DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

OPEN SESSION

Volume I

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(202) 546-6666

C O N T E N T S

C O N T E N T S (Continued)

OPEN SESSION

P R O C E E D I N G S

DR. HOLMBERG: If we could have the committee members come to the table, please. We are going to do a quick roll call. Before I do the roll call, I just want to make sure that people understand some of the circumstances that we are under. We were in hopes that we would have new letters for the new members of our committee signed by Secretary Thompson before he left. He had his walk-through yesterday to say goodbye to everyone. So, the letters did not get signed and so what we have done, as permitted by our charter, is that we are permitted to call back our previous members who have had their terms expire. Fortunately, one of the four, Dr. Gomperts, was able to join us.

So, I did a quick check to see if we had a quorum even for any recommendations or actions that we have and, Dr. Gomperts, you make the quorum. So, thank you very much.

DR. GOMPERTS: I trust it will be in the record and everybody will see that!

DR. HOLMBERG: Dr. Brecher?

DR. BRECHER: Thank you, Dr. Holmberg. I would like to welcome everyone to this 25th meeting of the

Advisory Committee on Blood Safety and Availability. Jerry, did you want to say anything about the 06 committee rotation off?

DR. HOLMBERG: Yes. Let me just go on down. I will do the attendance. So, we have Dr. Brecher here. Dr. Bianco?

DR. BIANCO: Here.

DR. HOLMBERG: Dr. Bowman?

DR. BOWMAN: Here.

DR. HOLMBERG: Dr. Epstein:

DR. EPSTEIN: Here.

DR. HOLMBERG: Dr. Gomperts?

DR. GOMPERTS: Here.

DR. HOLMBERG: Dr. Haas?

DR. HAAS: Here.

DR. HOLMBERG: Chris Healey?

MR. HEALEY: Here.

DR. HOLMBERG: Dr. Klein?

DR. KLEIN: Here.

DR. HOLMBERG: Dr. Kuehnert?

DR. KUEHNERT: Here.

DR. HOLMBERG: Dr. Linden is absent. She is not feeling well. I just want to make a comment that she has put a lot of work into this meeting so her efforts are recognized by the committee. CDR Libby?

CDR LIBBY: Here.

DR. HOLMBERG: Karen Lipton?

MS. LIPTON: Present.

DR. HOLMBERG: Dr. Sandler?

DR. SANDLER: Here.

DR. HOLMBERG: Mark Skinner?

MR. SKINNER: Here.

DR. HOLMBERG: John Walsh? John e-mailed me also and, because of illness, he is not here either. Dr. Wong?

DR. WONG: Present.

DR. HOLMBERG: Merilyn Sayers? Absent. Dr. Heaton?

DR. HEATON: Present.

DR. HOLMBERG: And Mr. Allen?

Let me just go through a few things as far as the conflict of interest. We all went through that brief introduction this morning. Once we get the new members of the committee to the table, they will undergo swearing in

and also ethics training on a smaller group basis. So, consider that you have had your ethics training done for the year.

I also want to remind the people that when they do speak, if there is a potential conflict of interest, please identify that. I would also ask that from the audience. If you speak at the microphone, identify yourself and then also, if there is any potential conflict of interest with the statement that you are making, please do wo.

For the minutes of the last meeting, the minutes have been posted on the website. They are required by the Federal Advisory Committee Act to be posted within 60 days, and they are signed by both myself and Dr. Brecher. Does the committee have any objections to the minutes that were posted on the web?

[No response]

Thank you. The review of the charter--the charter was also posted on the web and I think last time we highlighted some of the changes. At the time that we presented the new charter, the charter had not been signed by Secretary Thompson but, again, some of the functions of the committee are that the committee will advise on a range

of policies, including identification of public health parameters around safety and availability of blood supply broad public health ethical-legal issues related to blood safety; and the implication of blood safety and availability on various economic factors affecting product cost and supply.

The makeup of the committee has been changed a little bit not to be as prescriptive as the last charger. Then also, as far as the funding for the committee for my office, it was extended to the Center for Medicare and Medicaid Services. So, this year CMS will also be contributing to the operation of this advisory committee. We have representation on the committee from CMS and it also brings a closer tie into the blood safety and availability.

The charter was signed by Secretary Thompson on September 8 and it is effective until October 9, 2006.

If I could have the next slide? As a quick reference, I just want to go over those individuals that will be rotating off the committee for next year. As you can see, we have quite a list of individuals that will be rotating off: Dr. Angel Beck, and I apologize that I did not identify her on the list here; Dr. Bianco, Dr. Brecher, Dr.

Haas, Dr. Heaton, Mr. Healey, Dr. Lipton, Dr. Sandler, Dr. Sayers and Mr. Skinner.

Now, we will be posting a notice in the Federal Register of those individuals, asking for nominations for the committee. That usually happens in the springtime, with a close to the applications sometime in June. That will give us enough time to be able to get the paperwork in process.

One of the other things too is that our charter does permit us to renew people on the committee. There is quite a review process that goes on within the Department of Health and Human Services so I would encourage both the committee members and also the members of the audience, if you would like to nominate somebody for the committee, please do so and look for that Federal Notice sometime in the April-May time frame.

This year we want to ensure that the dissemination of that information gets widespread so we will be sending that Federal Register notice to various organizations, interest groups, to get the word out there, organizations that have a newsletter or a journal that could disseminate the information. So, we are looking for broad

dissemination. Many times the Federal Register is not available to the masses and it is very difficult to find something in the Federal Register. So, this is an attempt within the Department to try to get wider dissemination of the Federal Register notice.

DR. BIANCO: Jerry, when is the last meeting?

DR. HOLMBERG: August of this year will be the last meeting. The government's fiscal year starts October 1st and that will be fiscal year 06. Dr. Brecher?

DR. BRECHER: Thank you, Jerry. We are just going to review a bit about what happened in the last meeting and discuss the response from Secretary Thompson.

In the last meeting there was a recommendation regarding transfusion-related acute lung injury. The committee reviewed transfusion-related lung injury data. They did not find any scientific evidence to recommend an intervention at that time, but did recommend that the Secretary support the expeditious development of a standardized definition, implementation of clinician education, effective surveillance modeling, the impact of deferral or screening intervention and research into the etiology, diagnostic testing, epidemiology, treatment and

prevention. We are going to have follow-up on most of these resolutions in just a minute.

The second recommendation was regarding access to treatment for individuals with rare blood disorders. While the committee recognized the lack of licensed treatment for individuals with rare blood disorders presents a significant health risk and a discrepant therapeutic standard for persons with some other blood disorders, such as hemophilia, the committee notes importation for personal use and off-label use are not adequate long-term solutions or acceptable alternatives, and the committee concurred that there was a need to promote the development and licensure of treatment products for these individuals, and that it may be appropriate to adopt approaches for therapy for rare blood disorders.

The committee recommended that HHS promote the development of products to treat individuals with rare blood disorders, including facilitating, one, obtaining additional license indications for already licensed products and, two, approval of products and their indications in the U.S. for European licensed products and, three, develop of new products.

The committee also recognized the importance for industry investigators and regulators to cooperate in both pre- and post-market approval of potential new therapy and indications. The committee encouraged the government to invest in research and support adequate reimbursements to optimize treatment for rare blood disorders.

The third recommendation pertained to bacterial detection of platelet concentrates and seven-day platelets. The recommendation was whereas consistent with previous recommendations of the committee, the committee has concluded that bacterial contamination of room temperature stored platelet components represents one of the most significant remaining infectious risks of blood transfusion. The transfusion committee has adopted a voluntary standard that requires the implementation of methods to limit and detect bacterial contamination in all platelet components. There is now inconsistent practice in the applicability of currently available bacterial tests. The committee recognizes that public health would be improved by the availability of a released test, approved for this purpose.

Given the current inadequate supply of platelets, the committee recognizes the need for seven-day storage for

platelets to meet patient needs, and the currently proposed study of bacterial screening for release control seven-day platelets would take at least two years to complete. Therefore, the committee recommended that the Department support the use of grant or contract funding that would allow availability of funds to support applications to development bacterial screening for release testing of platelets for use in routine practice, and the Department should consider alternative strategies that could expedite licensure of seven-day platelets in significantly less than two years.

The committee heard evidence that most apheresis platelets are currently tested by an approved quality approved method. Individual whole blood-derived platelets are not and cannot be similarly tested by practical and validated assay for contamination.

The situation has resulted in a dual level of safety for platelets prepared for transfusion and it represented a threat to platelet supply in regard to the inventory of whole blood-derived platelets which are in decline. Given the availability of in vitro data, supporting the acceptable quality of pre-storage pooled

whole blood platelets, the European data supporting the clinical efficacy and safety of pre-storage pooled whole blood-derived buffy coat platelets, which are different, the data from the McMaster study which was presented to this committee of the clinical safety and efficacy of pre-storage pooled whole blood derived platelets, the committee urged HHS to adopt strategies to expedite licensure of pres-storage pooled blood-derived platelet components for transfusion based on the critical review of the available information.

Recommendation for this public health impact implicating hepatitis B, virus minipool and NAT for blood donor testing, it was stated that whereas hepatitis B virus risk for transfusion analysis from immunodeficiency virus and hepatitis C and that HBV minipool NAT testing as currently configured has limited ability to reduce the risk of transfusion-transmitted hepatitis B compared to individual NAT technology that is under development, the average morbidity of hepatitis B infections is significantly less than that of HIV and HCV, but donor screening by minipool NAT would incur a cost comparable to other NAT testing. And, vaccination is an effective strategy for

hepatitis B, unlike HIV and HCV. Therefore, the committee concluded that in regard to introduction of minipool, as currently conceived, hepatitis B NAT for blood donation, the committee believes that for comparable expenditure of healthcare dollars the general public health would be better served by expanding the hepatitis B immunization program. The committee believes the Secretary should encourage the development of multiplex direct pathogen testing on the individual donations.

Committee members, in front of you, among the papers that were put out on the table, is the response from Secretary Thompson. We only received this last week and that is why it was not in the CD that was distributed to members. It is dated January 13, 1005. Secretary Thompson wrote that, in regard to TRALI, since the committee first recognized the importance of TRALI as an issue in blood transfusion safety in 2003, there has been increased awareness within the Department and the blood community. While we review the recommendation to determine appropriate action, I request that you continue to monitor progress by the scientific community and bring the topic to the

committee as needed, and we will be talking about TRALI is just a few minutes.

The committee's review of access to treatment for individuals with rare blood disorders was timely. Currently, recommendations are being considered by several agencies within the Department, specifically the FDA is considering alternative pathways to improve the process for additional clinical indications and new product introduction. This issue will be discussed in a co-sponsored public workshop in June, 2005.

The Secretary went on to say he was pleased by the continuing progress made by the blood community and the Department's agencies regarding the safety of platelet products and standardization of protocols for the detection of bacterial contamination. The recommendations are being carefully considered and we are hopeful that resolution can be achieved soon.

The committee's discussion and recommendations made regarding hepatitis B virus minipool nucleic acid testing has been extremely helpful to the Department and its agencies in weighing cost and public safety benefit. A

status report on this issue should be available to the committee at the next meeting.

Please express to the committee members my sincere appreciation for their advice on these issues.

Any comments or questions on the resolutions and the response from Secretary Thompson? If not, we are going to go with the agenda. We are only a minute behind. We are first going to hear about transfusion-related acute lung injury. Dr. Traci Mondoro, who is a health science administrator with the National Heart, Lung and Blood Institute, will give us a short update on the progress that NHLBI is making in promoting research in transfusion-related lung injury. Traci?

DR. MONDORO: Good morning, and thank you for the opportunity to speak about what NHLBI is doing about TRALI.

First, for a brief introduction I just want to let you know that NHLBI, of all the NIH institutes, has the primary responsibility for initiating and monitoring programs that support translation medicine and blood safety. As far as TRALI, we always welcome investigator-initiated applications and I will go into the difference between those and institute-initiated programs. TRALI is an NHLBI's top

priority of all the non-infectious transfusion complications and we are working on putting programs into place to address some of the unknown of TRALI.

As I said, investigator-initiated applications, which are those an investigator decides he has an idea about TRALI--we always welcome those applications. We encourage these investigators to talk to us first and we try to make sure that our review panels are equipped with experts who can review these applications in the manner that they deserve.

We also currently have two ongoing programs that were institute-initiated, meaning that we have set aside dollars specifically for these programs and they have not only the capacity and the interest to study TRALI, but when the request for applications was written TRALI was mentioned in both of these programs as specific examples of research topics that would be welcomed by the Institute.

We are also in the process of writing another initiative that will be presented for approval to our board of extramural advisors. We hope that the BEA, as they are called, will accept this and that our budget office will accept it as well. But there is an intensive review process

that this initiative must go through. And, that initiative is the focus on TRALI as a hematologic complication of cardiovascular surgery and, if approved, that initiative would be released this fiscal year.

So, in 2002 our interest in TRALI manifested in a working group that was held on May 30th. It was chaired by Dr. Pearl Toy from the University of California at San Francisco. There were other members, including Mark Popovsky of the Hemanetics Corporation, Edward Abraham, Dan Abrusco and Crhis Silliman of the University of Colorado. Dr. Abraham, if you are not familiar with his name, is a pulmonologist. And, this working group was co-sponsored not only by the Blood Division of which I am a member but also of by our Lung Division because they have an interest in TRALI too since it is related to acute lung injury. Also, the Lung Division sponsors an acute lung injury network and other programs in acute lung injury and we would like to tap into that expertise to address TRALI issues was well, and we are encouraging the transfusion medicine community to work with the pulmonologist community to address these questions and also to educate others. Les Holness, of the FDA, was on this working group, Patricia Capcol of Blood Source, Jan

McFarlan from the Blood Center of Southeast Wisconsin, Avery Nathans who is a pulmonologist from the Seattle area, and Dr. David Strogheck from the NIH Department of Transfusion Medicine.

