 1987, where it was determined that 50 percent, or some 70 percent - I am sorry, 50 percent of recalls of medical devices were due to manufacturing errors. They put the wrong part on the machine, and it got out into use, and it did not work.

The other 50 percent could not be assigned to problems in manufacturing. They were design problems. It could not do what it was supposed to do. So based on that,

CDRH spent almost 10 years putting together this new quality system regulation with the full intent of trying with a reasonable balance to address those types of concerns. Since this equipment falls under those GNPs or quality system regulations, we view that that is an added benefit to this type of equipment.

Designs will always improve, and they will not be perfect, but what we feel is that in consideration of the low frequency but very serious effect of a false negative result based on these types of equipment, that prudent measures would be appropriate where sensors and flags, which are again not viewed to be state of the art or extraordinary in design or implementation, ought to be included in these designs.

DR. HOLLINGER: Just a question, based on chip designs and sensors and everything else that is made, if a manufacturer makes a change - let*s say he has something that he finds, some chips or other parts that may be cheaper, could be manufactured cheaper by somebody else, do they have to come through and notify you about that, or can they make this simple, what looks like a simple change, and it may turn out that it is not as stable as -

MR. WILSON: That is an excellent question, and one of the concerns in the quality system and regulation

development was how far back do you go? The FDA did not really want to get into regulating microchip manufacturers, because most microchip manufacturers are not in the medical device business. So there had to be some type of a balance struck.

The onus for the suitability of a component part for a medical device is squarely on the device manufacturer. The device manufacturer is obligated, regardless of whether a 510(K) is exempted or not, all the way up through HIV test kits - they are obligated to ensure that their raw materials are adequate for their intended use. Manufacturers need to conduct that measure of quality control testing on raw materials if they feel that there is a possibility that if a defect occurs in that particular raw material that it would be - they have to conduct that measure of quality control testing to ensure against the product being released that does not perform to its intended use. So if a manufacturer has done a poor job of raw material testing - chips, et cetera - they would likely get a 483 observation, and if there were complaints against the performance of that product, other regulatory action may ensue.

They would not need to file a new 510(K) specifically for those types of changes, unless it had

profoundly different technology or something well beyond what was originally cleared.

Does that answer your question?

DR. HOLLINGER: Yes, it does, but I do know that things are changed by manufacturers, and we see them in quality control - for example, if you are following things very closely, you will see changes in ranges, changes in values, and they are perceptible changes. The other day - I have been following albumin, for example, which I follow very closely in patients, and I noticed that in a two-week period there seemed to be an increase in the albumin level that I have not seen. It was clear by just looking at a number of patients that were coming through, and I asked the people after they went back, and the investigator said, oh, yes, there was a change in some of the equipment, and for about a two-week period there was a clear, decided change in the background.

These things go on all the time. It was a manufacturer*s change actually, and they are often just picked up through the quality control, in most cases. Sometimes they are not.

DR. HOLLINGER: Yes, Dr. Khabbaz?

DR. KHABBAZ: Yes, I think this was asked earlier,

but I remain unclear on how does reclassification affect existing devices? These reviewer guidances, how will they apply to existing devices? You said that it will not - the existing device manufacturer will not resubmit 510(K).

MR. WILSON: What we plan on doing is developing an interim period by which there would be a notice to manufacturers that if by such and such a date - just like with the CMV test kits. Manufacturers and the users were told that by such and such a date, any testing for CMV, for example, needed to be done with a test kit that is labeled for use in screening donor blood. So there is a model to follow, and there is a time frame in which we allow manufacturers to do that.

It would affect test equipment in the field. Manufacturers would need to file a new 510(K) for the new intended use of blood screening, and at that point, we would look for the types of flags, et cetera, in the equipment design. The purpose of this meeting right here is to publicly discuss our concerns, obtain a recommendation from the panel if they feel it is appropriate to follow this route, and then we would take it to another level of public comment in the Federal Register, and these types of comments - for example, if a manufacturer felt that it was an undue burden because of

such and such, we would have to take into account that consideration.

In some instances we agree with comments; in some instances we overrule them. So it is a stepwise process with the ultimate goal of converting all of the test equipment, at least from a proposal point of view, to class II, have it labeled for blood screening purposes, and have these safety flags in place.

DR. HOLLINGER: Thank you, Mr. Wilson.

I think we will move into the open public hearing. There has been one group that has been asked to speak today. Elizabeth Hunter is representing America*s Blood Centers.

Ms. Hunter?

Agenda Item: Open Public Hearing

MS. HUNTER: Copies of our statement are out front. So if you do not have one, you may receive one later. America*s Blood Centers collect and provide over 45 percent of the United States blood supply. We thus have an enormous interest in assuring that the most efficient and effective technology is available to protect the safety of the blood supply.

We applaud and strongly support the proposed reclassification of medical devices used in the processing of

blood components as a good first step. We especially support the reclassification to class II of test equipment used to screen blood donations such as equipment used in viral marker testing.

It remains a continual embarrassment to our regulatory system, which is both the finest and the slowest in the world with regard to this type of blood diagnostics, that state-of-the-art technology is available in Europe and elsewhere many years before it is available in the United States, the country in which it was invented. For example, after nearly 5 years of use in Europe, the so-called Fame microplate testing system is still not available in the United States. We are also aware that the next generation PRISM system has been available in Europe for over six months while it may not be available to improve blood safety in the United States - the country that invented it - for several more years.

Finally, FDA*s reclassification does not go far enough. With one major stipulation, blood screening tests themselves should no longer be classified as biologics, but as class III devices. This could greatly speed the availability of improved blood screening tests to make the blood supply even safer than it already is. Our one major stipulation is

that lot release requirements remain important to assuring that each lot of tests is as specific and sensitive as the next. Clearly FDA has the legal authority to regulate blood screening tests as devices, but not licensed biologicals, and still require lot releases. This is the best of both worlds - making the consistently safest and most effective tests available as quickly after development as possible.

Less than three years ago, the United States* major manufacturer of clinical and blood screening tests warned FDA that if important changes were not made in the test approval process, not only would manufacture of tests and equipment for export be switched overseas, but that the next step would be that the tests and equipment themselves that were invented in the United States would be manufactured overseas and shipped to the United States. This is already starting to happen. FDA must act soon to assure that the United States does not lose its biotechnology advantage.

We urge that the proposed changes and these additional changes be made as soon as possible.

Thank you.

DR. HOLLINGER: Just as a piece of information, the America*s Blood Centers used to be the CCBC, is that correct? The Council of Community Blood Centers.

We have some time, and I would like to ask if anybody in the audience has anything they would like to say, and this is the open public hearing, so if any of you there want to speak on some of the issues that were raised this morning, we would like to give you some time to do so. Anybody?

Yes, please, and please state your name and who you represent.

MS. SMITH: Hi, I am Judy Smith with Sienna Biotech. It is a small medical device manufacturer in the Columbia area. I just wanted to ask Len to get a clarification. This proposal for class II for the automated systems, are you now proposing that any new products go through two submissions if there is a clinical laboratory use and a blood bank use, that the manufacturer would submit a 510(K) to CDRH for the diagnostic use of the washers, et cetera, and then would also turn around and make another submission to CBER?

MR. WILSON: That question really was answered in our 1991 inter-center agreement. Products that have dual-labeling, i.e. for diagnosis and for blood screening, would need to be filed with the Center for Devices and Radiologic Health. They would review it for diagnostic purposes. We would co-review it for blood screening purposes, because

screening blood is different from diagnostic testing. So the system has already been set up to handle that.

MS. SMITH: So these new - the requirement for in the next X years to bring the previous, the already marketed products, back in for another 510(K) would still go through CDRH but go to you for review?

MR. WILSON: If the product was labeled for dual-labeling. In the situation that we had with the CMV test kits, they were not labeled for blood screening. Manufacturers were instructed to label them for blood screening. Manufacturers of test kits had to make the decision whether or not they wanted to have them available for blood screening, have them available for blood screening only, have them marketed for diagnostic only, or for both. That is a decision that the manufacturer of the test kit makes.