The results of this working group have been accepted and will be published in the forthcoming issue of Critical Care Medicine. They did work out a working definition of TRALI, with the main points being that there had to be new acute lung injury in the patient and that the onset is during or within six hours after the end of transfusion of any plasma-containing blood products.

This definition became the foundation for discussions of the 2004 Canadian Conference. Dr. Toy presented the results of the working group. The definition adopted by the consensus panel at the Canadian Conference was based on the NHLBI working group's definition, and the results of the Canadian Conference were recently published in the December issue of Transfusion.

So, two programs that NHLBI currently has in place that have been approved and the dollars have been set aside for are called REDS-II and the transfusion medicine SCCOR programs. Many of you may be familiar with REDS-I. This

was the retrovirus epidemiology donor study. There was a very active program for the past 15 years. We recently held a competition for the new REDS-II centers. There are six blood centers, Hoxworth in Cincinnati, the New England Red Cross, Emory University and the Southern Region Red Cross, University of California at San Francisco and Blood Systems, the University of Pittsburgh and Life Source, and the blood center of Southeastern Wisconsin. The data coordinating center for REDS-II is Weststat which was also the coordinating center for REDS-I.

This program is very large. There are many dollars set aside for it and it is equipped to not only do epidemiology studies but also we had some studies proposed in TRALI, and I will describe a protocol that the steering committee received with great enthusiasm, at the end of this talk.

The other program we have is called the SCCOR. This stands for Specialized Centers of Clinically Oriented Research. NHLBI uses this mechanism for transfusion medicine and for hemostasis and thrombosis as well. The transfusion medicine program recently received applications and there were some applications that will be reviewed at

the end of March. There were some applications that were devoted entirely to TRALI research. When we wrote the request for applications for this TRALI was one of the top suggested topics for research. There was at least one application that had a very comprehensive trial program, with projects ranging from basic research at the bench all the way to epidemiology.

I will just briefly describe the TRALI protocol that has been proposed by the REDS-II steering committee. The entire committee--well, proposed by a subcommittee of the REDS-II committee. It was received with great enthusiasm and we hope that if it is chosen for implementation that it will be done within the next three to four months.

The protocol is broken down into two studies. There is a donor study and a recipient study. The donor study will examine the prevalence and characteristics of antibodies to white blood cell antigens in donors with a history of pregnancy and/or transfusion. The recipient study will call for chart review of FFP recipients to identify TRALI cases and then to compare the incidence of

TRALI between patients receiving antibody-positive units to those patients receiving only antibody-negative FFP units.

So, that is a summary of what NHLBI is doing in the area of TRALI. Are there any questions?

DR. BRECHER: Questions from committee members? If not, thank you, Traci.

DR. MONDORO: Thanks.

DR. BRECHER: We are going to move on to critical pathways initiatives and access to care for rare blood disorders. We have two speakers. The first is Dr. Paul Meid, Deputy Director of the Division of Emerging and Transfusion-Transmitted Diseases in the Office of Blood Research and Review at CBER. He will be updating us on the critical pathways initiatives and access to care for rare blood disorders. In addition, we have Dr. Mark Weinstein, Associate Deputy Director at CBER who will update the committee on an upcoming workshop.

DR. MEID: Thank you, Dr. Brecher. I am going to talk very briefly this morning about FDA's critical path initiative. What is the critical path initiative? Well, it is an FDA initiative to bring attention and focus to the need for targeted scientific efforts to modernize the

techniques and methods that are used to evaluate the safety, efficacy and quality of medical products as those products move from product selection and design to mass manufacture.

Here is the critical path for medical product development. It extends from prototypic design or discovery through preclinical development and clinical development to application to FDA and product approval and launch. Now, why FDA? Well, the agency has a unique role vis-a-vis the critical path. FDA scientists are involved in review during product development. They see the successes and the failures and the missed opportunities. FDA guidance documents are issued and they are based on science and they foster innovation and improved chances of success. And, the FDA has a convening and coordinating role for new biomarker and clinical method development. So, that is why FDA.

Now, here is the critical path challenge for blood products, to find critical path opportunities to improve blood product safety and efficacy while minimizing disruptions to the blood system.

CBER held a public workshop in October, 2004. The title of the workshop was from concept to consumer, CBER working with stakeholders on scientific opportunities for

facilitating the development of vaccines, blood and blood products and cellular tissue and gene therapies. There was a panel session that focused exclusively on opportunities for FDA and industry to work together on the critical path of blood product development and commercialization, and this panel consisted of representatives from the blood and plasma organizations, academia and consumer groups.

The panel identified some opportunities for FDA to increase communication with industry. It was felt there should be an information sharing partnership between FDA and industry, and the creation of new forms for information exchange between FDA and industry. Establish a mandate--it was felt there was a need for FDA to establish a mandate for public health on a particular issue rather than just market-driven product development, however, not where the technology does not exist. Mandates would confirm the agency's thinking on market need and will, in effect, bring more technologies to the market.

Set standards in advance of product development. For setting of standards by FDA, it will give industry defined targets for product development. Analytical standards, physical standards and process standards as

targets will help industry proceed in the right direction. For example, in bacterial contamination in blood products, blood donor testing panels and blood cell survival times FDA should set objective, firm approval requirements. This would help industry in product development prior to submission of an application to the agency such as FDA did at BPAC in stating requirements for licensure of a test for chagasis.

FDA should make better use of preexisting data to make rational regulatory decisions, for example, using epidemiological data to support the possibility of testing for West Nile virus only during the appropriate season, or testing for chagasis only in different geographical regions--use preexisting data in that way.

FDA should help to reduce product development time. FDA and industry should access European technologies, for example, automation of blood component production to improve blood safety. FDA should facilitate licensure of blood components with data from Europe.

FDA should develop consistency with other agencies in regulatory guidelines; work with agencies nationally, such as HRSA and CMS, to achieve coordination, harmonization

and partnering for consistency of standards, for example, in patient identification and in bar cording, and internationally with regulatory agencies and groups developing standards in other countries.

FDA should accept the use of alternative measures to validate product or process changes; allow the use of model systems and surrogate endpoints for safety and efficacy, comparability studies or analytical studies to obviate large clinical trials to validate these changes, for example, in the immunogenicity of Factor VIII. Imaging technologies could be valuable as surrogate endpoints for quality of blood components at or near expiration; use risk management strategy, for example, to reduce clinical study requirements for blood components in the setting of comparatively small risk.

Also, FDA should help with research and product development in specific area such as gene chip and nanotechnology for direct detection of infectious agents in products, including viruses, bacteria and prions. Prevention of and/or detection of bacterial contamination in blood products; pathogen inactivation; animal models and

tests for prion diseases. Lastly, FDA should provide more guidance on structure of clinical trials.

So, FDA CBER is listening and thinking creatively about solutions in these areas, some of which will involve our stakeholders for sure. But FDA will be publishing this list and similar lists for the vaccines and cellular tissue and gene therapy panel sessions in a scientific journal and in a trade journal for comment soon. Any questions?

DR. HOLMBERG:

DR. BRECHER: Yes, Karen?

DR. LIPTON: Thank you, Paul. Actually, the AABB participated in that critical path initiative workshop. We thought it was very, very helpful. I just wanted to ask a question. When you talked about better use of preexisting data your examples all dealt with epidemiologic data in terms of whether you could do a test at a certain time of year or a test in a certain geographical location. But I also thought there was some discussion along the lines of what we had the last time about using preexisting clinical data to support product licensure too. Did that theme pick up in this workshop?

DR. MEID: Yes, it did. That is another example of using preexisting data. We should make better use of that and base decisions on that type of data including foreign data, data from Europe especially where trials have been done.

DR. LIPTON: Thank you.

DR. BRECHER: Yes, Crhis?

MR. HEALEY: Thank you, Paul. You said in your discussion that there was a mandate for CBER to focus on public health rather than marketplace product development and, yet, a lot of the things you did talk about seemed to be market-based product development. I was just wondering how that shakes out. Clearly, from the plasma sector you can expect that market-based product development is an important feature of the critical pathway.

DR. MEID: That is absolutely true. What I am giving you here are suggestions, feedback that came from the working group at the panel session. Establishing a mandate for public health is difficult quite often. Usually you do end up with market-drive product development. But this was just a suggestion for us to think about how we can do this,

areas in which FDA can do this type of thing and perhaps issue a mandate--something for us to think about.

DR. HEATON: Paul, is there any relationship between this and the HHS new medical innovations initiative which has just been published?

DR. MEID: That question I can't answer.

DR. BIANCO: Paul, thank you. This is the new FDA and we really wish this would happen because it is very important, that is, instead of the FDA being seen as it has been, as an obstacle to innovation, as a facilitator of innovation. I am very excited about it.

Regarding mandates, there is the point that Chris raised. I think that is very important, that is, industry needs reassurance and that is the case with West Nile. The epidemic may go up, may disappear, and what is the assurance that the industry has to invest millions and millions of dollars and a lot of people to develop assays, and do it without having the reassurance that the blood centers and are going to use it?

DR. MEID: Yes, these are suggestions that we heard. The bottom-line message here is that FDA is listening and the challenge now is to figure out how to

implement these suggestions, how to make them happen in ways that will be meaningful.

MR. HEALEY: Just to follow up, is CBER going to pull together a document or publish sort of its charger or mission vis-a-vis the initiative here?

DR. MEID: Yes, I think the intention is to publish both in a scientific journal and in a trade journal from all of the sessions, including vaccines and cellular and gene therapy.

DR. GOMPERTS: Dr. Meid, one particular issue in regards to individuals with rare blood disorders where therapeutic agents are available in Europe, for example, and not available in the United States and, clearly, it takes time to license these products with the new regulations and the new guidance and the new policy of interacting with consumer groups, industry and so on, which is very good and, of course, the upcoming workshop should be excellent. In the meantime, and it is probably a number of years, there are individuals who do not have access. Are there activities going on within FDA and industry and consumer groups to try and bridge this gap?

DR. MEID: Yes, I think there are, and I think this is something that we need to focus on specifically in the future. You know, we certainly welcome suggestions from everyone about how to make something like this happen. So, we are certainly open to that.

DR. GOMPERTS: Thank you.

DR. BRECHER: Thank you, Paul.

DR. WEINSTEIN: Dr. Brecher has already mentioned the committee's recommendations to promote the development of products to treat rare blood disorders. As part of that initiative of the Department, the FDA is organizing a workshop on biological therapeutics for very rare plasma protein disorders, to be held on the NIH campus, Lister Hill Auditorium, on June 13 and 14 of this year.

The primary objective of this workshop will be to examine current and potential pathways to the licensure in the United States, and elsewhere, of products to treat rare diseases such as deficiencies of Factor V, Factor XI and fibrinogen, among others. At the same time, we anticipate that information obtained from this workshop, particularly with regard to clinical trial design, will aid in the

development of products with somewhat larger patient populations.

The agenda for this meeting is still in the planning stage. At this point, we plan to discuss the need for these products from the patient perspective; challenges that industry faces in developing these products, including regulatory and financial considerations; the current situation in the United States and Europe; and potential modifications of clinical trial design.

As part of the discussion of future directions, we anticipate talking about the potential of having similar regulatory requirements in the United States and Europe; the development of global patient registries to use in clinical trials; the role of NHLBI to support studies; and are there ways to increase incentives to industry; and can we rely more on post-licensure surveillance to help in licensure making clear to patients level of risk and benefit?

At this point, our organizing committee has representatives from several offices in the FDA, including the Orphan Drugs, Biostatistics and Epidemiology and the Office of Blood. We also have representatives from CDC, NHLBI, European medicine agency, the National Hemophilia

Foundation and PPTA. Others may be included as the project develops. Are there any questions?

DR. BRECHER: Mark?

MR. SKINNER: I just want to thank the FDA. I mean, this is directly in response to our resolution last time and this should go a long way toward addressing our concerns and helping us find solutions for the problems. Thank you.

DR. BRECHER: I think the whole committee welcomes this workshop. It is a good outcome that directly comes from this committee so thank you. We have a follow-up now on hemolysis associated with the Pall filter. Hal Baker, who is senior Vice President for Pall BioMedical Global Marketing and Product Commercialization with make his presentation. Well, he was around. Why don't we put that on hold because he seems to have stepped out for the moment, unless, Rich, you want to make a presentation?

Are there any discussions on items that have been presented from this morning? Oh, here comes Hal. Hal, you are on.

MR. BAKER: Good morning, Mr. Chairman, Mr. Secretary, committee members. Thanks for giving Pall the

opportunity to come and present by invitation at the committee meeting today.

My objectives here are twofold, pretty straightforward by important nevertheless. I will provide a brief situation update about the voluntary limited field action affecting the BPF-4 filter, and discuss some other noteworthy issues that I think have implications for our community to ensure a safe and adequate supply of blood to meet future patient needs.

Just to put recent events into perspective, I will take a close but brief look at a short profile of red cell leukoreduction in the U.S. It is fast becoming a standard of care and we take great pride in knowing that nearly four million units are leukoreduced using the BPF-4 filter. It was the first pre-storage leukoreduction filter licensed in the U.S. nearly a decade ago, and one of its important abilities is to be able to be used throughout the entire 42-day red cell storage period.

For the benefit of those who couldn't participate on one of our two web casts, this slide summarizes the situation and its current status. In early December several centers in the southeast part of the U.S. reported higher

than expected hemolysis in a limited number of Pall BPF-4 filters. I am happy to say that these events have not recurred. The good news is that there have been no patient events reported at any time throughout this situation, and since the initial reports no new significant observances have been reported either.

While I am sorry to say that this has caused some of our customers concern and some inconvenience, we certainly are pleased that this has had no impact on the delivery of health care during this period of time. We appreciate our customers continued support and the cooperation that we have received from the blood banking community as well. This is underscored by the effect that an AABB task force on domestic disasters and acts of terrorism subgroup concluded that the measures taken by Pall and the FDA were sufficient to address the acute issues that led to convening of the task force.