Most manufacturers elected, for the sake of expediency, to have two test kits. In other words, one that was submitted to the Center for Biologics specifically for the blood screening claim. In some instances, that was the most expedient way to handle it. It required some labeling changes, but the content of the review from the Center for Biologics point of view, you know, was still the same.

So this is the distinction that we have between a

test kit for diagnostic use versus a test kit or a piece of equipment for blood screening purposes. Does that answer your question?

MS. SMITH: Yes, I think so.

DR. HOLLINGER: Could you restate your name of your company again, please, and your name?

MS. SMITH: Judith Smith, SMITH, Sienna Biotech, SIENNA.

DR. HOLLINGER: Thank you. Appreciate it.

Yes, please?

MR. KLAMRZYNSKI: Matt Klamrzynski, Abbott Laboratories. We are a manufacturer of blood test systems, and I am going to represent certain biases as a special interest group here, but I hope these remarks are taken objectively. I was just taking some notes as we went through here, and the malfunctions and defects that FDA presented are real. There is no question about that. But as a panel member, I would have a difficult decision here to make regarding the change that has taken place, I guess, in the last 10 to 15 years, which spurs FDA to have these S&E concerns, safety and effectiveness concerns, now. Is it due to increased MDRs, increased recalls, increased look-back due to equipment malfunctions?

Secondly, will the additional controls that FDA proposes to put in place be monitored to see if MDRs, look-back, recalls decrease? I do not think there has been sufficient time. I know there has not been sufficient time to look at the effect of strengthening, as FDA said, the GNP through QSR, and the design control features which may mitigate these instances that have been reported. So it is difficult for me with the amount of information that was presented, and I would think difficult for a panel, to make a prudent decision on this issue.

Thank you.

DR. HOLLINGER: Thank you.

Yes?

MR. CUMMING: I am Paul Cumming with Talisman, a small consulting firm in Vienna, Virginia. I work in automated medical devices primarily. My concern is with the delay and keeping new products off of the American market. There was the mention this morning of a blood system software that got through in 22 days. That is only one, that is the only new technology that is on the market, and that is only the one manufacturer, as far as I know. The rest of it is 10 years outdated. It is fragile, and it breaks, and as was presented here, the mistakes that seem to be made are

transcription and other things in the manual processes, and the rules are keeping the new technology off the market. I do not think that that is in the public interest.

So how do you address when the rules are in place for the automated, what do we do with the unautomated? How do we get it through? I presented to the National Library of Medicine last year, for example, put a process in place that takes 90 days and does not require eight volumes of documentation, which virtually makes it impossible for small firms to submit to the FDA. Eight volumes - you are talking a minimum of a man-year or two man-years of paper. There is nothing less than eight volumes of documentation that has been accepted by FDA to the best of my knowledge.

That is all I have to say. There has to be a balance here. Thank you.

DR. HOLLINGER: Okay, thank you.

MR. SANDERS: My name is Steve Sanders. I am with Viamerier Vytech[?], a medical device manufacturer. I have some questions relative to the use of reviewer guidance. It is my understanding that reviewer guidance can be applied to any classification. Is that correct?

MR. WILSON: That is correct, depending on how it is written. If it is written specifically for a particular

discrete product, it may apply to that one classification, because that is what the product is in. If it is written broadly to cover a number of products that are in a group but because of their intended use they are in different classes, I mean, there is a lot of flexibility in how that would be written.

MR. SANDERS: The second question that I have relates to the slide that you had, talking about the reasons for reclassification in general. It appeared to me as I read those two bullet points - and I do not remember exactly what the slide was entitled - that the current class I for automated products basically covers all of those controls, and I am a little bit confused as to why do we need to go to class II for automated products. What is the advantage, in essence, in doing that, because the control systems that you are talking about are available in class I.

MR. WILSON: That is true, but they are not necessarily applied and applied effectively in these products. That is where we have our concern, that we need to see these applied to these products. They are available. There are some instrument systems that have certain types of flags in certain areas, but what we are saying is that we have a regulatory obligation to ensure that the test kit package

insert is followed, and the instrument, we view, should have, by technology that was available, you know, a decade ago, those types of controls in place, and our view is that a special control is warranted here, and a form of a special control can take, in our view, reviewer guidance. It will help manufacturers know what FDA*s current thinking is, our concerns about what we find on inspections.

What we described on our inspection findings was just a summary. We did not disclose, you know, lengthy lists of these types of things. We felt that we would pick the ones that made our point most appropriately: flags being absent, flags not working when they are fully expected to be working. So that is where we are coming from.

DR. HOLLINGER: Anyone else?

Dr. Holmberg?

DR. HOLMBERG: Well, just to follow up on several of the comments by the public, can you give us a clarification, Mr. Wilson, as far as how many days are we talking about in each one of the class reviews? I mean, is it all supposed to be 90 days, or is there a different breakdown on the difference between class I, class II, and class III?

MR. WILSON: For a class I and class II, the review at FDA should take action within 90 days. If it goes over 90

days, the Safe Medical Devices Act of 1992 prohibits a manufacturer from distributing it until FDA gives it a clearance. Class III medical devices are a 180-day review cycle.

DR. HOLMBERG: Mr. Wilson, could you also respond to the America*s Blood Centers comment about the classification of the blood screening test from biologicals to class III devices?

MR. WILSON: Yes, I did not quite fully understand how some of those remarks - lot release is a regulatory element of a product license application. It is not a regulatory element of a premarket notification, and I think I am -

MS. GUSTAFSON: Could I just add that possible changing the regulatory scheme from licensing to medical device review is not within the scope of this discussion today. This discussion is about devices that have been classified into class I, II, or III, primarily in class I and II in terms of whether they should stay in the classification that dates back to 1980 or whether they should be put into a different classification, and remember that devices are classed based on risk, with the highest risk being the class III devices, the very lowest being the class I. In looking at

the devices that were classified in 1980 by 1997 standards and also looking into the future in terms of size of government, extent of regulation, we were looking to see which devices looked like they perhaps had more of a risk than was thought back in 1980.

The one that stood out obviously were the testing equipment for infectious disease testing for blood screening, and our objective in the reclassification from a I to II includes use of special controls, but it also would ensure premarket review of these types of devices in the future.

DR. SMALLWOOD: For the record, the previous speaker is Captain Mary Gustafson of the Center for Biologics.

DR. HOLLINGER: Yes, Dr. Martone?

DR. MARTONE: Have you done any pilot studies or field tests to show that your proposed reclassification will, in fact, do what it is supposed to do?

MS. GUSTAFSON: The short answer is no, but we have been looking at historical information in terms of review and review elements, and we have been looking at the MDR reports, also reports from inspectional findings over the years. So no, there is no piloting, but we do think that these devices are risky enough that we should ensure the continued premarket review of these types of equipment in the future.

DR. HOLLINGER: It is 11:01 now, and we will take a half an hour break now. We will reconvene this - this will end the open public hearing. We will reconvene at 11:30 to begin the open committee discussion.

Thank you.

[Brief recess.]

Agenda Item: Charge to the Committee as a Medical Device Panel

DR. SMALLWOOD: As indicated on our agenda, the executive secretary will read the charge to the committee as a medical device panel. This will become a part of the record.

The charter of the Blood Products Advisory Committee permits the committee to sit as the medical device panel when it is necessary to review or discuss issues relating to the seeking of advice, recommendation for approval, or reclassification of medical devices which are regulated by the Center for Biologics Evaluation and Research. Today the committee will be considering the agency proposal to reclassify certain medical devices used for blood collection and processing and for infectious disease testing of blood donors as has been previously discussed this morning. The authority for such reclassification of a device is found in

sections 513(e) and (f), 514(b), 515(b) and 520(l) of the Federal Food, Drug and Cosmetic Act as amended, and the Code of Federal Regulations Title 21 part 800 subpart C.

The Blood Products Advisory Committee will sit as a medical device panel to recommend reclassification of the following: class I products proposed to be reclassified to class II under special controls; class I products proposed to remain as class I general controls but exempted from a premarket notification 510(K) submission.

Accordingly, this advisory panel will be asked to provide recommendations for the reclassification of these devices as proposed. The questions for consideration by the committee will be presented by FDA personnel and will be restated by the committee chair, at which time you may discuss them and request further clarity as necessary.

Thank you.

Dr. Hollinger?