To address the most current topic that is on everyone's mind, the determination of the root cause of hemolysis, we continue to work hard and fast in analyzing all possible causative factors. While there are no definite answers at the moment, our continuing investigation

indicates that the likely cause may be linked to some variability in the priming of the affected filters. A reduced surface area, causing higher flow velocities for blood passing through the open areas, combined with the more sensitive red blood cells of older blood, may result in a higher shear rate causing the hemolysis observed in the implicated lots.

We know blood is a complex business and we know some hemolysis occurs despite everyone's best efforts, and it is acceptable during the red blood storage period. Nevertheless, we certainly recognize the importance of detecting excessive hemolysis which can cause complications in some patients. That is why we immediately assembled our best talent--manufacturing engineers, scientists, technicians with decades of experience working with the BPF-4 filter to become part of an immediate technical response team.

Taking a look back, this slide presents just a few of the actions we took to quickly respond to the situation. In agreement with the FDA, we initiated, on December 17, a limited voluntary recall of 24 implicated filter lots and immediately set out to make sure that customers were aware

of this situation. We have reached out in a number of ways with several mailings, two web casts. We have had our product application specialist visit many of these centers to collect blood, collect filters, take them back for analysis. We have spoken to many of our customers and many within the ARC and ABC, and BCA by phone. We have also changed the IFU or the BPF-4 from the entire 40-day storage period of red blood cells back to 5 days as an extra precautionary measure to further reduce any risk. And, we have also quickly brought any of the unused filters from implicated lots back in and replaced them with new inventory to make sure that customers had the capabilities that they need and that blood is available for patients as well.

Now, in addition to sharing this information, I wanted to take a moment to also point out a few things that we learned from this experience as a result of the time that we spent going out to customer sites, speaking with them, bringing back product and bringing back blood for further analysis. We know that routinely red blood cell units are visually inspected for excessive hemolysis before release from blood centers, collection facilities and again before transfusion. Visual assessment is subjective, however, and

even with a visual color comparator as a reference point the visual method is one that can easily result in an overestimation of hemolysis in red blood cell units, which can certainly affect availability for patients.

We know that the spectrophotometric tests for free hemoglobin have been used and they are the gold standard, but they are really not suited to detection in blood processing settings. There are, however, now some simple, rapid, portable, low complexity point of karyotype devices that could be integrated into blood product or transfusion service settings. It was obvious from the work that we did that at the moment that is not typically what is happening or what is being used.

But even if an objective method was easily available, the estimate of true plasma for hemoglobin, the value needs to be compared to a standard against which a clinical decision for transfused units needs to be made and right now that doesn't really exist in our industry. We think that moving in that direction would be very beneficial for everybody. It would certainly help our customers and many others, blood bankers throughout the industry as well as transfusion services have a better understanding of what

they would be able to do with product once that information was available.

Now, I am not suggesting that the blood banking industry needs another set of routine quality control procedures for blood manufacturing, far from that. I am just suggesting that combined with an inexpensive test method to measure free hemoglobin in plasma a target value for assessment might be a good way to help create an objective definition of what excessive hemolysis might be and that could be feasible today and, as a result, it could potential prevent the discard in the future of units which might be otherwise safely used for transfusion whether those products are leukoreduced with a Pall filter, another organization's filter, or not leukoreduced at all.

So, we are going to take these steps to assist our customers. We have decided to ensure that everyone of our dozen product application specialists who support customers in the field now have hemacues, which are one example of this device that I have alluded to. We have established a protocol for their use. We have purchased controls so that product application specialists can conduct confirmatory measurements as part of any on-site investigation, and we

are making that service available to our customers for any Pall product, for any non-Pall product that they might use or for any non-leukoreduced product that they might use. We also have our spectrophotometric capability in our labs, and we have compared the two methods and found them to be comparable and we are making it possible for customers, any time they want to get a better understanding of what they might see in a unit, that they could send that to us for analysis and we would provide that information back to them.

What we would like to recommend, however, is that AABB standards committee consider taking this up for a possible recommendation and perhaps publication in a future edition of the technical manual. Having a reference standard for the measurement and assessment of plasma free hemoglobin for transfused units we think would be beneficial for our entire community. And, we hope that the advisory committee will support an initiative for the development of objective criteria for excessive hemolysis in blood components.

I want to thank you for the invitation to come here today, and reiterate again that blood safety is our utmost and highest priority.

DR. BRECHER: Questions? Andy?

MR. HEATON: Yes, in terms of looking hemolysis in stored units, there is a generally accepted FDA standard that for approvability hemolysis has to be less than one percent. It is also true that it is quite tricky to measure plasma hemoglobin very accurately. So, I believe that it would be appropriate to set up an industry-based task force. I would urge you to include international standards. The BASK committee is probably the best group to assist you in developing that, as well as having an AABB task force as well. You know, hemacues is okay in terms of measuring plasma hemoglobin. It certainly wasn't designed for that purpose and, in the ranges of interest that you would be looking at, it probably is a stretch to its maximum to give you an accurate number. So, I do believe that this is an appropriate area of safety review, and one that you should receive support from ACBSA on developing a standard, but I would urge you to make it international as well as domestic.

MR. BAKER: I think that is a good recommendation. We would be happy to work in that direction.

DR. BRECHER: Gerry?

DR. SANDLER: Thank you very much. That was very helpful. I would like to add a clinical note from the perspective of the hospital transfusion service. This presentation, and much of what I have read, focuses on hemoglobin and hemolysis. From the hospital perspective, the issue is potassium and almost exclusively potassium. We were lucky no one had a fatal outcome but a unit of hemolyzed blood could kill a person who is very, very young when it represents a large infusion. AS we look forward to further presentations, I hope we are going to hear the word hyperkalemia because, to me, that is the core of the problem. It is not the hemoglobin; it is not the color; it is not hemolysis--it is potassium, and I think we want to keep the focus on that because if we don't clinical who aren't experienced are going to miss the whole point.

DR. KUEHNERT: Just to follow-up on that, I just had a question on your statement that there are no adverse patient events. How are you determining that?

MR. BAKER: Well, we have reached out to all of our customers and asked them to also be in touch with all of their consignees. We ask that they pay particular attention to any evidence, visual evidence of higher than expected

significant, you know, very dark cherry red type of hemolysis, recognizing again that visually it is still hard to determine what that really means and, if so, to certainly not use any of those products. So, through that process and through speaking with our customers, communicating to them and relying on them to communicate with their hospitals, we have not received any reports. We are not aware of any that may have come back to any of our customers. So, on that basis I think it is reasonable to be able to say that.

DR. KUEHNERT: So, it has sort of trickled down to the clinicians but there is no direct notification to clinicians, and also is there any active surveillance, for instance, looking at patient outcomes in those that may have received the blood that was filtered using the implicated lots?

MR. BAKER: I think that the normal process for reporting that information would apply or be in effect if there was any kind of patient reaction or patient event that was untoward. We would expect that that information would be made available back to the blood collectors and at Pall we are one step removed from that process since our

customers are the blood collectors and theirs are their consignees, the hospitals.

DR. BRECHER: Hal, I was thinking that a few mL of hemolysis is probably of little clinical significance, however, a cherry red supernatant plasma would be very worrisome. And, I don't know that you need a hemacues to see cherry red plasma. You can see it. Are there other correlates that you could use, such as supernatant potassium or lactate dehydrogenase levels that are easily measured in the chemistry lab that can also be used as an alternative to, say, hemacues?

MR. BAKER: Well, I think the answer to those questions, Mark, are probably a little bit above my pay rate, but we were concerned, as our customers were, about anything that was very dark cherry red but the issues that came up and a lot of the concern was when it was a little bit more pink but certainly not that obvious, and then the question becomes, well, how do we really know, and how can you help us, and what should we tell the hospitals, and how would be advise them what to do or not to do, and it was on that basis that we decided to take this action in order to err on the side of being safe and just to identify any lots

that were implicated, remove them from use and replace them with product that had been manufactured on a different date that we knew, from the units that had already been used, weren't likely to be subjected to that same concern.

DR. BRECHER: So, is Pall recommending that there be a routine examination for hemolysis is you are spinning down and looking at the supernatant, or how are we supposed to go forward?

MR. BAKER: We are not recommending that our customers do anything different than they have done before, other than to continue to be observant of product that may be manufactured, BPF-4 or any units from any manufacturer, leukoreduced or not, and if there was a concern that they saw we are going to be able to give them an objective indication of how much of that free hemoglobin might be in the plasma so that they would have something more quantifiable to go on. But, again, against a lack of any kind of standard it is difficult to be able to answer the question about the concern for the patient.

MR. HEATON: Mark, one of the difficulties one faces is that supernatant plasma becomes very visibly pink at as low as 20 milligrams percent. So, if you attempted to

implement a national standard you would end up with the bulk of your units looking like they were hemolyzed. And, from the symptomatic perspective, the key issue you heard about is not so much the hemoglobin level but the associated complement activation of hemolysis. So, probably some form of visual inspection, greater attention to visual inspection to the current standards would be enough, and providing that patient's report of hemoglobinuria which might be more significant.

DR. BRECHER: Celso?

DR. BIANCO: Hal, thank you very much for the presentation. Thank you for the effort that you and the company put into that. There was a lot of concern among a lot of centers and I recognize that effort.

I am just a little bit disappointed that you don't have a scientist here presenting to us what you found. We know that your response was very effective but we have no scientific answers to what happened at this point. You gave a hypothesis but we didn't see any data as yet.

The second thing is that I think that, at least as it appeared in your presentation, you are focusing on the symptom not on the actual problem. Hemoglobin in the

supernatant is a symptom that can be caused by a lot of stuff. What led to that is what we are concerned about. The solution is not for people to inspect more. The solution is to prevent it from happening when we use the filter. So, I hope that you will be able to have your very good scientists come up and tell us what really happened and how we can prevent it from happening in the future.

MR. BAKER: I appreciate the concern, Celso. So, we are in constant communication with the FDA and meeting, and discussing, and sharing information, the results of all the investigations and working through this hypothesis that I talked about. So, I think we are close to being able to do that and we certainly will share that once we have reached the definitive conclusion and have that information available for everybody. And, we are not suggesting that solving that problem isn't important. We are certainly focused on that. That is one of the reasons that I am here today and we want to make the very best product that we can for customers and that is our highest priority.

DR. BRECHER: Gerry?

DR. SANDLER: Let me give you an example of the kind of perfect storm that I would like to be concerned

about. It is the standard in this community and many others that if a young child is going to get a liver transplant or cardiac surgery we give them five-day old blood or we wash it because of our concern about potassium.

The discussion, as I understand it, is to focus on hemoglobin, the color, which might bring us back, let's say, from something that looks like 42-day old blood to something that might look like 15-day old blood. Since the blood is being filtered in the community blood centers out of one lot of the manufactured product, the perfect storm at my hospital could be that five units of perfectly clear plasma with a very high potassium level would just slip right by me because it is five-day old, specially filtered blood, out of one lot. I think the standard of looking for hemoglobin as the endpoint of safety is erroneous. Thank you.

DR. BRECHER: Hal, you do have the chairman of the standards committee here and I am sure he is listening in the audience, as well as the chairman of the technical manual committee. So, I think there will be some ongoing discussions regarding your recommendation to look at this.

MR. BAKER: Thank you, Mark. I just want to make one final statement, if you don't mind. Again, we are not

suggesting that the way to resolve this is for blood centers to look for visual signs of hemolysis and, you know, that is the safeguard. That is the standard practice and it is there really to detect excessive--the potential for bacterial contamination. It is used sometimes in this way to intercept product that might not be safe for transfusion and I think some of the points that have been raised really are very pertinent to that fact. So, we are not suggesting that that is the safeguard or that is the thing to do. It is just what is done and it is something that I think we can augment and make better as long as that is still going to be part of the practice of blood banking. So, thanks for the time today. I appreciate it.

DR. BRECHER: Thank you, Hal. We are just a few minutes behind schedule. We are going to move on to the next topic, which is current status of bacterial detection in platelet concentrates, availability and progress toward seven-day platelets. As I have in the past, I am going to step down in this session to avoid any possibility of conflict of interest. I don't think I have any but I do receive research funding and have been a consulting advisor for a lot of these companies, although the only specific

shares of stock my family own are two shares of Disney stock. Each of my girls has one share. But Mark Skinner is going to chair this section.

MR. SKINNER: Good morning. We are going to begin this section by hearing the presentation from Marianne Silva, with the AABB task force, summarizing the 2004 fall survey and review of their industry guidance documents. She is the compliance officer in the Division of Transfusion Medicine at UCLA Medical Center. She is also the chair of the AABB standards committee, responsible for the 23rd edition of the AABB standards for blood banks and transfusion services. Marianne, over the last month, has been actively involved with the AABB task force on reduction of bacterial contamination. She will present an update on the fall survey and also the guidance documents developed by the task force.

MS. SILVA: I want to thank you for the opportunity and the privilege for representing the AABB and the bacterial contamination task force this morning. As stated, my name is Marianne Silva and I am here on behalf of the task force. I have been a member and actively involved

in the task force since its initiation and, additionally, as chair of the 23rd edition of standards.

Additionally, because I will be referring to a number of different products or methodologies or things that are available, I wanted to as well say that I have no conflicts of interest. I have no grants, scholarships. I have no stocks. My only source of income is through my employer, UCLA Medical Center, and through my husband. So, there is no conflict whatsoever.