**Agenda Item: Committee Discussion and
Recommendations**

DR. HOLLINGER: We are now into the open committee discussion, so we will open it up to any discussion that the committee might have.

Dr. Smallwood has suggested perhaps we might want to

look and just have the questions put up - tell me, how does the committee want to do this? There are a group of questions. We can do them one by one, which is probably the easiest way to do it, but if so we can just put it up there and discuss it specifically. Is that what you would like to do? And then raise any issues at the time. Why don*t we go ahead and put the questions up if we could, please.

So the questions to the committee are as follows. The first one is does the committee agree that automated test equipment used to test donor blood be reclassified from class I to class II? This is now automated test equipment, and the others that - all of these are the automated group here. So let*s just deal with this one here.

Yes, Dr. Piliavin?

DR. PILIAVIN: I remain quite confused. There was one question earlier that suggested that rather than reclassifying that the FDA could indeed simply add some guidance to a class I and accomplish the same thing. So I would like some clarification of that.

The second thing I would like to know is some figures on how long on the average it takes to approve a class I as compared to a class II.

MR. WILSON: The second answer first. There is no

distinction between the time frames for class I or class II. They are statutorily 90 days. The level of complexity in a class I may take more time than a particular class II. The greatest rate limiting step is the quality of the information supplied by the manufacturer. That is why we are trying to promote the notion of going with a reviewer guidance to get better communication with the manufacturer.

DR. PILIAVIN: About how long on average do they really take?

MR. WILSON: I think an average would be misleading, because some are more complex than others. I think that a range might give a better sense. I quoted one 22 days. We have some that have been in for well over a year.

DR. PILIAVIN: What about a median rather than the mean.

MR. WILSON: I have to be honest, I just simply do not have that number in my head. We could try to track that. Some can take years, depending on the quality of the submission. If it is a regulatorily complete submission - in other words, I had a slide up earlier - FDA is obligated to review it if it is complete. That does not mean that it has adequate information to determine safety and effectiveness. So we go through the review process, and then we spend time

writing a more information letter, and it is up to the manufacturer if they respond to that in a timely manner or with adequate information. Oftentimes there are two or three cycles of letters that are exchanged. It is not something that FDA can necessarily control. Ideally, what we are trying to do in this case is promote the idea of reviewer guidance to say, look, this is what we think is appropriate, and it is up to you if you provide it to us. If you do not provide this type of information, we may not be able to clear your device.

DR. PILIAVIN: Now my first question?

MR. WILSON: I forgot the first question, sorry.

DR. PILIAVIN: The first question is someone mentioned earlier the possibility of simply adding this kind of guidance to a class I classification.

MR. WILSON: Yes. We have been, in the recent year or so, been directed by our top management to be more mindful of all the regulatory processes that we are supposed to be following, and in this case we are trying to follow the regulatory process. It is in our view, which the commissioner has the appropriate authority to declare, that we feel there is new information that would affect the classification of such devices, and as such we feel that special controls should be proposed.

Now, again, this is a special control that FDA is proposing, that the regulations allow for anyone of those - any one of those special controls that we had listed, patient registries or other, if the committee feels that an other special control would be appropriate, I would be happy to listen to that, but considering our experience, our hopefully balanced view that what could enable the manufacturers to get their products cleared in the most expedient way that would be determined to be safe and effective - it is in our judgment that a reviewer guidance can help because it allows manufacturers to get a view of FDA*s current thinking on these concerns and hopefully make the process more efficient.

DR. PILIAVIN: Couldn*t you do that under a type I classification, give reviewer guidelines?

MR. WILSON: I believe it is possible to do that.

MS. HWANGBO: The critical difference between class I and class II is, among other, among other special controls, performance data is required. I mean, the performance data requirement is the critical difference. So according to our guideline, a manufacturer submitted those data, you know, we review those. Under class I, we look at - just compare with what other device, predicate device - we just compare - it is simple review, while under class II it is very detailed

scientifically in the area of performance data.

MR. WILSON: I think I might be able to help here. The term of substantial equivalence is a very, very critical term to understand. It is substantially equivalent to other products on the market, and the concern that we have is that we have identified areas where we feel uncomfortable relative to the performance of such products, and that is why we feel that an upgrade in regulatory control is warranted, in this case because of the need to work with the regulations, the logical approach would be to go to class II relative to the need for a special control. So we decided a special control was necessary. That is our view.

Now, how do you institute a special control? One option would be reviewer guidance.

REV. LITTLE: As a consumer, if I hear any concerns expressed over the performance of any piece of equipment and the suggestion is made to look at it more closely and move it from class I to class II, I have to say I cannot imagine why I would not want to see that happen. My question would be, well, what then would you add, and I understand that that is a different question, and I understand why the secondary question was withdrawn, but in regard to the first part of that question, I cannot imagine sitting here and hearing you

tell me that you have additional concerns and my saying, well, I do not think you should upgrade it to class II. So I would support it.

DR. HOLLINGER: Dr. Holmberg?

DR. HOLMBERG: Maybe I just need clarification on my thought process here, but if I look at question number one, what basically the agency is asking us to do is to classify the equipment for donor testing, blood donor testing. That would then move it from the review of CDRH over to CBER, and also they are asking us for a reviewer*s guide that looks at performance data. Is this correct, Mr. Wilson?

MR. WILSON: Yes.

DR. HOLLINGER: Yes, I would like to also ask Dr. Tuazon, who is on the Microbiology Device Panel and has some experience in these areas, if she would share with us some of her thoughts, please.

DR. TUAZON: My question is once you have reclassified equipment from class I to class II and we have certain concerns and goals we are trying to accomplish in terms of reclassifying the equipment, after reviewing the data, at the time period that they have been reclassified as class II, and these goals or concerns that we had set were not met, do they go back to being classified as class I?

MR. WILSON: The regulations provide - no, it does not happen automatically, but there are provisions to do that. The proposal to reclassify medical device can come from the commissioner, it can come from industry - industry can petition - it can come from a private citizen. So in the course of this proposed action, if we play it out for just a moment, if it is determined some point further down the line that this effort did not basically mitigate the hazards, then a person could petition FDA to change the classification or even petition the FDA to propose a different type of special control if they felt that the special control did not do the job but it still has a measure of concern to keep it as a class II. So there are mechanisms to do that.

DR. HOLLINGER: Yes, Dr. Verter?

DR. VERTER: Yes, I must confess that I am in a real quandary. My gut feeling is to go with Reverend Little, that anything that smacks of potential hazard, that we should err on the very conservative side. On the other hand, I have not heard anything today that makes me understand why I would vote that way. There is no data. There are some anecdotal reports that you have presented, although I imagine the FDA has had more reports than you have tried to give in a brief overview. Therefore, I cannot draw any confidence that what you are

proposing to do would actually resolve a problem. In other words, would this reclassification force manufacturers or users to supply more regulated data, in other words, be monitoring the equipment more, be supplying you with more data, give you an insight as to whether it is a mechanical issue, a human issue. I don't have a sense of what benefit would come out of it, other than a psychological sense that it has to be better because we are monitoring it better.

MR. WILSON: Could I briefly respond to that? I mean, we deal with what we know. We deal with what we know. What we know is that this type of equipment, based on our inspectional findings, based on recalls of the equipment, et cetera, a summary of that, indicates that we probably should take some measure of action that is appropriate. There is a mechanism by which to do that, and that is this forum here for a recommendation and then following it through to the Federal Register notice, et cetera. This is targeted at blood safety. I do not think we have the ability to project with absolute certainty that this type of special control will in fact eliminate those numbers of recalls. We just cannot tell. However, we do have experience in knowing that when a piece of equipment does not do what it is supposed to do, intuitively one would say, gee, maybe there needs to be a different

approach to this, and this is one of the different approaches.

There were options of other special controls that we would be happy to entertain. Does that help you? I am concerned that -

DR. VERTER: It helps to hear you say it, and I have confidence that you folks do have a lot more data than we do, but if I was - usually when I make a decision on something, I have some report to look at or some data to look at, and I guess I do not have a sense of - for example, if you take a piece of automated equipment that is out there now that you want to reclass that the FDA is suggesting reclassification of. Are these just random things that you hear about? Are there more of them? I mean, if it something that is running eight hours a day in a shop and a person is not there and a bell and whistle does not go off, was it just random chance that they happened to find one of the things you put up there, and is that the only one that occurred in a year, or is it 50 times that?