The task force was charged with conducting a survey, and the goals are as stated above. Truly, the goals were to evaluate platelet usage; supply an outdating; to identify the currently used bacterial detection methods; to identify what follow-up procedures were being conducted after the initial positive or abnormal result was obtained; to find out what was happening really to the notification of physicians and donors when positive or abnormal results were obtained; and to identify the rate of the initially positive and confirmed positive test results. Additionally, overall we wanted to see the impact of bacterial detection testing on many of the QA activities that were being performed in centers.

The survey was divided into specific areas so each facility would answer questions specific to their operations, with it be a blood center, a hospital blood bank or a transfusion service. Each section was about 40 questions long. The electronic survey was sent to about 1000 facility contact names, and there were about 100 that bounced back. So, all in all, about 900 facilities had access to the survey but it was only for a two-week period of time. It was only available between September 17 of 04 and October 1 of 04.

Overall, if you were to look at the bounced back and the number of e-mail responses that were received, you would look to see that there were about 350 out of 900 responses received, which would indicate about a 38 percent response rate. So, I have to say though that there is a caveat there, and that caveat is, is that related to the American Red Cross? All sites submitted one response, together, collectively, it was one response. Additionally, Blood Systems all sites, collectively responded as one facility. So, while we can say that there may have been numerically only 35 responses as far as from blood centers, it is not just 35 blood centers that responded but, in

addition to the American Red Cross and Blood Systems, it is 33 additional blood centers who responded to this survey. We know statistically that the American Red Cross and Blood Systems collect approximately 50 percent in the nation's blood supply facilities--clearly, 33 facilities, blood collection facilities over that 50 percent that were captured in this survey.

Also, it is helpful to define what some of the terms that we used here are. A hospital blood bank is a facility who collects, processes and transfuses blood components. There were 47 facilities of that type, and transfusion services would be a facility who is not involved in the collection process at all but receives all components from outside sources.

When we look at the volume of platelet components manufactured by these facilities, we can see that our response rate accounted for a considerably higher number. I will say as well that my definition on the slide--you know, writing out whole blood derived platelet concentrates becomes truly problematic in any type of format so you will see WBDPC abbreviated for whole blood derived platelet concentrates. But you can see related to the blood centers

and the facilities that responded to the survey that they were involved in the manufacture of over 1.6 million whole blood derived platelet components and about 900,000 apheresis platelets in 2003. Related to hospital blood banks, they additionally supported the inventory by providing 132,000 whole blood derived platelet concentrates and about 65,000 apheresis platelets. So, the survey in number really captured facilities involved in the manufacture in 2003 of over 1.8 million whole blood derived platelet concentrates and about 960,000 apheresis platelets.

How does that really compare with the total number of platelet components available nationwide? Really all we can do is compare it to the National Blood Resource Center survey from 2001 comparing how many platelet components are available. According to that comparison, it would appear that the survey respondents included facilities responsible for the manufacture of about 66 percent of the apheresis platelets and about 44 percent of whole blood derived platelet concentrates for 2003. So, it clear that the survey truly captured data for the majority of suppliers of platelet components nationwide.

Related to the number of platelets transfused, quite honestly, we asked the facilities how many platelets did you transfuse between the time period of May through August, 2003 and, additionally, how many did you transfuse between May and August of 2004. Probably the most interesting information that I could gain from this slide was that it appears that there may have been a modest transition to the use of apheresis platelets between 2003 and 2004.

The survey asked a specific question and I will quote it for you, has your ability to provide platelets for transfusion been affected since 30 days after implementation of testing? We wanted to provide a little bit of a transition for the facilities in getting their implementation and their process down. Ninety-one percent of the blood centers stated that there was no change in their ability to provide platelets for transfusion. Additionally, 64 percent of hospital blood banks stated that there was no change in their ability to provide platelets for transfusion, and 68 percent of transfusion services stated there was no change in their ability to provide platelets for transfusion.

Now, you can clearly say wait a minute, what about the other 9 percent or what about the other 30 percent? Absolutely an excellent question. That was not divided strictly with an either yes or no answer. It was either did you have a problem? Yes, I had a problem but I was not sure whether it was related to the implementation of testing for bacterial contamination, or, no, I had no problem.

Really what was found was that platelet components are in processing for a longer period of time, with the limited shelf-life of five days by the time it gets to the user the time available on the product is really quite limited. So, it is really not the number of product that is available that has been affected, it is the shelf-life, the actual shelf-life of the product.

One thing, anecdotally, that I have to say that was not a result of the direct question to the survey but was identified in additional discussion with some of the participants was that actually, because of the shorter time, this has led to, let's say, a more creative way of thinking operationally of how can I get a product to the transfusion service. So, what some blood centers are encountering is that they are, let's say, expanding their horizons and

rising to the occasion truly by saying, hey, I'm not going to wait for the four o'clock FedEx shipment, I'm going to send it out by some other commercial method of transport so that the product can get to the patient more expeditiously. They are not waiting for their routine methods. They have truly expanded their methods of transport to include alternate options.

For transfusion service experiences with the inventory management, overall the management of platelet inventory for most of the days of each month was no worse than prior to implementation of testing for bacterial contamination. Now, that does not mean it has been smooth and easy for everyone 100 percent of the time. I am not saying that whatsoever. What was specifically asked was how many days per month are you having a challenge with platelet inventory. Is it I'm not having a problem? Is it less than four days per month, less than ten days per month? By and large, it came to the point where most facilities, probably around 70-74 percent I believe, had no problem under four days, in the range of up to four days per month. Some facilities had a problem up to ten days per month. But it was truly the rare facility that had a problem with

inventory--transfusion service facility that had an inventory issue more than ten days per month.

So, there were days during the month when management of platelet inventory was more challenging for some institutions. Some institutions found that that actually led to a change in practice in the management of their inventory for platelet components in truly now they managed and whether or not they maintained the current inventory all the time at their facility.

When asked about platelet outdating, specifically, are you currently experiencing increased platelet outdating as a result of the implementation of the bacterial contamination standard, for blood centers, 66 percent of them said that there was no increase in platelet outdating; 17 percent additional said that there was a 1-5 percent increase in platelet outdating.

Now, with that we have to say that one of the reasons that blood centers may not have experienced an increase in the platelet outdating is related to a change in policy by many of the centers that does not allow for return credit of platelet components that were not transfused prior to expiration. So, any change in outdating rate would

really be reflective in transfusion service data and not in the blood center data.

One concern of mine when I actually saw this data, and this is where I put my hat on as chair of the standards committee, was one a blood center or any center--you will see the other centers said this as well--when asked are you currently experiencing an increase in platelet outdating, their answer was "unknown." Now, I would like to think that that doesn't mean that they don't track it, it is just that they don't have the number at hand because one of the requirements is to identify monitoring of blood utilization, including discards and, clearly, outdating would be a discard. So, I would prefer to say that "unknown" means they don't have the number immediately at hand rather than truly meaning unknown.

Related to hospital blood banks and their experiences with platelet outdating, remembering that this data was from 47 hospital blood banks who manufacture about 132,000 whole blood derived platelet concentrates and about 66,000 apheresis platelets, by and large, the increase in platelet outdating was under five percent. There were facilities that had experienced outdating in the beginning

when processes and operations were just in the process of implementation but, again, notice hospital blood banks. Again, there is a whole category there of what is your platelet outdate rate and the answer is "unknown." So, clearly, we need to provide additional assistance for the facilities, in saying how are we tracking this, making sure that that is being tracked.

Related to transfusion services and the increased platelet outdating, transfusion services overall, again, as you can see, about 77 percent of them had either no increase or under a five percent increase in platelet outdate.

What we did find though is that as a result of the no return policy and the changes for platelet components, was six percent of the transfusion services no longer maintained a platelet inventory on site. The platelet components were requested from their blood supplier only specifically when there was an order for transfusion. This was a change in practice as a result of the implementation of this standard.

Additionally, if you calculate my percents you will see that there is one facility short. This one

facility reported a 39 percent outdate rate. I sincerely hope that that has changed at this point.

Related to the screening methods for apheresis platelets for blood centers, 88 percent of blood centers were using a culture method; 12 percent of the facilities were using a pH or glucose by dip-stick; and one center responded "not applicable" as they performed what would be considered a visual check. Clearly, as a routine method that would not be consistent or more compliant with the AABB standards.

Related to hospital blood banks, 80 percent of hospital blood banks used a culture method if those products have not been previously been tested by their supplier; 88 percent used a culture method for those that they manufacture in-house.

Related to the screening methods for whole blood derived platelet concentrates, some of the blood centers did use a culture method, otherwise they would be using glucose and pH. Transfusion services would be using a culture method, glucose, pH or also a gram stain. These elements were evaluated by multiple different methodologies, whether

they be dip-sticks, electrodes, paper gas analyzer or the chemistry analyzer.

If a facility was using BacT/Alert or a similar culture method, for the blood centers, 85 percent of them were using the aerobic bottle only; 15 percent were using an aerobic and an anaerobic bottle. Remembering that for blood centers these involved the testing of about 900,000 apheresis platelets a year and about 1.7 million whole blood derived platelet concentrates, so 85 percent of the facilities who were using BacT/alert were using an aerobic bottle only.

Related to hospital blood banks, there was almost a 50/50 split, 54/46 using aerobic versus anaerobic bottle. As you can see, the number of cultures performed at blood centers far exceeded the number of cultures performed at hospital blood banks, actually by a factor of ten, which we will see in a few minutes. The hospital blood bank may actually be using the anaerobic bottle more consistently because of familiarity with performing a patient because culture and for uniformity in process.

I should note as well here that there were several transfusion services, eight in fact, who actually performed

testing by a culture method as well, but their data was really too small to analyze.

For those facilities who were using a culture method, the component was held 24 hours prior to sampling for bacterial testing. The components were actually held for varying periods of time following sample prior to release for transfusion. This may actually have been related to location and transport issues as well because some of the facilities, depending on where that product had to be transported to, may actually have sampled and then put it on the method of transport, knowing that it was going to take a number of hours prior to receipt by the facility. But there were a number of varying periods of time following sample prior to release for transfusion reported.

For facilities using BacT/Alert or similar culture method, in virtually all facilities surveyed the cultures were continued for five to seven days from initiation or until the expiration of the component. Both of those parameters are consistent with manufacturers' directions. Most of the facilities inoculated each bottle with 45 mL of inoculum, and the next most common was between 6-10 mL.

Related to the results of the culture methods, for the facilities who were blood centers the actual total number at the time--remember, at the time of the survey, this was September 17th of 04 through October 1st of 04--at that time blood centers had performed 429,000 cultures. Their initial positive rate by what they reported to this survey was 1/930. The true positive rate was 1/4723.

Related to hospital blood banks, the number of cultures performed at that time were just over 45,000 and their initial positive rate was 1/328 but the true positive rate was 1/1686.

Related to non-culture methods, as the result of the survey blood centers actually performed 51,000 tests with an initial abnormal rate as 1/158 and a true positive rate in 1/5672. Hospital blood banks performed 118,000 tests and their rate of initial abnormals was 1/184 and they found no true positive tests.

For transfusion services, they performed 89,000 tests and, again, their initial abnormal rate was 1/244. Their rate of true positives was 1/17,986. Now, there are a couple of things to note here. Related to initially abnormal, there was no consistency defined as far as what is

abnormal. When someone has an abnormal pH or glucose, what could be considered abnormal by one facility may not have been considered the same abnormal cutoff by another facility. So, it is a little difficult to correlate this data. Even with that, even with knowing that some facilities may say, hey, anything under 7.0 is abnormal; anything under 6.4 is abnormal; anything under 6.2 is abnormal--even with that disparity, to have an initial abnormal result rate that is that close is truly remarkable.

Related to the number of true positives in hospital blood banks being zero, truly we would have expected some but we can't really say why. It may be related to that cutoff as to what is abnormal or, quite frankly, it may be whether or not they are doing additional confirmatory testing on that product or whether they are just pitching it thereafter. That was not something we were able to assess from the survey result itself.

So, the rate of true positive results based on the number of tests performed by culture methods, based on 475,000 cultures for blood centers was 1/4723, and for the hospital blood banks it was 1/1686. For non-culture methods

the total number of tests performed was 259,000 and the true positive rate was 1/5672.

Some of the additional survey findings were that when an abnormal result is obtained by a non-culture method most facilities were performing additional investigator. While 19 facilities discarded the product with no additional investigation, this was only found to apply to whole blood derived platelet concentrates. Most facilities quarantine the co-components, whether it be apheresis or whole blood derived co-components, pending the results of the investigation. If a confirmed positive result was identified following transfusions, all facilities had a plan of action that was well defined, including notification of the facility, the physician and follow-up as well.

Additional findings from the survey related to the follow-up action related to the donor. And, it was pretty consistent that what action was going to be taken depended upon the results of the culture.

One of the very positive things--many positive things that were found in this survey is what did we change, or how did we improve our practice; what did we do when we were seeing positive results or maybe a false-positive

result? Some of the practices that were reviewed or modified as a result of the implementation of testing for bacterial contamination was a tremendous focus on the training to perform the bacterial detection test and the sampling procedures. That, by and large, was the issue that everyone focused on.

There were additional facilities who looked at the evaluation of the blood bag or collection system and the choice of arm scrub materials, and instructions on interpreting the test but, by and large, everyone looked at the training and the sampling procedures.

So, what changes in practice had occurred? Clearly, as stated, there was increased scrutiny and training. Additionally, what appears is that there may have been an increase in trend in the use of apheresis platelets. Transfusion of apheresis platelets, as you saw earlier, appeared to have increased from 2004 as compared to 2003. And, this trend actually was seen in the national blood data resource survey from 2001. While we really can't determine from the survey if the implementation of testing for bacterial contamination accelerated this change, we can say that it does appear to be happening.

Anecdotally, I have to say that it was confirmed by one blood center that they are almost exclusively preparing apheresis platelets at this time and whole blood derived platelet concentrates is becoming a component that is only available by special order. So, that transition is occurring. It may be due in part to bacterial contamination testing, but we are on that road.

Additionally, a change in practice was the development of time in inventory in some transfusion services in that they are no longer retaining a stock inventory just waiting for them. Truly, this practice would need to be evaluated by each facility as to their patient needs. It may not be appropriate for every facility.

To summarize some of the issues identified in the survey, the platelet usage, supply and outdating, there was a moderate shift to apheresis platelets. Ninety-one percent of the blood centers state the availability of platelet components has not changed significantly since the implementation of the AABB standard; 66-68 percent of the facilities surveyed have experienced no increased outdate rate; and up to 17 percent of additional facilities have experienced less than 5 percent increase in outdate of

platelet components. Some of the transfusion services have revised their practice for maintaining a platelet inventory in that they only order platelet components when there is an order to transfuse.

Additionally, summarizing what we identified from the survey was that the currently used bacterial detection methods for apheresis platelet components are usually tested by a culture method, and that is usually performed by the supplier, and whole blood derived platelet concentrates are usually tested by the transfusion facility using a non-culture method, with it be glucose, pH or whatever methodology they choose.

Additionally, follow-up procedure after an initial positive or abnormal result was to perform a culture, and the rate of initial positive and confirmed positive test results for culture methods, we said the largest pool of data from this survey would support an approximate initial positive rate of about 1/900 and an approximate true positive rate in about 1/4700. The rate at some institutions may be higher and that could be related to the use of the anaerobic bottle or different sampling processes,

but that information to come up with that conclusion should truly be a subject of further research.

For non-culture methods, the yield of the method may be related to variation in what is considered abnormal, what truly that cutoff is.

I would really like to extend my personal appreciation to each institution who took the time to complete this survey. The bacterial contamination task force could not have gained this information and could not have known what to do next to provide for the membership and to ensure the availability of blood product for all the patients nationwide. Without their participation this data would not have been made possible and the task force truly appreciates the time and efforts that all of the institutions took in completing this survey.

I was also asked to identify or review some of the information on the Association bulletins that have been made available to support or to provide additional guidance and direction on the topic of bacterial contamination.

This is a series of related Association bulletins on bacterial contamination, and what we tried to do is to show the progression of information that has been provided

to the membership and the time-line for when the guidance was sent out.

We recognize that the 22nd edition of AABB standards was implemented on November 1st of 2003, however, their standard relating to bacterial detection requiring methods to limit and detect became effective actually on March 1st of 2004. So, you can see that there were three Association bulletins provided to the membership prior to implementation. Actually, it is my understanding that this last bulletin was distributed yesterday. So, we do have a fifth bulletin that is now out and available to the membership.

To summarize the content of what these bulletins state just briefly, Association bulletin 02-08 was providing information on the frequency, cause, outcomes, prevention and detection of bacterial contamination in platelet units. It also announced the draft standards, discussing some of the skin preps, diversion, detection, swirling, things like that. It also included an annotated bibliography of some of the scientific literature so some of the membership could begin their investigative process related to bacterial contamination in platelets.

Next came the Association bulletin 03-10, which provided guidance on implementation of the new bacterial reduction and detection significant. So, this was actually provided full six months prior to the requirement to implement these methods. It provided guidance in developing strategies to implement the standard, and it supplemented the information in 02-08. It encouraged transfusion services to initiate a discussion and coordinate plans with their blood provider, but really it talked about the methods to limit bacterial contamination related to careful phlebotomy technique, the diversion, and the use of apheresis platelets as methods to limit.

Additionally, it defined methods to detect bacterial contamination, whether it be staining, culture, dip-sticks, and it acknowledged that swirling was acceptable as a supplemental test only and not as your primary test of record, to be used only in emergent situations.

That was followed by Association bulletin 03-12 which gave additional guidance on methods to detect bacterial contamination and it was a supplement to the Association bulletin 03-10. It gave additional background information on risks and the approaches that were considered

to limit and detect bacterial contamination. It was a practical guidance on the implementation techniques. I believe this was the one that in total was, like, 41 pages long. So, there were extensive appendices and guidance and direction provided to the membership on implementation.

More recently, and this was a product of the bacterial contamination task force, was Association bulletin 04-07 on actions to take following an initial positive test for bacterial contamination in a platelet unit. This is where we have definitions provided for initial positive, true positive, false positive and indeterminate test.

Additionally, it gave direction related to what to do if you encounter a positive test after the unit was transfused, or it had discussions related to recipients should they develop a suspected or proven post-transfusion sepsis after receiving platelets that had previously tested negative.

The Association bulletin that was distributed just yesterday gave general guidelines for medical decision-making and managing donors with a positive result on test for bacterial contamination and additionally discussed organisms that have public health significance.

So, as you can see with the implementation of the standard, we are listening to the membership. We are surveying the status of availability, and we are committed to providing the education and guidance necessary so the membership has the information they need not only to comply with the standard but to ensure the safety of the blood supply.

I would like to thank you for your time and attention, and for the privilege of speaking before the committee. I know that we are all looking forward to hearing additional information provided by others during today's session. So, thank you.

MR. SKINNER: Thank you for your presentation. Are there questions? Dr. Epstein?

DR. EPSTEIN: Thank you, Marianne, and also I would like to express appreciation to the blood organizations for conducting this survey since this has been essential information to understanding our system.

My question is a simple one. Can you tell us the percent of apheresis platelet collections that are being cultured and the percent of whole blood derived platelet

units that are being cultured? I am sure it could be derived from the numbers you gave us but not instantly.

Just a parenthetical remark, it would appear that the non-culture methods are inferior to the currently available culture methods, both on the specificity and sensitivity, comparing these rates. Would you agree?

MS. SILVA: Related to your first comment as to whether or not I could calculate the actual numbers, yes, I probably can because I have the actual hard copy of the actual survey and all results, but I don't know that I would be able to do that while standing at the mike. I don't know if that would be the best use of time.

Related to the non-culture methods, I think probably what would be the most helpful would be to establish some level of consistency as to what is acceptable, what is an acceptable pH? What is an acceptable glucose? I think that would truly be the first step before going any further. There needs to be consistency. It is a little hard to put everything in the same pot when not everybody is using the same cutoff. So, I think that would need to be the first step before any additional assessment can be made.

MR. HEATON: Thank you for an excellent survey. It was very helpful to see such a comprehensive survey. It is also most impressive. There has been a very modest change in platelet outdating as a result of the introduction of this assay, or so your survey would suggest.

I would be interested to know whether you segmented those centers that performed a much simpler, more expeditious method of identifying bacterial contamination, like a dip-stick. Did they experience a different or less rate of outdating compared to those that introduced a more comprehensive and culture-based assay?

MS. SILVA: One of the challenges of this particular survey was that we were not able to correlate specific questions between institutions. So, the institution that answered that they have a four percent outdate rate, I could not correlate that they were the same institution that performed a non-culture method or that they had any other information related to the survey. So, you could not correlate one question to another so it is just a function of the actual survey process itself. You could not correlate one response to another so there would be no way from this survey to identify that information.

ME. HEATON: Because one might reasonably conclude that those that used the most expeditious method of conducting their bacterial screening sustained the lowest rate of outdate increase.

I have a second question in that you made a statement that the component could be held 24 hours prior to sampling for bacterial testing. In the service that we perform that was very much not the case. In fact, the 24 hours was interpreted quite liberally by many of the centers. Did your survey specify that the concentrate had to be held not less than 24 hours before the culture was taken and that the result had to be held for not less than 24 hours before the result was read? Or, was there considerable flexibility allowed in the exact timing of the first culture and the exact timing in the read of the culture?

MS. SILVA: Well, there are two different timings that are involved. One is--let me get to the actual wording because that is a very good question.

MR. HEATON: It is on page eight of mine. You say the component is held 24 hours prior to sampling for bacterial testing. My understanding is that many centers

collect at about 12 hours and then ship it off to another center for culturing. So, whilst it is generally true it is on the next day, it isn't 24 hours after collection.

MS. SILVA: The actual question read if your facility is performing bacterial contamination testing using a culture method, how long are you holding the collection before sampling? The options were either no hold, 1-12 hours or 12-24 hours or 24-36 hours.

MR. HEATON: So, when you say 24 hours you mean 24-36 hours.

MS. SILVA: That was predominantly the response, yes.

MR. HEATON: I am most surprised. Thank you.

MS. SILVA: For blood centers.

MR. SKINNER: I am just going to work around the room. Dr. Sandler?

DR. SANDLER: I don't have a question but I do have a comment to address to the committee. I think we have heard a very comprehensive and a very expert state of the nation with regard to platelet availability and bacterial testing, and a perfect introduction to our deliberations.

We are going to have to interpret from what we have heard the urgency for change. Some of us are going to look at this the way the blood centers did and say that the glass is 91 percent full, there isn't much of a problem. Coming from a hospital, I am going to suggest to you that we look at this from the point of view that 36 percent of the hospitals saw the glass empty.

I would like to re-interpret or restate, paraphrase the question that was asked to the hospitals and the blood centers. Instead of the question as it was put about availability since implementation, which is inventory kind of terms, I would like to suggest the question might have been asked was any adult or child in your community placed at risk of a life-threatening hemorrhage, because of lack of availability of platelets, since the implementation of the standard? And, 36 percent of hospitals said yes. That, I think, should set the tone as we look into what we have to do with the wonderful, very, very fine presentation of data that we heard.

MR. SKINNER: Dr. Kuehnert?

DR. KUEHNERT: I want to echo everyone else's sentiments that this really is a tremendous task that you

did so I would like to commend, especially you and the subcommittee, for putting all this together, really a tremendous amount of information.

I wanted to just ask a couple of specific questions. You have the true positive rate and was the true positive defined as has been put forward in the guidance, or was it their own definition of true positive?

MS. SILVA: No, I believe we included that.

DR. KUEHNERT: So, that was included.

MS. SILVA: That was the whole point of us agreeing on what a true positive was.

DR. KUEHNERT: Right, so that was put forward. I didn't know if that was done at the time of the survey. So, that is great.

The other is I just had a suggestion about analysis. You mentioned the problem of sort of certain blood centers being one very, very large or two very, very large responders. It may be possible to do some weighting based on the number of platelets transfused since you know that for each blood center. So, you could actually created weighted responses to better reflect the national picture. If you were concerned about one respondent being

inordinately large an skewing responses, that weighting might help to correct that.

MS. SILVA: I think that could be a function of the survey itself and being able to track responses between questions, but that would be very helpful. That was exactly why, after the survey, I actually contacted the people at the American Red Cross and Blood Systems who completed the survey to ensure that things like inventory management or platelet outdated--I specifically called them to say what was your experience with platelet outdating, to be sure that they weren't the one that said 39 percent. I mean, clearly, that would have been of tremendous significance. But, in fact, that was not the case.

DR. KUEHNERT: And just one final comment, I think the biggest benefit of this survey will be looking at this as an evolving picture and doing follow-ups. I know this is a very, very complicated data set, but is there going to be any ability in the future to be able to do some cross-tabulation and analysis in future surveys?

MS. SILVA: I think that would be dependent upon whether or not we would be charged with conducting another survey and what the format of that survey would be.

MR. SKINNER: Dr. Klein?

DR. KLEIN: Yes, thank you for the presentation. Could you tell us what percentage of true positives were transfused? Do we have those data?

MS. SILVA: You know, I do know from one presentation that I saw actually from another source, from the Red Cross data they stated that there had been no true positives transfused. Whether or not I can get that from the survey, I would have to get back to you.

DR. KLEIN: The other question was whether we know if the centers that had SOPs for testing did not follow their SOP in order to provide platelets to patients who might have needed them or to avoid outdating?

MS. SILVA: That question was not asked.

MR. SKINNER: Dr. Holmberg?

DR. HOLMBERG: I just want to make a comment and then I maybe have a question to Marianne. First of all, thanks for all the work. The task force really did a fantastic job not only on the survey but also on the guidance documents, and I think that the blood community appreciates that.

The comment I really want to draw attention to for the committee is the rate of true positives, the difference between the blood centers and the hospital blood banks. The blood centers are reporting a 1/4723 and the hospital blood banks are reporting a true culture method positive of 1/1686. So, there is quite a discrepancy there and do you have an explanation for that?

MS. SILVA: Actually, I was speaking with Dr. Kuehnert about that just briefly on one of the conference calls, and it could actually have two potential causes, one of them being that hospital blood banks were more likely to use an anaerobic bottle. The second possibility was related to facultative anaerobes. Is that right?

DR. KUEHNERT: I think, if I recall the conversation, it is just basically being a volume issue and that it is an anaerobic bottle but just the fact that it is more --

MS. SILVA: Additional volume--

DR. KUEHNERT: Right.

MS. SILVA: --being cultured.

MR. SKINNER: Dr. Brecher?

DR. BRECHER: Just to get to Jay's question about what percent of apheresis platelets were being cultured, just looking through your presentation quickly and doing a quick weighting, I think it is quite clear--well, first of all, only 6.8 percent of all apheresis platelets are collected by hospital blood banks--

MS. SILVA: Correct.

DR. BRECHER: --since 93.2 percent are collected by the blood centers. If 88 percent of all blood centers used the culture method but two of those were Blood Systems and the Red Cross--

MS. SILVA: That is correct.

DR. BRECHER: --which collect well over half of apheresis platelets, I think you can clearly say that well over 90 percent of all apheresis platelets are cultured in this country.

MS. SILVA: I believe the Red Cross data as far as the numbers--

DR. BRECHER: Whole blood is probably less than five percent.

MS. SILVA: I believe the Red Cross data for the number of--oh, no. I do have the number, the actual number for the Red Cross, but thank you for doing the math for me.

MR. SKINNER: Are there other questions? If not, then the committee will take a break and we will return at 11:10.