MR. WILSON: No, this has been accumulating over a period of several years. That is why we did a five-year retrospective look for the MDRs, and again, in our recent findings with CBER inspectors at blood test kit manufacturers who happen to also manufacture test kits, what we have found

are some of the problems that we have identified up here. We felt that in consideration of the types of problems and its substantive effect - in other words, the point of it being an infrequent event with very, very serious consequences - that is hard to quantitate. We felt that the best move to make would be to take one step up in regulatory controls, and those types of problems clearly have the potential for the release of unsuitable blood.

In one instance, we do know that unsuitable blood was released. In other instances, it could have been released but because of the statistics involved, it was too hard to nail down, but all the look-back and everything else was in place. So we know we have a risk here that we have an uncomfortable level with, and I guess maybe one of the other things that we are thinking about is, well, we have this data, we know it. You know, do we take action or don't we? That is what we are saying to the committee. We have a feeling that these types of controls can be put in place, and they are not, in our view, so burdensome to the manufacturers because they are in other instruments. It is just that we need to have them focused to make sure that all the package insert steps for the products for the HIV test kits are followed on an automated basis. I guess maybe one of the things that would

be helpful is to provide the committee with an extensive list of 483 citations, which are public, where flags have been -

DR. LEITMAN: What numerous members of the committee are really asking the FDA is to justify why it exists. Does an increased level of review by in-house experts really result in increased safety and efficacy? Everybody has asked that question. In other words, if we recommend that reclassification occur from class I to class II, does it really increase safety and efficacy? Where is the data that it does that? Where are the reports? Where are the audits? And FDA does not audit such things.

The track record is almost certainly that it does. How could increased scrutiny and increased level of data review, increased requirements for submission of performance standards not result or not have that result or at least be more likely to have that result than lesser safety and effectiveness. So I do not see that we can ask the FDA that question. It is an assumption that the entire Food and Drug review process assumes is true.

I have a complete separate question, which is -

DR. HOLLINGER: Just a minute. Let*s end up with this issue here.

DR. LEITMAN: My second question is a different

topic.

DR. HOLLINGER: But it is an issue. I think, you know, you presented it along these same lines. You did present all this information. It could have been interesting, at least to me. You talked about just in pipettor dilutors, automated pipettor dilutors, picking up too much sample, unequal volumes of diluent dispensed, conjugate delivered to half a plate, et cetera. It would be nice at least for me to know was this something unique, I mean, that you could design or change or alter or have the manufacturer alter that would make a difference, or was there some reason for it, other than just somebody noted this. That piece of information would be very important.

MS. GUSTAFSON: Yes, I do not think we have the complete information on each individual report, but there is enough problems with the equipment that - and Dr. Leitman stated it very eloquently as what we are trying to do is shift the responsibility from a postmarketing finding problems after they happen to looking at the appropriate design and testing of the equipment prior to marketing, including having the premarket review, with the goal of preventing problems at the user site later on.

DR. MARTONE: Let me response to the comment about

increased controls and scrutiny automatically resulting in the outcome that you want. I disagree that that is the case. We have seen this time and again in the field of hospital epidemiology where there has been guidelines, recommendations, controls, and then when you go look at the actual outcomes, you find in some instances that these guidelines, recommendations, and controls have been no more than ritual and have done nothing to actually decrease infection rates. That, of course, is the impetus to study the effectiveness of the controls and the guidelines that you put in place, and that is basically the error that we are in now. So I disagree that what the recommended controls may be here is going to lead to the outcome that you desire. It actually may make it worse.

MR. BALICK: This is Howard Balick again. I think this issue has come up in a couple different forums, and the forum is basically what Mr. Wilson has spoken about, the notice and comment period that we would look forward to with the guidance document and the acknowledgment that the public, typically the public, various factions of the public, the manufacturers, would have the opportunity to respond, and not only would they have the opportunity to respond, in particular I think we welcome and eagerly encourage manufacturers to give

suggestions in this area.

I mean, we can go through as mentioned, we can go through a package insert, we can line up all the package inserts, we can line up the EIA inserts and the Western blot inserts and all the inserts and we can extract out all the things that could go wrong, and we could put in the guidance document we want to flag for this and this and this and line it up, and yes, maybe we will miss something. The manufacturers do not want these errors to occur. I mean, hit it from a slightly different angle. Let's hit it from a marketing angle. We presented it from a safety issue, and that is our focus. That is FDA's focus, from a safety issue.

You know, your concern that possibly it is not implementing the special control guides is going to have an effect, well, certainly the manufacturers after having these types of MDRs, the manufacturers again that I did not disclose that have these problems certainly want them remedied. It is not in their best interest from a marketing perspective. Even if they are not 100 percent concerned with blood safety, there is a component of survival for the company, they want to minimize for various reasons those instrument effects. The technology is out there. If it is possible, the manufacturers have the wherewithal and they certainly have the capital to

identify the computer resources, the coding, the software, whatever needs to be done to incorporate that information in. Essentially by having comment by manufacturers and probably the ones that have the most experience and the most capital and the most resources are going to funnel in their comments. They are going to probably give us comments that we have not thought of, and suggestions. We will incorporate that.

It will become quite a rigorous and robust document, and in a sense what it will do is in funneling that back out, the people who might still have the most problem - either they have a new instrument, a small company, a starter company. They have a new instrument, or they are struggling, or they do not have the resources. That is where the malfunctions are primarily going to continue to occur. By funneling back out the technology we built in the document by having manufacturers of the resources comment, in a sense, you know, you have a collaboration of sorts.

Now, there was one argument that said, well, if this technology is out there, how come people are not just running around getting what they need? Why do they need a guidance from FDA? I mean, there are various reasons. You know, there is a marketing drive, especially a smaller company. You want to get the product out on the market, and we know that

marketing components unfortunately drive getting products out, and they will not build everything in unless asked to get the thing out there. They will deal with the effects of the malfunctioning equipment more so after the fact than before the fact. We cannot ignore the fact that this is not an ideal world, that everyone is on the bandwagon for protecting the blood supply up front, and they are going to build the time into it, but the fact is that having a succinct comprehensive document that is funneled out by the agency, everyone will know what is available as far as pinpointing the errors, and they can then have the opportunity to build that in.

DR. MARTONE: Yes, don*t misunderstand me, I agree that if you have identified problems and wish this additional measure of control, I am very much in favor of it. I guess the only thing that bothers me about this whole thing is the philosophy behind this. It looks like the FDA is coming up with the remedy for the problem without the data that you might require a manufacturer to provide to show that the remedy is in fact efficacious. I guess it is just a conceptual thing to me, and I would approach the problem differently. If I found a problem with a device, I would put the device on probation or do something and require the manufacturer to prove to me that the changes he has made will

in fact make that particular device safer. So I guess the thing that bothers me about this is you are coming up with a solution for their problem, and yet you have no data to suggest that your solution is, in fact, the solution.

MR. BALICK: Well, but again, this is the system we have to work in, and I am in favor of the request being made.

DR. MARTONE: I have one more general comment, and then I will let the panel and Mr. Wilson speak. I would agree with you; we do not know to what extent the situation will improve, but I cannot imagine it is going to get worse, and having the guidance document would at the very least, I think, improve the situation. I know some of the committee members* concerns that they do not have specific numbers here; they do not have specific numbers for projections, and that would be helpful as additional information, but I do not think that is needed to make the general assessment that it should be under class II special controls.

MR. WILSON: Just one other point, reviewer guidance has been successfully used. Now, we do not know if every reviewer guidance is going to hit every nail on the head, but it has been successfully used at FDA and particularly CDRH for many years. So while we cannot run a clinical trial on a reviewer guidance, we do know that the elements that were

placed up on the slide where there were problems with the test kit not performing or the instrument not performing in fact are in violation of 606. It says you must follow the test kit package insert instructions, in so many words, and it is not doing it.