[Brief recess]

MR. SKINNER: If everyone will take their seats, we will reconvene. The next presentation will be presented by Dr. Arjun Srinivasan, the medical epidemiologist for the Division of Healthcare Quality Promotion of the Center for Disease Control and Prevention. He will update the committee on septic transfusion reactions despite implementation of methods to reduce bacterial contamination.

DR. SRINIVASAN: Good morning. Thank you very much. I would like to really thank the committee for giving me the opportunity to present this morning.

Since the implementation of the standard for screening platelets for bacterial contamination the CDC has been made aware of a handful of septic transfusion reactions that occurred in recipients who received platelet units that had screened negative for bacterial contamination. What I

would like to do this morning is present three of these cases because I think they nicely illustrate some of the challenges of platelet screening.

The first case was that of a 74 year-old patient with leukemia who was receiving weekly platelet transfusions. On October 30th of 2004 this patient received a 5-unit irradiated pool of platelets as an outpatient. The transfusion was tolerated well, with no evidence of sepsis during or after the transfusion. However, on the way home from the clinic the patient became ill and was taken to a hospital.

On arrival to the emergency department hypertension was noted and the patient was admitted. Blood cultures done on admission did grow Staphylococcus aureus and, unfortunately, the patient died after a 21-day hospital admission.

Upon notification of the transfusion reaction, the blood center did culture the five bags that had comprised the platelet pool and two of the bags, in fact, grew Staphylococcus aureus. The isolates from both the patient and from the bags were sent to us, at CDC, for molecular

typing and were found to be genetically identical by molecular typing using pulsed field gel electrophoresis.

An investigation done by the because banking center on the co-components indicated that one of the released red blood cell units was also cultured and was negative for Staphylococcus aureus, and donor follow-up of all of the donors who had comprised the pool was unremarkable.

Now, of the five units that were in this pool, the oldest unit was four days old, and of these two contaminated donor units, both of them were two days old and they were, in fact, the first two units that were put into the pool via a common spiking device. We know from the records that the unit was pooled and then irradiated within three hours of the transfusion.

For screening, this facility uses pH test strips. These test strips are regularly validated using a pH meter for validity and colony control. The standard at this center is to reject the unit if the pH is less than 6.4. I will note that the actual pH is not recorded, only a pass/fail determination. So, for this particular unit we

don't know what the actual pH was, we only know that it was recorded as having passed the screening test.

The second case is a 79 year-old patient who received a jumbo 480 cc platelet apheresis unit for thrombocytopenia following coronary-artery bypass surgery. Now, the transfusion itself was tolerated well, but about an hour post transfusion the patient developed shortness of breath, chills and fever of 39.4 Celsius.

In following the transfusion within really several hours, the patient began developing multiple thrombotic events and actually died 27 hours after the transfusion was received.

Blood cultures from two different sites grew coagulase negative staphylococci which we identified at CDC as a Staphylococcus lugdunensis. Upon notification of the transfusion reaction, an investigation was undertaken. A gram stain of the material left in the bag that held the platelet transfusion did reveal gram positive cocci, and culture of the material in the bag grew Staphylococcus lugdunensis within eight hours. Again, those isolates were sent to us, at CDC, and were found to be molecularly indistinguishable using pulsed field gel electrophoresis.

The unit, we know, was five days old at the time of transfusion and donor history is still being gathered at this time. In terms of the screening methodology used for this unit, the unit was held for 24 hours before screening in accordance with the protocol at this center. After the unit was mixed, a 4 mL sample was removed from the bag via a sterile connection and inoculated into one aerobic BacT/Alert bottle. That bottle was placed in an incubator which reads the bottle every ten minutes for evidence of CO2 product for bacterial contamination, and the bottle is held for the length that the product is stored on site.

The screening cultures were incubated for a minimum of 12 hours before they were released. We know in this particular case that the sample from the unit was negative on day five, which was the day the transfusion was performed. That blood culture bottle was actually retained and was sent to us, at CDC, at 10 days of incubation. We tested it again and were not able to recover any organisms by culture or gram stain of the bottle, and this was after ten days of incubation.

The final case is that of a 700 g premature newborn who received two doses of a single donor apheresis

platelet unit 24 hours apart. Several hours after the first transfusion was given, the first dose of this unit, the baby's condition began deteriorating with hypertension and respiratory distress.

Blood cultures of the recipient in this case were negative, however, the baby was on broad spectrum antimicrobials at the time the culture was done. However, there is a note that gram negative rods were actually seen on a peripheral blood smear soon before the child died--evidence of bacteremia with a gram negative rod. Unfortunately, this recipient did die about 72 hours after the first transfusion, with signs and symptoms of sepsis.

What we know about the platelets in this case was that the first dose was transfused after three days of storage and the second dose was transfused 24 hours later, after four days of storage. Again, the donor investigation on this is still pending.

However, we do know about the screening details. Again, this unit was held for 24 hours before screening was undertaken. Here a 1 mL sample was taken from the bag and one-tenth of that, 0.1 mL, was placed onto solid blood agar media. The culture was incubated for 24 hours and,

following negative results at 24 hours, the unit was released for transfusion.

Now, as part of an ongoing quality control study at this center, just prior to release of that first dose that was transfused an additional 1 mL sample was taken from that main mother unit and cultured again on solid blood agar media. This second culture, second aliquot actually grew Serratia marcescnes. Unfortunately, both of the two unit doses had already been transfused by the time these results were known and it was too late to interdict the unit before that second transfusion had occurred.

When they went back upon notification of the reaction and recultured the unit bag which had been the source of both doses, that culture in fact did grow Serratia marcescenes. When they found that out, they went back and actually recultured that initial first aliquot that had been drawn and had been culture negative, using a broth filtration method, and they estimate that this method of culture, the broth filtration method, is highly sensitive in their hands and could detect as few as 2 CFU/mL. Interestingly, they were not able to obtain any organisms on this first sample that they had obtained.

They actually checked the pH of the main unit bag which had originated both doses at the time they had cultured it for Serratia, and actually found that the pH at that time was 7.3.

So, I presented these three cases of breakthroughs of bacterial contamination despite screening. So, what are some potential explanations for why these breakthrough cases might occur? Well, in thinking about this, I think there are three main categories that I was able to come up with.

The first are clerical types of errors, for example, a mismatch of the unit tested and the report that is generated so you may be looking at a report for a unit that, in fact, was culture positive but was reported as being culture negative.

Another might be a clerical error resulting in a failure to actually test the unit. For example, a unit could fall through the cracks in terms of testing, or there could be a clerical error that results in two samples being taken from one unit but no sample being taken from another perhaps.

Another explanation might be problems during handling of the unit where contamination would occur after

the testing, during storage or handling, which obviously would lead to negative culture results on screening but then subsequent contamination of the unit that you wouldn't detect.

The other broad category I think are some of the methodological issues. For example, perhaps the contamination is below the limit of detection of the method that is being used. But, clearly, a number of steps had been taken to try and address this problem. For example, units are held for 24 hours before they are cultured to give the bacteria time to divide. Also, a lot of places are using blood culture methods which we know are very sensitive. In fact, if you look at the literature, it is estimated that blood culture systems can detect organisms in quantities as few as 10 organisms per mL or even less. However, I think it is important to remember that as we try to extrapolate that data the literature reports on the sensitivity of blood culture bottles are generated from studies using two blood culture bottles, each of which is inoculated with between 8-10 mL of blood, with an incubation period of generally 5-7 days. And, I think we are still learning more about the impact there is going to be of

reducing that volume to, say, 4-5 mL and shortening that incubation time.

Another problem from a methodologic standpoint that has already been addressed in the survey is the issue that there aren't generally accepted cutoffs for using the pH and other metabolic indicators which, obviously, poses some challenges if you are going to use these for screening.

Now, I have talked about some screening breakthroughs but I think it is very important to put these three cases into the overall context of bacterial screening for platelet units. We would expect that there are going to be more than 100 true positives based on screening each year from data that has been reported in the literature. In fact, since implementation of the standard in 2004, there have been a number of positive results of screening of platelet units that we think have had very important implications not just for the potential recipients of those units, but also for public health, and clinically for the donors in some cases.

For example, on the gram positive side there is a report of a Streptococcus bovis that was found in a platelet unit which led to a diagnosis of a colon cancer in the donor

of that unit. Likewise, there were two reports of units contaminated with Listeria monocytogenes that led to investigations by state and local health departments for sources of that potential contamination.

On the gram negative side, we know that a number of units have been interdicted because of contamination with gram negative organisms which, of course, has very important implementations for the potential recipient, given the severity of transfusion reactions in platelet units contaminated with gram negative pathogens.

It is also I think very important to frame this discussion with the fact that the AABB standard is a dynamic process. The issue of platelet screening for bacterial contamination is not static but dynamic. Since the issuance of the standard there have been a number of guidance documents which we have heard about, things like case definitions to aid with quality control and reporting consistency; algorithms for the workup of suspected contaminating units, particularly false negatives or late positives; and also algorithms to help centers work up organisms that are clinically relevant and those that have public health significance.

I think as we move forward, it is important to keep in mind that anything we can do to help nationalize both the collection and analysis of this data is going to greatly enhance our understanding of platelet screening for bacterial contamination.

So, in conclusion, I think that it is important to note that the implementation of the standard to screen platelets for bacterial contamination is having the desired effect of promoting transfusion safety. A number of contaminated units have been interdicted.

I think as we move forward with learning about the standard and this process, we need to continue to assess and reassess the methodologies that are being used now that they are being implemented in the clinical setting in the real world. And, I think this real-world experience is going to greatly augment our understanding of these methodologies and will augment the data we have from laboratory simulations, like spiking studies.

I think it is important to emphasize, as these three cases illustrate, that we can't limit our focus to any one particular method as both the metabolic and the culture methods have been associated with false negatives.

Finally, I think it is very important that we spend some time really investigating these breakthrough infections because I think that can be a very important tool to help improve our detection methods. Thanks very much. I will be happy to try on any questions that the committee might have.

MR. SKINNER: Dr. Brecher?

DR. BRECHER: As a result of these breakthrough cases, what did these facilities change in their processes?

DR. SRINIVASAN: Well, actually all of the facilities that were involved are still in the process of investigating. These cases are fairly recent and they are still investigating what has occurred. So, I don't think they have made final decisions on what changes, if any, are going to be made yet. That is a very good question though.

DR. BIANCO: All of the reports that you have received--you didn't tell us how many, but do you see any that would have been picked up by anaerobic bottles versus aerobic bottles?

DR. SRINIVASAN: That is another very good question. No, I don't think that any of these cases were organisms that would have grown better in an anaerobic

bottle, any anaerobes or even facultative anaerobes. I think, as has been raised, the issue may simply be a volume issue that the anaerobic bottle adds but I don't think, at least in the cases that we are familiar with, adding the anaerobic bottle would have made a difference for cultivating organisms.

MR. SKINNER: Other questions? Dr. Brecher?

DR. BRECHER: I will be presenting some data later this morning, but at very low concentrations the addition of an anaerobic bottle, which may just reflect a greater volume, probably would have picked up greater numbers of low concentrations.

DR. SRINIVASAN: I think that is a good point. It is the question of the volume versus the anaerobic environment. And it will be great to see that data.

MR. SKINNER: Thanks.

DR. SRINIVASAN: Thank you.

MR. SKINNER: Our next presentation will be from Dr. Jaroslav Vostal. He is the senior medical officer in the Division of Hematology of CBER. Dr. Vostal will update the committee on the current thinking of the FDA regarding

extended storage of platelet concentrates and pre-storage pooling of whole blood derived platelets.

DR. VOSTAL: Thank you for this opportunity to present the FDA's current considerations for seven-day platelets and bacterial detection in single and pooled platelet products.

Let me start off by describing where we are in terms of the regulatory aspect of this issue. So far, FDA has cleared several storage containers, two for apheresis platelet storage bag for storage up to seven days, and one whole blood derived platelet single unit storage platelet bad for storage up to seven days. Now, even though these bags are on the market, seven-day platelets themselves are not because the seven-day platelets are not approved because platelets need to be tested with an FDA approved bacterial detection release test. So, we have to resolve the issue of being able to detect bacteria in these platelet products before we can store them out to seven days.

In terms of where we are with the detection test, three devices have so far been cleared for quality control monitoring of the platelet collection process. These are the BioMerieux BacT/Alert, the Pall eBDS and the Hemosystems

scan system. There are other non-approved, non-validated methods also being used to meet the AABB standard for bacterial detection.

Now, FDA has concerns with bacterial detection as it is being currently applied to platelet products. First of all, the test performance characteristics of these devices and methods are unknown. The use of the non-validated tests, such as glucose and pH by dip-stick and swirling are producing certainly false positives and false negatives. There is non-standardized methodology being applied even with the culture-based devices and, therefore, there is potential for excessive false positives and false negatives.

Finally, the less reliable methods are used on whole blood derived platelets, creating a two-tiered safety system for apheresis and whole blood derived platelets.

Here is a list of desired improvements to the current state of bacterial detection and storage. We would like to see standardized methodology for the automated culture system being applied, and this would be in terms of timing of sample collection, the volume collected and the duration of culture.

We would like to see validation of the automatic bacterial culture system as a platelet release test. We would also like to see application or automatic bacterial culture system to whole blood derived platelets so we can eliminate the use of the non-validated methods, and this can be achieved by testing pre-storage pools of platelets or testing of pooled samples.

Now, the major hurdle in getting to having a viable test has been the validation of the automatic bacterial culture as a release test. In the past FDA has advocated a large field study to demonstrate the performance of these devices under actual clinical use. The transfusion community has actually pushed back on this idea and it led to a standoff that lasted for approximately two or three years. However, last summer the FDA and the AABB bacterial detection task force got together and came up with an acceptable scientifically-based design of an appropriate field study to validate the performance of these devices.

This slide outlines the design of the study. We are looking for a sampling of the platelet product early in storage, such as day one; then confirmation of the results with a second culture at day seven. The second culture

would estimate the residual bacterial risk for a seven-day old platelet unit tested for bacteria on day one. So, it would define the residual risk of platelets that tested negative on day one.