So we have to react to that, and that is what we are trying to do here, and I think that Mr. Balick*s point is well-taken that while we cannot with absolute certainty predict that this is going to make all the problems go away, make the 483s disappear, make unsuitable blood not get released, it is going to incrementally increase our measure of confidence that at least those areas where we have seen problems, we are taking some measure of action to try to eliminate. And we are trying to do it by the system that was set up to do it with a dialogue with the committee, dialogue with the manufacturers, and the public.

MS. PIERCE: Is there a mechanism to ensure that once these special controls are in effect that they are actually measuring and obtaining the data that they are supposed to, as Dr. Martone pointed out, and there is some way to evaluate the effectiveness and whether or not they need to be changed again?

MR. WILSON: Well, I think that we can track that.

We do track many of those elements right now with errors and accidents and the MDR reporting. So we would certainly look back at it. If we continue to get the same type - we continually reinspect these firms. If we continue to see the same types of problems not being reduced, then over a certain period of time, because there is going to be a lag time of design changes, we will look at that and say, gee, maybe we could have done a better job. Is there something else that we could do?

But hopefully that will not have to come to fruition, because the notice, comment and rule process will allow manufacturers to integrate their concerns, too. So it is not a perfect world, and there will be some negotiations and debates and discussions, but we feel that this is an open mechanism by which we can proceed so that with the best effort it is not overregulated and with the best effort it is not underregulated.

MS. PIERCE: I guess I would also voice some concern basing the effectiveness of those special controls based on the reports of manufacturer errors or the device errors as pointed out by the copper sulfate here where we have got an article in Transfusion of events that happened in 1994 and 1995. This is now 1997. Were those not reportable to the FDA

at another time frame?

MR. WILSON: The medical device reporting requirements are such that the manufacturer of the device makes the decision as to whether or not it is reportable based on how the regs are structured. Essentially it is death or serious injury, and there is a whole section devoted to that, and that is why we are going to go back and take a look at that particular situation.

MS. PIERCE: Right, but then I guess what I am concerned about is we were going to be asked to change some regulations for that classification of that product based on incomplete information that was not available to us because it is not reportable, and that is a concern.

MR. WILSON: Well, there could be a question as to whether it should have been reported. That is why we had to withdraw the question and take a step back and take a look at it. You know, we sent our information to the committee approximately two weeks ago. The paper was published less than a week ago, and when we saw it we took action. We can only operate on the information that we have.

DR. NESS: It seems we are being asked to approve or agree with some changes in regulatory policy which are based on some anecdotal reports, and if in fact part of what we are

trying to do is to get data as to how often these things really occur, that might be useful. The other thing I guess I have not heard is even with that data is there some sort of standard that you use as to how often a manufacturing device or a process can have a tolerable failure rate. Is that part of the process, as well?

MR. WILSON: That is not an easy answer. It is our view that the blood safety issue is an extremely important one, and where we have been over the last 10 to 15 years scrutinizing blood establishments for the way they conduct their testing and ensuring that all the steps in the package insert, in fact, have been followed and the like. So I think where we are at is that we have a blood safety concern that is at the point at which we have a level of concern which we are proposing to take action on, and the action is to, as I had stated earlier, to up-regulate this with some guidance which we would hope would be beneficial to FDA and both the industry and the blood industry, too. They do not want to release unsuitable units.

DR. HOLLINGER: Yes, Reverend Little?

REV. LITTLE: I would just like to add that I guess I see this reclassification not necessarily in terms of a solution to the problem, but I think it will certainly, if

nothing else, draw attention to some of the existing problems. So on a very basic level I think it is important.

DR. HOLLINGER: Yes, Dr. Leitman?

DR. LEITMAN: I would like to return to a different topic, a question of clarification for Mr. Wilson. Is FDA intending to increase the distinction between class I and class II? Is it hoping to move all class Is to be 510(K) exempt?

MR. WILSON: Well, the distinctions between class I and class II are not new. That has been around since the 1976 amendments. What we are doing is looking at those, and I think I articulated in my opening comments the reasons for doing this, and one of the reasons is that we are trying to work with our sister agency, CDRH, to better allocate resources based on what we believe to be ranking of risk, and that is why we are coming to the agency and saying - coming to the committee and saying, look, these are the things that we think have some lower risk.

We could probably exempt them from 510(K) but not all the other general controls, and here are the other ones where we have evidence that there is a concern, relatively based on automation, and it is based on the walkaway concept which I think where we are headed for in the future - there is

no question in my mind about it - that therefore we would propose to up-regulate those into class II, and we feel that the best thing, the best balance that we have seen, is to go with the reviewer guidance so that the manufacturer is aware of our concerns, and we can develop that reviewer guidance in a parallel open mechanism with the manufacturers, and then hopefully it is a win-win for everyone - FDA, blood safety, as well as the manufacturers.

DR. MARTONE: For these devices that are used for diagnostic and screening purposes, are there reproducibility and durability criteria that you apply when somebody wants to put a new device out?

MR. WILSON: I am not sure I understand the question. Are you trying to draw a distinction between the clearance criteria for a device?

DR. MARTONE: Right.

MR. WILSON: Well, I think that what we have is that our concern is that there would be differences, and those differences would be related to things like large-scale automation, fast turnaround time, those elements that are unique to the blood screening and delivery system that would make our concerns higher or different.

We also have some differences, for example, with CMV

testing. We feel strongly that there should be a higher level of sensitivity for CMV tests because of the potential fatal outcome on transfusing presumed CMV-negative blood. So there are those things, but they are always related to blood safety, and CDRH uses its criteria for diagnostic determinations based on the fact that they have medical intervention and the whole diagnostic arena. So there are some differences. There is a lot of overlap, but there are some distinct differences and that is where we are coming from.

DR. MARTONE: I do not think I have made myself clear. When somebody has one of these devices, do you have criteria for reproducibility? Do they have to run a batch of samples a million times with an error rate of such and such a percent?

MR. WILSON: What we do is we do ask for clinical data on these pieces of equipment. Oftentimes it is three clinical sites, and it is oftentimes associated with licensed viral marker tests, and reproducibility data, et cetera, are looked at. We do not have a finite threshold in some of these areas, because depending on the type of test and the design of the equipment, it is very hard to draw a perfect statistical line.

I think it is safe to say that we are consistent in

what we expect in the performance of the instrument, and it is reflected in the test kit package inserts in many instances. There would be instrument data when it is run manually versus automated. Does that help?

DR. MARTONE: Yes, I think so.

DR. HOLLINGER: Yes, Dr. Nelson?

DR. NELSON: Well, I would agree with Reverend Little that any - since there are problems, and anything that - any step that would be taken that might identify the problem earlier and prevent malfunction or some problems later would be desirable. The only reason that I could see for not upgrading from a stage I to stage II would be if this actually changed the likelihood that a new device would - or the time that it would take for a new device to be licensed or get onto the market, or maybe it would not get on the market in the United States.

We have heard some testimony suggest that maybe this is a problem. Does Mr. Wilson or anybody else know is this really a significant problem, or is this really not an important issue? How important would the changes in the guidelines be to impede the licensure of a - particularly from a small company - of some sort of equipment that would really improve perhaps blood safety or lower the cost or whatever?

MR. WILSON: It is very difficult to answer. I think I can try. What other countries do in terms of allowing medical devices on the market is their business. We have export laws. Manufacturers can export.

DR. NELSON: But there are - I mean, it is their business, but it still is a comparative - I mean, there should be some data to suggest what the difference is.

MR. WILSON: That is not submitted to FDA. We do not get the opportunity to review it. We have had some concerns, however, that there have been products that have been approved outside the United States that may have greater sensitivity to certain viral markers, but manufacturers have not elected to submit those to FDA. Now, if the argument is that, well, it takes too long to get an FDA approval, our position has been that we have a set of regulations. Also, the rate-limiting step in many instances is what the manufacturer submits. Let me roll it back to the original point. Reviewer guidance ought to help in that area.

DR. LEITMAN: The question of time has come up from numerous panel members. How long will it take? Will this increase the time to licensure or approval of a product? My experience is - well, listening to the agency, they perceive a problem, not a major problem but a problem, and the agency

is going to give closest scrutiny to these submissions, no matter what this panel decides. It is going to take a manufacturer a longer time to get something approved if they do not submit the original information, and we have heard Mr. Wilson say this, as part of their initial submission, because what will happen after that first 90 days is the agency will reply with five pages of questions. We need this data; we need this clarification; we need more of this.

If that is submitted up front, because there is a guidance that says we have to see this, it is going to take a shorter time, and we know this when we submit establishment license amendments. The more you submit up front, the more likely in 90 days you are going to get a very small number of questions. So this will in fact decrease the time once the agency receives a packet, although it will increase the time it takes the manufacturer to submit that packet.

MR. WILSON: Right. I would also like to add we are proposing, you know - de facto, it would be an interim period. We are opening up the issue. There would be a time frame which manufacturers could think about it. The time frame in terms of developing such types of changes to products can be up to several years, because there is a pipeline for engineering, development, et cetera, and what we are saying is

this is a place to start.

DR. KHABBAZ: One additional comment, I share Dr. Ness* and Rev. Little*s point of view. I think what I heard you express is concerns regarding the performance of the safety and effectiveness of these devices, and I think it makes sense to up-regulate to allow you to reduce risk of errors. Now, I am again, remove the question of whether a reviewer guidance is the way to go or other, and I am not sure I am prepared to advise you on what best - what I wanted to say is that I think what is needed and what I hope to see - and I think I heard this - is that there be a mechanism for you to assess the effectiveness of whatever mechanism you use to up-regulate these devices so that you can go back and assess whether this was the appropriate change or whether you should change up or down or sideways as needed.

MR. WILSON: Certainly that is going to take place. The quality system regulation, the new and improved GNP, was largely driven on inspectional findings. It is the same kind of thing we are talking about right now. Manufacturers were having recalls, 50 percent of them, based on manufacturing errors, but the other 50 percent were based on design. It could not meet the intended use of what it was supposed to do. So as a result, over a period of notice, comment and rule,

meetings with manufacturers - I was on that committee also within FDA - a new quality system regulation was published, proposed, comment, revisions, comment, revisions, and as of June 1 of this month, it has now been - it is now in place. Manufacturers are obligated to comply with that, and it is viewed, you know, based on those types of data that this will hopefully be an improvement.

The basic premise here is that you cannot test quality into a product; you can only design it in, and when you are talking about trying to determine whether random errors exist and the like, the only way to really effectively handle that is putting your weight on the design side, and that is what we are trying to get at here.

DR. HOLLINGER: I know we have had a public hearing, but I would like to ask if there is anybody - and looking at it from an opposite side - anybody from industry would like to comment about some of the things that have been noted here. I would like to hear how this works basically back and forth. Anybody want to make a response? I would like to just hear what the issues are from your standpoint.

MS. MELERSKI: Yes, I am Pat Melerski with Abbott Laboratories regulatory affairs, and I would just like to get some clarification from the agency on a couple of things. One

is how will any new mechanisms - and I heard that brought up by one of the committee members that their main interest is ensuring that there is a mechanism in place to ensure that the safety is designed into the device. So I would like to ask the agency, compared to explain how or what they are planning to implement in terms of new mechanisms that would go above and beyond offering them information that they currently have available to them today, and by that I mean today there is a reviewers guidance that applies to both class I and class II devices, as currently classified by the CFR, and within that reviewers guidance for blood bank products, there are things such a hazard analysis where the manufacturer has to go through and do an analysis of predictable failures by the product and also identify the controls implemented within that product to mitigate or eliminate the error.

There are also design controls that are also components of the current GNP design controls that are also submitted as a requirement for that reviewers guidance, and those are the same design controls that are called out in the new design controls for the GNPs which are required to be in place. So really the difference that I see is that between the class I recommendation and moving into a class II is the level of product testing, because for class I you only have to

show substantial equivalence, which is a comparison study. For class II and above, you have to do actual substantiation of product claims, and that is pretty intensive testing.

So the real issue would be will this increase testing, and what is the proposal for the level of increased testing if you follow this logic will offer the agency above and beyond what they have today. From what I am hearing, they want to move class I devices, that being automated systems - not necessarily the test kits that are going on that automated system, but the automated system itself - into class II, where the real substantiation of product claims comes from running the test kit system on that automated system, and those test kits for blood products are already falling into a level of class III for the majority, which are PMA and PLA products, and they are already getting a lot of infield customer testing going on.

So I have to ask the question: how will these infrequent improbable errors that even the manufacturer cannot predict was in the design of the product going to be identified by the agency by requiring more information be provided in submissions and increased testing on the system itself, not the final product that is going on that system? You have to remember, too, that the time when an automated

piece of equipment is being submitted to the agency for approval or for clearance, some of the assays are not even in development - they may be in the early development process at that point, because you want to get your testing system to the point where you are able to test your assays and test your test kits and get them out and into the clinicals. So there is a chicken and an egg kind of thing, and also level of information and whether it is going to offer you anymore than what you currently have available.

So if the agency could kind of walk through that logic and help the committee and ourselves in the audience understand that, it would be appreciated. Thank you.

MR. WILSON: The reviewer guidance here would be directed at specific equipment that is used to screen the blood supply, and I think what Mr. Balick tried to articulate is that if you are going to be required to follow a package insert, there ought to be some type of mechanism that an automated equipment, piece of equipment, can alert you when you are not doing that. These are the kinds of things - we are not trying to invent anything new here. What we are trying to say is they need to be applied. So it is specific to blood screening equipment, and anyone of those types of pieces of equipment can compromise a run.

The fourth element for safety and effectiveness I want to underscore is reliability. Maybe it does not give you the wrong answer, but it still has to work, and if it is breaking all the time, maybe those platelets do not get out. You know, we are trying to look at the entire picture and say what can we do on a reasonable basis to increase performance of these products to increase the level of confidence that an unsuitable unit is not going to get released, and this is our proposal.

DR. HOLLINGER: Well, let*s - I think we have had quite a bit of discussion. Oh, please, Dr. Linden?

DR. LINDEN: One more question, if you could clarify, Mr. Wilson, this is my understanding, that you are going to be applying this to equipment currently on the market, right? That they will have to come up and be re-reviewed?

MR. WILSON: That is because there will be a new intended use statement that says for blood screening, and that will trigger a 510(K), and then the model would be, if I could play it out, that the manufacturers - and we have done this routinely with other medical devices - call us up and say, hey, can we come in and talk about this, and we have a pre-meeting. I give lectures at FDA about how to conduct pre-

meetings with sponsors to get the most bang for the buck, and we ask them to send in a proposed agenda, give us all the information, and please, please, put down those questions in that agenda that are really difficult for you that really are horrible situations. Let's get those on the table, and let's try to resolve those up front rather than saying, well, we will work around it later, and then when the 510(K) review comes in and all of a sudden we find that there is a substantive hole or a problem, then we have to say to the manufacturers insufficient information to determine safety and effectiveness; please go back to square one, so to speak.

The manufacturers would then provide - we would have a meeting. We would agree in many areas or maybe have a secondary meeting, talk it over, and it is really great if you have a reviewer guidance, which by the way, manufacturers have asked for this continuously for licensed test kits as well. So this is not anything that we have just all of a sudden decided is something that we needed to promote. They have asked for this. When are you guys going to promote guidance? Medical device manufacturers, I have met with them, and that is what they have asked for. Part of the problem that we have is some of our resources do not permit the time to do just everything at once, but we are doing the very best we can.

So, with the reviewer guidance presumably, and the discussion, manufacturers will be able to go ahead and submit a new 510(K). We did have the situation with the CMVs where we gave a time frame in which manufacturers had to file the 510(K) so that we would not have a disruption in the availability of CMV test kits. So we have already been through this exercise, and we know how to basically work it so that we do not create any unnecessary risk by unavailability of products.

Now that does not mean that if we take a look at a piece of equipment and we feel really uncomfortable with its design that we are obligated to clear it. The objective of this presentation is to say, okay, here is where we have these concerns; how do you mitigate not completing step number four, because you do not have a flag that automatically does it? What do you propose? We have some ideas here. Do you have any other ideas? And you know, that can be resolved up front, for the most part. Ninety to ninety-five percent of the issues can be resolved up front if they are told to FDA.