We would like to approve seven-day platelet storage if the bacterial risk at day seven is lower than the current bacterial risk of untested platelet products. The goal of the study was to demonstrate the point estimate of risk at day seven to be less than 1/10,000, with a 95 percent upper confidence limit that the risk is than 1/5000. Based on the statistical design, the study size was approximated to be about 50,000 platelet units.

Even though everyone could agree that this study was scientifically sound--let me actually go through this slide first. This is a graphic demonstration of what the study will look like. The yellow bar represents storage of the platelets out to day seven. The first sample would be taken around day one, 24 hours. It would define the bacterial risk of untested products. The second sample would then be taken at day seven and this would define the residual risk of tested products that were ruled to be negative at day one. Then the confirmation of the results

would lead to a conclusion whether this device was acceptable or not.

However, even though everyone could agree that scientifically the study was sound, there were still concerns about the logistics of this field trial. There are problems with high cost due to the size of the study of approximately 50,000 units. There is no manufacturer support so far to undertake this type of a study. If you try to find public funding through NIH, it requires time for protocol review and competition against other research initiatives so it wasn't clear whether this study would ever be funded. Finally, even if we did get funded, the data collection would have taken a significant amount of time.

So, between all these points we were looking at about two to three years before would could approve seven-day platelets for clinical use. So, it was at this time that we started to look for alternative methods for getting the information that we were looking for. We realized we could use the data that has been collected in order to meet the AABB bacterial standard. The data was collected for over six months and there is a large body of data that could be used to evaluate some of these devices.

We decided that we could use the data as a basis of approval of seven-day platelets provided there was a commitment to perform a post-market study on the additional performance under clinical use. The post-market study would consist of an additional culture on outdated products on day seven to confirm the day one negative culture reading. And, the size of the post-market study would be determined by the contamination rate identified by the Q/C testing data.

Graphically, the study design will look as this. You would have a unit that was tested for quality control at day one. If it was a positive unit there would be repeat testing to determine if it was a true positive or a false positive. This type of data makes up what is available through the AABB standard testing.

Now, if the initial culture is negative, then this product could go into clinical use, could be stored out to seven days, and outdated products could then be tested, repeat tested again with a second culture to determine if the first one was a true negative or a false negative.

So, eventually we would be able to get both types of data that we were looking for in the first place, but this would allow us to put seven-day platelets on the market

immediately and not wait the two to three years for the post-market study or the field trial to take place.

So, the data we would obtain from this type of design--in the Q/C testing we will confirm that early culture positive or the repeat culture would identify true positives and false positives and from this you can derive the expected rate of the positive tests and you can also derive the positive predictive value of the device.

The post-market field trial would confirm the early culture negatives with the seven-day culture and this would identify true negatives and false negatives, and from this data you can derive the sensitivity of the device, the negative predictive value of the device and the residual risk of the bacteria in those seven-day products.

So, here is a summary of what the plan would look like to get to seven-day platelets. We would expect sponsor to compile the existing Q/C data on the performance of the bacterial detection device, and this data is already available so it would mean just putting the data in a format that we could use to evaluate the device itself. The sponsor would also develop a uniform standard operating procedure, an SOP, for screening platelet products by the

device. This would again be based on the data that has already been collected. Then FDA would approve storage of platelets out to seven days if the platelets are stored in bags approved for seven days; if a bacterial detection SOP is followed; and the sponsor commits to a post-market study to further track the bacterial detection of the device performance under clinical use.

So, that was for single unit platelets, apheresis platelets, and I am going to talk a little bit about pre-storage pooling for whole blood derived platelets. FDA's current thinking is that pre-storage pooling systems can be cleared if Q/C by culture monitoring is performed by tests with analytical sensitivity similar to that cleared for single units. The bacterial detection devices applied to pools will need to be validated by analytical testing to demonstrate sufficient sensitivity to account for the dilution of the bacterial inoculum by the pooling process. Since for whole blood derived platelets the final transfusion product usually consists of five to six single units, there is about a five- to six-fold dilution of the inoculum if one of the bags is contaminated. So, the increased sensitivity of the device should be demonstrated

in pre-storage pools or pooled samples taken from individual whole blood derived units.

Besides being able to demonstrate sufficient bacterial sensitivity, there is an additional requirement that we need to meet before we can approve pre-storage pooling. It will require validation of the platelet storage containers to preserve the platelet efficacy in a pool for five days or longer. So far, we don't have a bag that is approved for pre-storage pooling of platelets either for five days or for seven days.

The validation approach of these bags was discussed in the March, 2003 Blood Products Advisory Committee and it consisted of testing platelet efficacy by following correct count increments in thrombocytopenic patients, and the idea was to compare pre-storage pooled platelets to post-storage pooled platelets in two separate arms of the study, and each arm would have approximately 50 patients per arm.

Now, an additional thing that needs to be discussed is that pre-storage pooling creates a new product and we should also look into establishing quality standards

for these new products, such as what would be the minimum platelet dose associated with a pooled product.

So, here is a summary of our current thinking in terms of seven-day platelets and pre-storage pooled platelets. As I already mentioned, the extension of platelet storage to seven days will require compiling existing Q/C data on bacterial detection and evaluation of the device performance. It will require development of uniform SOPs for testing of platelet products with the device based on the Q/C data, and also require a commitment to a post-market study.

For pre-storage pooling, we need to evaluate analytical sensitivity of bacterial detection devices on pools where one of the units in the pool is contaminated. We also need to evaluate the storage bags for pools to preserve efficacy in a pool for five and seven days, and we need to discussion quality standards of these new products. So, thank you very much and I will be happy to answer any questions.

MR. SKINNER: Are there questions?

[No response]

Thank you very much. Next the committee will hear from Dr. Mark Brecher. Mark is a professor of pathology and laboratory medicine in the University of North Carolina, and director of transplantation and transfusion services at McClinton Laboratories UNC hospitals. Dr. Brecher has been involved over the last year with the AABB task force and will provide progress made in field studies for extended storage of apheresis platelet concentrates and whole blood derived platelet concentrates. Dr. Brecher?

DR. BRECHER: Thank you, Mark. I am a member of the AABB organizational task force and my expectation was that most of my talk would have been presented by the previous speakers and I could go fast and get us back on time. So, fortunately, that has happened.

Just a little history to remind the committee where this organizational task force came from. As the result of the AABB standard 5151 which went into effect March 1, 2004, there was concern on the part of HHS that implementation might cause effects on the availability of platelets, and the Acting Assistant Secretary of Health requested the AABB to carefully consider delaying implementation.

After careful consideration of this issue the AABB responded that they believe that further delaying the implementation of the standard would compromise both patient safety and public health, and the AABB went on to require testing. This led to a major discussion at the April 2004 meeting of this committee and the formation of the organizational task force.

The purpose of the task force was to serve as a focal point for all issues related to the AABB bacterial detection standard, that took effect in March of 2004; provide a forum for discussion between the transfusion medicine community which included translation services and blood centers, subject matter experts, public health service agencies including FDA, CDC, HHS and NHLBI, on specific safety and availability issues, and to interact with test manufacturers as appropriate.

It also took up the task of providing guidance to AABB membership. Issues to be addressed included standardized definitions of test results, follow-up of initially positive tests, identification of organisms and what to do if you have a positive even though it has been transfused, notification, possible deferral and interactions

with public health departments, and to conduct a survey which we have already heard about.

As Marianne Silva already stated, two Association bulletins have come out from the organizational task force. Priority action items of this committee have included going to seven-day storage of platelets, pre-pooled random, by which I mean whole blood derived PRP, platelet rich plasma platelets, and to conduct a survey on platelet testing.

FDA's current thinking, as presented by Dr. Vostal, allows for a much easier pathway to seven-day platelets, particularly apheresis platelets. As he outlined, and I have simplified here, the final protocol that we wanted to put forward to the country from the task force was that approximately 1,500,000 platelet units would be tested after 24 hours of storage with either the BacT/Alert aerobic bottle or the Pall enhanced eBDS system. Then 50,000 outdated apheresis platelets would be tested on day eight or nine with both an aerobic and anaerobic bottle to define the number of bacterially contaminated units that would not be detected with an early culture.

This proposal was taken out to most of the manufacturers on behalf of the AABB committee. Several

companies have said that they are working on going forward with various protocols. The committee has been involved with some companies more than others. In particular, there have been some major discussions with BioMerieux. BioMerieux countered the proposal by saying they would like to see a study where both an aerobic and an anaerobic bottle is tested early, on day one or two, and then as previously described, an aerobic and anaerobic bottle would be tested on day eight or nine. To encourage the major blood centers to participate in this, they offered to discount both bottles and additional incubational cabinets for their machines.

The task force reviewed this proposal and does not support the need for the day one anaerobic bottle as part of the protocol. However, the task force believes that it is a valid medical scientific issue to determine whether bacterial testing of platelets should include the detection of anaerobes, and recommends that BioMerieux sponsor a protocol to study this issue that is independent of the post-market surveillance study.

The task force has had in-depth discussions with representatives of the American Red Cross and Blood Systems,

which are the two largest collectors in this country, about the task force protocol and the BioMerieux revisions thereof. The task force recommends that BioMerieux follow up with these two blood collection organizations, and others, to ascertain their willingness to participate in BioMerieux's proposed protocol.

The task force does not see a further role for itself with regard to the seven-day storage issue as it believes it has successfully worked with FDA to clarify what is required for seven-day storage of apheresis platelets to occur. The task force has been influential in providing a road map for manufacturers such as BioMerieux to work with FDA and licensed collection agencies to achieve this goal.

The question of pre-pooled random platelets, while a high priority item, has basically stalled at the moment for lack of additional bags and studies that need to be done, as outlined by Dr. Vostal. So, I will take any questions.

MR. SKINNER: Questions for Dr. Brecher? Dr. Epstein?

DR. EPSTEIN: Mark, when the task force reviewed the issue of the anaerobic bottle you focused on detection

of the anaerobe, but there is also the issue of doubling the input volume, and can you comment on that?

DR. BRECHER: Yes, thank you, Jay, I neglected to mention that. There was still an open question as to whether we would want to test 4 mL up front or 8 mL. That hadn't really been resolved, but that is a question. The main thought is that the addition of an anaerobic bottle would give you additional volume, although there is some data to suggest that you would pick up anaerobic organisms which have very rarely been implicated in post-transfusion sepsis from platelets, although there is one case of clostridial death in England that was a strict anaerobe. Additionally, however, would provide more volume and even what we would think of as aerobic organisms frequently will grow in these anaerobic bottles, and in some cases, particularly with strep., they will grow faster in the anaerobic bottle than they would in the aerobic bottle.

DR. EPSTEIN: I would also ask whether you see the study designs with and without the anaerobic culture up front as mutually exclusive. In other words, why could not both studies go on concurrently with the different products? In the end, if there is a study containing anaerobic bottles

we will learn two things. We will learn whether the increased volume affects detection of the aerobes and we will learn whether you need to detect the anaerobes up front. Both study designs involve detection of anaerobes at the seven-eight day point. So, you know, the question here is are these exclusive designs or is it they desirable to have both?

DR. BRECHER: The committee recognized the scientific merit of having an up-front anaerobe bottle to answer both of those questions. Actually, the committee was somewhat split as to whether to recommend the use of anaerobic bottle up front. The majority felt it was not required. Nevertheless, in discussions with the large blood centers there was a great reluctance to include an anaerobe bottle up front unless someone was paying for it. That is sort of the logistical holdup.

MR. SKINNER: Celso?

DR. BIANCO: Mark, you said that the task force does not see a further role for itself. What is going to prevent this project from falling apart since it is entirely at the good will of a few people?

DR. BRECHER: Well, I think the task force is optimistic that the lines of communication have been opened; the layout of the protocol is established; and that it will happen. So, the task force has basically taken the task of declaring victory and leaving the field. However, should this fail I am sure the task force will reinsert itself into the question to make sure that it does happen in one form or another.

MR. SKINNER: Other questions?

[No response]

Thank you, Mark. The committee will next hear from Dr. Joseph Sweeney. He is the medical director of transfusion medicine with Lifespan, in Rhode Island. Dr. Sweeney is also professor of pathology and laboratory medicine, Brown University. He will discuss the importance of whole blood derived platelets as a viable means to meet community hospital platelet requirements.

DR. SWEENEY: Thank you very much, Mr. Chairman. While the computer is being set up, let me just state initially that there is one minor conflict of interest in that I am currently in receipt of a research grant from Pall Corporation and may show some commercial proprietary

products during this presentation. So, I would like to make that clear before we initiate.

Thank you very much. So, in my first slide I would like to show some data which is extremely well-known to most people in this audience here, and that is the fact that over the last decade or so there has been a substantial shift in use of platelet apheresis products within the United States and, indeed, also in Europe, and that between the years 1999 and 2001 there has been a substantial growth in apheresis, a 26 percent increase, and a relative decrease, of course, in the whole blood derived platelets and I will discuss why these factors have occurred a little bit later.

Unlike the national trends, however, in our own community in Rhode Island, this trend has now occurred, as indicated here. The red bars indicate the intra-state use of whole blood derived platelets and the blue bars indicate the intra-state use of apheresis platelets, and I think it is very clear that over the last decade or so we have seen substantial maintenance, if not increase, in our use of whole blood derived platelets. They are now approximately

80 percent of our total use versus apheresis platelets which are approximately 20 percent of in-state use.

This has mainly been brought about by the fact that our whole blood derived platelets are produced by in-line filtration so that all the platelets in the State of Rhode Island as expressed as PRP, as you can see here, and then filtered in-line to the platelet filter, similar to the apheresis products. All of these are pre-storage leukoreduced.