FDA does not know what a manufacturer is going to present. They only present what they present to you. Therefore FDA only knows what is presented. If there is other additional information that we are totally unaware of and that

is not laid on the table, then when a 510(K) review comes in, oftentimes we will say, well, where is this, because it was not mentioned at our pre-meeting or in other discussions. Please give us more information.

So we are viewing this whole scenario as something that can be beneficial to all sides, and it can be done in a balanced fashion so that these readily available flags can be instituted for blood screening purposes.

Does that answer your question?

DR. LINDEN: Well, sort of, but I did not really even get to my question yet.

[Laughter.]

DR. HOLLINGER: But it was a good response.

DR. LINDEN: Yes, it is was a great response.

[Laughter.]

I mean, it is on the general issue, but I guess my specific question is what if one of the existing pieces of equipment, in the course of the application you identify that they need to make XYZ modifications, which may not be able to be made on the existing equipment that is out in the field, and there needs to be new equipment manufactured or a lot of software changes? What happens during that interim time? I am just concerned about lack of product availability, that if

you would propose saying, well, once we determine this equipment is unsatisfactory, it has to be immediately taken off the shelf?

MR. WILSON: FDA has had to deal with that in instances, at least in my recollection, over 25 years. What happens when something does not fit today*s expectations? I mean, that is really what you are asking. There are mechanisms by which the manufacturers are notified, and there is a time period. Again, we are concerned about blood availability, but it has to be balanced with safety, and we are in a position where we have to make some of these cuts.

Most recently, the HCV 1.0 test kit was deemed to be unacceptable when an HCV 2.0 was licensed for blood screening. So, you know, we have to do these things, and it has to be done on a very, very careful basis, but there are mechanisms of dealing with that.

DR. LINDEN: Okay, thank you. My concern is that the reviewer guidance be so clear up front that the manufacturers very well know what is expected of them so they do not in 90 days get a surprise of a huge laundry list of things that they were not expecting. It sounds like the agency is fully intending to involve them in the process, and that will be known, but that would be my advice, to make sure

that that happens.

MR. WILSON: By the way, reviewer guidance, for example, one of the things that I was describing up there about a pipettor - how do you know that an automated pipettor delivered what it was supposed to deliver and did not do it into the right well, et cetera? What we would do in such guidance is we would pose those questions. How does the manufacturer propose to ensure that this happens, and when it does not happen, what kind of a flag goes up? We can propose options, but one of the things that we want to make sure manufacturers do is come up with a better idea than FDA has. So we would not lock in, well, you must do it this way or you must do it this way.

What we are going to do is take it from the other side. This needs to get done. Here are some options that we have shown to be successful in certain designs. You may want to consider that, but if you have a better mousetrap, be our guest. By the way, you will need to show us that it works, too. You cannot just say I have a high technology attribute here without providing some measure of data that, in fact, not only is it high technology, but it in fact functions to the claim that is being promoted.

DR. HOLLINGER: I think we will go ahead and call

for a vote at least on this first question which has to do with automated test equipment, and that includes automated pipettor dilutors, incubators, automated washers, automated spectrophotometers, and so on. That is really what the issue is on this test equipment. So if there is no further discussion, then I would like to ask for a vote on the first question of reclassification of these class I products to be reclassified as class II and special controls.

All of those in favor of this reclassification, raise your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: Any abstaining?

[No response.]

DR. HOLLINGER: And our two non-voting members?

DR. NESS: I vote yes.

REV. LITTLE: In favor.

DR. HOLLINGER: Could we have the reading of the response?

DR. SMALLWOOD: The results are 12 yes votes, 2 no votes, no abstentions. The non-voting consumer and industry representatives agreed with the yes votes. For the record,

there are 14 members here that are eligible to vote, including our temporary voting members.

DR. HOLLINGER: I would like to move on into the second question. This has to do with automated vacuum-assisted blood collection systems such as those which are used under a vacuum, remove blood from patients and so on. Again, should it be reclassified? I want to open it up for discussion of this issue.

DR. LEITMAN: I have not used such a system since I was an intern, and that was in a therapeutic whole blood exchange, which is now performed routinely even in small centers by machines that do not use vacuums, continuous flow or discontinuous flow machines. How often is this used in the United States?

DR. HOLLINGER: Well, I got the impression it is not used very much, but it was an issue of should it be? Should a manufacturer come through with something like this, should - is that correct? Mr. Wilson is nodding his head yes. But it is not something that is used much. But I do remember the little round plastic things. You know, the bag would go in it and the suction would go on and so on. And I think they are just saying if a manufacturer comes through with such a device to remove blood rather than just through gravity and so on,

should it be regulated as a class II device? Anybody, any issues or questions on this particular thing that they want to raise specifically?

If not, let*s put this up for a vote, too.

All those in favor of this reclassification, signify by raising your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: Okay, and abstaining?

[No response.]

DR. HOLLINGER: And our two non-voting members.

DR. HESS: In favor.

REV. LITTLE: In favor.

DR. SMALLWOOD: The results of voting for question number two, 13 yes votes, 1 no vote, no abstentions. The consumer and industry representatives agree with the yes votes.

DR. HOLLINGER: The third question on the automated group has to do with the blood mixing machines and the weighing devices for the amount of blood that is removed and so on and whether it should be reclassified also from class I to class II. Any comments from the committee?

Yes, Dr. Piliavin?

DR. PILIAVIN: My question about this goes back to, again, the absence of data. On the first one at least we had a lot of pieces of anecdotal information. On three, I just do not know that anyone has actually come up with examples of when this has been a problem. All of the discussion seems to have been targeted towards the stuff under item one.

DR. HOLMBERG: I would like to get clarification from the agency. I think that probably where the direction this question is going is looking forward to the future of automation and automated blood collecting device, weighing and potentially some other processing, too, the blood product, which would require software to control that. If there is software involved, would it not come under a class II anyway, under the reviewers guide?

MR. WILSON: This is Len Wilson. I think the answer is not necessarily. In most instances, I think it would, but again, if you are looking at this based on a risk issue, our concern would be that reliance in those systems that are designed, automated systems that are designed to record donor identification, other demographic information, off a bar code reader that goes into a mainframe computer, we feel that that is just as important, for example, as a blood establishment

computer software system, that substantive error could be made if simple programming errors are integrated into such equipment.

If a blood mixing and weighing device is not necessarily microprocessor controlled, it has a spring-wound clock on it that has a bell that goes at a certain point, I do not think we are trying to go after those. I think we are trying to go after the equipment that cannot be confidently validated by the users. That is where we are headed, and what we found in terms of software is that it is so complicated that really the manufacturers are the ones that are in the best position to ensure that measure of validation. So that is why we are saying not only general controls, but special controls, and again, trying to keep our theme constant, issue a reviewer guidance saying, okay, these are the kinds of things that we think are important for you to design and validate to answer the following questions. If you have to have donor ID as part of your integrated system, what checks and balances do you have that when you do that bar code swipe that it is getting the right information in? And those are the kinds of questions. There is nothing really esoteric here. It is just ensuring that it is meeting its claims.

DR. HOLMBERG: But my question is is there not a

reviewers guide presently available for software, 510(K) of software.

MR. WILSON: Yes, absolutely, but it is written generally. The objective here is to write specific guidance for these types of pieces of equipment. The 1991 CDRH guidance has all the fundamental principles that we are asking for. We are taking it a step further and saying - and oh, by the way, this is not our effort to try to get products cleared through FDA quicker, that you have a specific intended use here for this particular product. That means that you have to do some specific design and specific testing to make sure that it does what it is supposed to do. Here are some thoughts on what we think are important so that you design a better product, we can clear it faster, and if it is a great product then people will benefit from it. I mean, that is essentially our bottom line, and that is what we are trying to get at here.

DR. HOLLINGER: Mr. Wilson, on this particular issue - maybe it could have been applied to the last one, too - we are often talking about machine - particularly the first issue, we understand. I mean, you start a machine and you run a lot of samples through and you often are not paying attention to it. You are off doing something else. Now, here

we are talking about something in which people are having blood drawn. Usually, at least in my experience, there are people around watching these patients, what is going on, all the time, and this is not quite the issue, at least as I see it, even though it is automated, of a particular risk here. You are going to see if the mixer is mixing. You should at least. It seems like that would be an obvious thing to look at. In the weighing device, the bags are only going to hold so much. So it does take 500 mls instead of 400 mls of blood, you know, or something like this if that happens. There is not quite as much of a problem here.

MR. WILSON: Maybe I can help. I mean, we are not intending to up-classify the manual types of equipment, and again, this is based on risk. So those where it is viewed that this type of equipment, although it may have some element of microprocessor control, but if it is not - if it is mitigated by other elements of the product design, then when the manufacturer proposes its 510(K), we could classify it as a class I.

So there are options that we do not have to necessarily force everything into that, and again, this would be the purpose of the Federal Register notice to say here we are; we are going to propose a guidance, and I would presume

manufacturers would come back to us and say, yes, but what about situations like this, and every one of those issues would be examined, and then our job would be to integrate those issues into a guidance, send it back out to manufacturers having them comment on it again, and basically work those things out.

We do not want to tie anyone up. We want to increase communication and make it effective.

DR. HOLLINGER: Any other comments from the committee?

DR. MARTONE: Aren't you still around, though, even though it is automated, watching the patient or the donor?

MR. WILSON: Well, yes, but the concern here is that we have had recent examples where training has been a substantive problem in terms of that type of monitoring or use of particular equipment, and our view that while no piece of equipment can ever be perfectly designed to eliminate human error, what we are looking at here is that those reasonably expected functions that the equipment is performing, if it is not performing it properly and it has an effect, an alarm will go off. I mean, that is basically the substance of what we are trying to get at here.

Yes, there will be some measure of question as to

whether or not it might be a I or a II, based on its complexity. The problem is that we cannot write the specific reg for everything, because we will never get through it. We have to make some cuts here, and this is what we are trying to do, and have the reviewer guidance basically articulate some of these concerns, too. We can put that in the reviewer guidance for manufacturers, but we do not know how manufacturers are going to be designing this type of equipment two years from now. We cannot predict. There could be a new way of reading information that is not even relative to bar coding. There is another way of handling it, but that has a particular potential for a defect.

What we are trying to do is get at capturing the whole issue and then asking those critical questions: how are you assured that this type of a function is being -

DR. MARTONE: So the answer to the question, as I understand it, for number three is that it is not such a big problem. The blood mixing and weighing is not a big problem right now.

MR. WILSON: No. Our concern is that when numbers one, two, and three are automated, there is a potential for - in one, we have hard data. In two, the equipment is not readily available, and number three, blood weighing and mixing

devices, more automation is creeping in, and we want to be prepared for it, and we want to take a step ahead. We want to try to work with the manufacturers before they send in a 510(K) and say, you know, why isn't this getting cleared? Now we have new issues of safety and effectiveness because of automation that the manufacturer needs to backtrack.

One of the biggest problems with software-driven instruments is that we get it when it is finished. It is not being developed gradually so that it is a very high level of concern by manufacturers, and we feel it at FDA when they go ahead and they build all this equipment and then we say, no, there needs to be some changes because it is not doing what we feel is appropriate or your data does not support it. So they have to go back to square one in many instances - in some instances. In some instances they may have to go all the way back to square one; in other instances, they may be able to correct 90 percent of - or fulfill 90 percent of the concerns. But we cannot tell what they are going to be doing. So we can only operate on what we receive, and that is why we are trying to take this step and say, okay, look, here are some of our concerns, and at least if you can capture these, everyone will be better off.

DR. HOLLINGER: If there is no further discussion,

let*s vote on the third question then.

All those in favor of the reclassification of automated blood mixing and weighing devices, raise your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: And abstaining?

[Show of hands.]

DR. HOLLINGER: And our non-voting members.

DR. NESS: I would not support this one.

DR. HOLLINGER: Would not?

DR. NESS: Would not.

REV. LITTLE: I am in favor.

DR. SMALLWOOD: Results of voting for question number three are as follows: 10 yes votes, 3 no votes, 1 abstention. The industry rep agrees with the no votes, and the consumer rep agrees with the yes votes.

DR. HOLLINGER: Thank you.

I will ask the committee what they would like to do here. We have the next - can we put up the next two questions, please, which are pretty straightforward.

MS. PIERCE: Before we go onto that, can I just reiterate a request that Dr. Holmberg made earlier? When the

reviewer guidance, the specific reviewer guidance, do come out for review that the committee members do receive those? I think that is an important request.

DR. HOLLINGER: Mr. Wilson nods his head yes.

We have two questions here, and I will ask the committee what they want to do, and actually they could probably be taken - we could either take them as a group and then discuss them and then decide what to do on them, or we could break it down. We could see how the discussion is. Or we could take a break. Right now there is a break scheduled for lunch. If you want to go on through it, and that is what I think most of the members would like to, and I agree with that. So we will go through with the next two questions.

The two questions are does the committee agree that heat-sealing devices should be exempted from filing a premarket notification, and again, these are not sterile docking devices. The second one is does the committee agree that a cell-freezing apparatus for in-vitro diagnostic use should be exempted from filing a premarket notification? Could we have any discussion from the committee on either one of these issues here?

[No response.]

It sounds like there is no discussion here.

Yes, Dr. Piliavin?

DR. PILIAVIN: The premarket notification, that is the 510(K), right?

DR. HOLLINGER: Yes, that is correct.

Yes, Dr. Verter?

DR. VERTER: As a non-blood banker, could someone just briefly tell me what the implication is of removing that restriction, either the committee or FDA?

MR. WILSON: The regulations allow for exemption. As a matter of fact, maybe can you put the slide back up that has class I on it, and it has the general controls listed.

DR. VERTER: I realize it allows for exemption. I am just asking what the implication is for the blood.

MR. WILSON: We feel that there is sufficient evidence that the product will be safe and effective in the absence of a 510(K) with the balance of the other general controls in place. Because we feel that this is a low level of risk - this is our proposal - that manufacturer would be registered with FDA. We would know that they are manufacturing the product. Premarket notification would be skipped. They would maintain records and reports; if there were complaints, et cetera, they would be filed.

If the manufacturer had something that looked like

it was a complaint relative to serious injury or death, they would be obligated to file an MDR with FDA, and as I was trying to articulate earlier, the good manufacturing practices literally 19 days were substantially strengthened to ensure that products are well-manufactured and adequate for its intended use. So those are the types of supplementary elements that continue to be used.

It is our view that, again, we were trying to work in the same direction as our sister agency, CDRH, where they are looking at the reengineering of such products relative to the review process, and in many instances they are saying, look, those products that are class I*s, is there any way that we could look at it and safely come to the conclusion that premarket notification would not be required, and have we lost anything there? That is what we are saying. In our view, with a heat-sealing device as well as a cell-freezing apparatus, we do not feel that there are substantial enough concerns that a premarket notification, 510(K), would make a substantive difference in determining the safety and effectiveness of the device.

DR. HOLLINGER: Well, with that response then, I think we will put these two - both those questions, actually. Can we do them both together? No reason not to. Or do you

want to do them separately?

DR. SMALLWOOD: For clarity.

DR. HOLLINGER: Oh, for clarity we will do them separately then. So the fourth question about the heat-sealing device should be exempted from premarket notification, all of those in favor, raise your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[No response.]

DR. HOLLINGER: Abstentions?

[No response.]

DR. NESS: In favor.

REV. LITTLE: In favor.

DR. SMALLWOOD: All right, the voting results, unanimous yes votes. The consumer and industry representative agrees with the yes votes.

DR. HOLLINGER: And the fifth question, under the same circumstances.

All those in favor raise your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[No response.]

DR. HOLLINGER: Abstaining?

[No response.]

DR. NESS: In favor.

REV. LITTLE: In favor.

DR. SMALLWOOD: The vote on question five, unanimous vote. The consumer and industry representative agrees with the yes votes.

DR. HOLLINGER: We are going to adjourn the meeting for a day to reconvene tomorrow at 8:30. I do want to thank the FDA for helping us sort of understand a little bit more about these processes, and also the public for helping us understand also from industry.

Dr. Smallwood wants to have the committee stay briefly to discuss a few items, so if you would, please, we would appreciate it.

[Whereupon, at 1:00 p.m., the meeting was adjourned until 8:30 a.m., the next day.]