Our platelet use is not greatly different from the rest of the United States. This is the estimate from the National Blood Resource report from 2001. Our use for that same year was about 39 or so units per 1000 per year. Our population is a little older in Rhode Island, 14.8 percent of the population are over the age of 65. The national average from the 2000 census is 12.8 percent. So, that probably accounts for slightly increased use. Our dose is pretty standard. This translates into approximately five units of platelets. Our median platelets are about 3.8 for a dose of five units, and that is the dose we use throughout the state. So, physicians ordering larger doses have to

justify them, and if they can't justify them, they essentially get our accepted dose.

Now, there have been many reasons, of course, advanced for the advantages of apheresis platelets over whole blood derived platelets and I don't have time to discuss these because of the short time limitations and most people in the audience have either read or lectured on the subject, but I would like to highlight some areas that are often suggested as being advantages for apheresis donors.

A pool of HLA typed donors is I think a genuine advantage. The donor exposure issue, of course, is frequently touted. Then, there is this question of whether it is intrinsically a better product than the whole blood derived platelets.

So, let me try and address that issue very briefly. These are some studies we conducted in Virginia with Stein Holme and Andrew Heaton in the early 1990s. What we were primarily looking at is the effects of pre-storage leukoreduction on platelet quality as measured by radiolabeled in vivo survival studies using 51 chromium and 111 indium. There are two papers published in the same issue of Transfusion approximately ten years ago.

To summarize the data here, you can see that the with apheresis platelets, filtered or unfiltered, that was no difference in percent recovery. Over here you have the data from the second paper showing manually pheresed platelets which were in-line leukoreduced, and it is pretty clear that there is actually no difference between these pairs. So, pre-storage filtration did not adversely affect quality of the product.

This is similar data for the multiple hit survival data. You see that the apheresis platelets that were filtered pre-storage did not differ and, similarly, the in-line filtered platelets did not differ pre-storage versus post-storage. But what is quite interesting is if we take the data from both these papers and add it together, we now have data for the multiple hit survival. This is the group of apheresis platelets that were both filtered and unfiltered. The data is pooled together. Note, their survival is approximately 145 hours, which is a pretty common figure that you will find in the literature from other centers. Interestingly enough, the whole blood derived platelets, their survival is statistically not different. In fact, the observed survival was somewhat

higher but, certainly as this data would show, there was no evidence that the whole blood derived platelets were actually inferior based on these in vivo survival or viability data.

Now, are there disadvantages to apheresis platelets because there is very little attention given to this topic? There is always this perception that these are superior products and, therefore, there are no disadvantages, and only advantages. But let me suggest to this audience that there may be disadvantages with this product.

First of all, we are seeing cases reported of plasma mismatched hemolysis, particularly in blood group O donors being transfused to non-O recipients. The context is that subpopulation of O donors may have high titers of anti-A commonly and perhaps anti-B. In fact, the recent report ion Transfusion advocates that some of these O donors should be titered routinely, which would be particularly cumbersome.

The second point is that if you use apheresis donors as a sole source of your platelets, as an adult dose, some donors, we recognize, store poorly in vivo and,

therefore, you may in fact be delivering a suboptimal quality to a specific recipient.

There is increasing data that many donors pre-platelet donation have impaired function. There are now three reports in the literature, one from Austria, Vienna; one from Oxford, in Transfusion last year; and a recent report from Sacramento, California showing that as many as 20 percent or more of platelet donors have suboptimal function as identified by the PFA-100 assay. So, this is a point that needs serious consideration because this was the entire source of platelets for the recipient.

Furthermore, these apheresis donors are supplying a large volume of plasma which could be implicated in a TRALI reaction, which would not be the case with a pool of whole blood derived donors. There is a report in Transfusion of a pheresis donor donating on two occasions, and on each of those two occasions the recipient came down with TRALI, two different recipients came down with TRALI.

Furthermore, platelet pheresis donors produce a product with a fixed potency. The yield cannot be altered, whereas this is not the case with whole blood pools. We can add or alter the dose by simply adding more to the pool.

Then there is the problem of dosing of low blood volume recipients and the so-called standard adult dose may not be necessary in some cases.

I just want to show you some data we generated and presented to the AABB at the last meeting. This is glucoprotein 1B-alpha expression on stored platelets up to nine days, and this is an X-and-5 demonstration of surface phosphatydal sereine. I want to show this point, that in these ten donors, two of these donors exhibited low levels of GP-1B by day one, and this pattern continued so by day five and day six a large amount of GP 1B-alpha was not present on the cell membrane, and these are also the same donors that expressed large amounts of phosphatydal sereine. So, these were apheresis donors that potentially could result in impaired response in an individual recipient.

So, we are left really with two possibilities, fewer donor exposures and pool of HLA typed donors, and these are good advantages for apheresis platelets. So, we continue to use apheresis platelets. I am not decrying this product, I am just suggesting we put everything in the proper context.

The advantage of fewer donor exposures is directly related to likelihood of infectious transmission by platelet transfusion. I think that is correct whether it is bacteria or viruses. The viral risk is only about 1/200,000 per unit. The use of apheresis platelets in our community prevent one viral disease in about 15-20 years, which almost statistically insignificant.

Put into a slightly different context, in our bone marrow unit when we were transplanting breast cancer in the mid to late 1990s, we looked at the relative risk and absolute risk of disease transmission if a patient were managed with either whole blood derived or apheresis platelets. You can see that the relative risk is quite impressive. It is about 1-3 or so. But the absolute risk is tiny when the risk of a disease transmission is low. In fact, put in a slightly different context, we estimated that if we used apheresis donors exclusively in a bone marrow unit instead of using whole derived platelets we would only prevent one viral disease exposure in 40 years of treatment which, for practical purposes, is insignificant.

Now, we have also noticed some other problems in the last couple of months, which I will show you, relevant

to one of the earlier presentations that may not have been brought out. First of all, with NAT testing, as you know, we have seen some shortening of the residual shelf-life of platelets, and with bacterial screening we are now seeing a significant shortening. We now only have probably about two or three days, and I will show you the impact of this in a moment. What we would like to obviously move to would be a product that we could store for seven days, and that has been discussed earlier.

This data may be difficult for many of you to read, and the yellow data is probably the more important, but since we implemented screening of whole blood derived platelets and apheresis platelets in February of 2004--we screen, by the way, all whole derived platelets using a bacterial culture technique--we can see that our outdating is beginning to creep up. In fact, our outdating rate has moved now from about 10.5 percent up to about 18.4 percent of the platelets outdating on our shelf. In the blood center, which historically has very low outdate rates, the blood center outdate rate has crept up to close to about 8 percent or so.

And, we are quite convinced that a substantial amount of this relates to the reduction in the residual shelf-life of the platelet. Part of it due to the problem that when we pool platelets we only have a four-hour period in which to transfuse. About ten percent of our platelets are lost because of this four-hour period, and the clinical context in which that occurs is nearly always cardiac surgery where the patients coming off the pump may be exhibiting bleeding. The anesthesiologist requests platelets and then, of course, the patient settles down and does not use the platelets. But by far, 90 percent of this outdating is because the shelf-life has been met or exceeded.

So, we would like to suggest that if we could move to pre-storage pooling, as illustrated here, this should be a fairly simple and straightforward process. After sterile docking, you can see the pool here to a harness, pool these platelets into a pooling container, as shown here. That is the pooling container. And then the pooling container is hung upside down and the platelets are then filtered, which is what we call off-line filtration, producing ultimately, through the filter here, this final product which is stored

in the storage container. I can't overemphasize the importance of a proper storage container because that is critical in evaluating both the in vitro and in vivo data that has been published previously. This is your final container. And the product that we produce is this, this is our pre-storage pooled five or six units of platelets, and this is the apheresis platelets for comparison. To me, they are almost identical products for practical purposes, identical to the hospital blood bank and identical to the end user, and I think that is our plea. And, as we do this, we are going to have to abandon our pre-storage platelets. Thank you very much, indeed. I would be happy to answer questions.

MR. SKINNER: Are there questions? Dr. Bianco?

DR. BIANCO: But you did not mention bacterial culture. Do you want to comment?

DR. SWEENEY: All the platelets are cultured for bacteria in the State of Rhode Island. So, all the blood derived platelets are cultured, as well as the apheresis platelets.

DR. BIANCO: And what volume?

DR. SWEENEY: Approximately 3 ML in the eBDS system. So, the loss of potency is very, very minimal in terms of the volume, which is about 60 mL--a very minor loss in potency.

DR. BIANCO: Thank you.

MR. SKINNER: Dr. Brecher?

DR. BRECHER: I just wanted to make one quick comment. Your slides about comparing the risks of apheresis platelets versus randoms where there is only 1/200,000 chance of viral transmission, that really is not the issue for us; it is the risk of bacterial contamination and we know we have two-tiered blood safety in regard to random platelets and apheresis where culture is much more sensitive than gram stain or pH or glucose. That is where the real risk is at the moment. If we pre-pool, hopefully, we can eliminate that difference.

DR. SWEENEY: Mark, I would just like to emphasize again that that is not relevant in our consideration because all the blood derived platelets cultured using the same technique as the apheresis platelets. Hence, we do not have a two-tier system. If we didn't, I would agree with you.

DR. BRECHER: But for most of the country--

DR. SWEENEY: Well, I can't speak for the rest of the country.

MR. SKINNER: Dr. Sandler?

DR. SANDLER: Dr. Sweeney, time was when a six-pack of whole blood derived platelets cost the hospital less than an apheresis unit. I know you can't speak to specifics, but if the technology that you describe, which adds a lot to the whole blood derived platelet technology, were to have an equivalent unit what is the relative cost of such a six-pack compared to an apheresis platelet?

DR. SWEENEY: Thank you very much for the question. We have looked at this. Quite frankly, we don't use six units, we use five. And the reason we use five is that the number of platelets in a five-pack is statistically similar to what we find in an apheresis product. So, it is about 3.8, 3.9 by 10^{11} and the distribution remains the same. So, we use five. So, the economic models we developed are related to five rather than six, because that actually is of some importance. In all our various models the cost of manufacturing of apheresis platelets versus whole blood derived pools, the whole blood derived pools are substantially cheaper, depending on how you assess the cost

of labor, donor retention, disposable device, maintenance, operator expenses, hourly rates of pay, storage containers, all of these variables are highly complex but we have done it and we believe it is substantially cheaper, probably on the order of about $100 per product in terms of acquisition costs at the hospital level. So, an apheresis product at $450 or $475, we can probably have this product at around $400 or less. So, we believe there is a substantial cost saving. The question is what do you do with that resource subsequently when you achieve the cost saving, but we believe it is less. You can construct models that would indicated it depending on how you appropriate these various costs.

MR. SKINNER: Any other questions?

[No response]

Thank you.

DR. SWEENEY: Thank you.

MR. SKINNER: The final set of speakers in this section will be Dr. Mark Brecher. He will again address the committee on the status of data collection in support of the pre-storage pooling of whole blood derived platelet products, and then he will be joined by Dr. Stein Holme,

senior scientist with Pall Life Sciences, who will address the activities of Pall. Dr. Holme's reputation is supported by his many peer reviewed scientific papers. Dr. Brecher?

DR. BRECHER: Thank you again. I am going to talk about some preliminary results that we have in my lab using the BacT/Alert for the detection of bacterial contamination in pooled whole blood derived platelet concentrates.

One of the things we have been searching for I think in blood banking, and we have already heard some discussion about this, is the ability to pre-pool random platelets--generally we are talking about four to six random platelets--into one bag and hold them for the entire storage period that the platelets are approved for, as opposed to the four hours that is currently allowed after pooling.

Now, as Dr. Vostal already outlined, FDA thinking had required CCI studies, some of which have been presented to this committee in the past by Nancy Heddle, and release control bacterial detection step. FDA's current thinking regarding pre-storage pooling is that such systems can be cleared if culture monitoring Q/C is performed by tests with analytical sensitivity similar to that cleared for single units. This also would require a storage bag that is

licensed for the pooled product, and would also require post-market surveillance.

What we have done in my lab is used the BacT/Alert 3D automated culture system which has these drawers that pull out of incubators and hold the culture bottles. They have colorimatric sensors at the bottom of the bottles that change from a green, I guess for go, to a yellow for sort of caution. The sensors have a light shone on them roughly every ten minutes. The detector picks that up. The machine looks at both the absolute color change as well as the rate of change, using computer algorithms to detect bacterial contamination. The color change is the result of CO2 product within the bottles.

This system has been extensively validated in the United States with apheresis platelets. There are many publications, most of them actually from my laboratory, as well as international publications from Europe.

So, with the thought of using this system for random platelets, we went to the FDA and had some informal discussions a few years, asking the question what is it that the FDA would need to see, our thought being that the real question was can you detect low levels of bacteria in a

pooled volume of platelets? Since the apheresis platelets have been approved for detecting bacterial contamination in the 10 CFU, colony forming units or organisms per mL, to 100 CFU/mL range, we suggested that if you make a pool and you have 10 CFU/mL in the bag that would be comparable to apheresis platelet. The volumes are very similar. If you have a four- to six-pack pool we are talking about 200-300 mL of platelet rich plasma and the volume for an apheresis pack is also generally in that range, 200-300 mL. So, the initial discussion was that that would be adequate.

So, on our initial setup we took six platelets, connected them with the sterile connection device, injected in our little bugs into a pool and then sampled them five times using a two-bottle set, aerobic and anaerobic bottles, 4 mL per bottle, as well as putting 0.5 mL on a plate, our thought being 0.1 mL may not have good detection on a plate and we did it times 2 plates for each pool.

The results are here and I know you can't read them but take my word for it. At 10 CFU/mL every bottle that was inoculated was positive, as expected. The final concentration in the pool actually turned out to be approximately 5 CFU--we were going for 10. And, as in

previous experiments, we found that the anaerobic bottle actually picked up the aerobic organisms, particularly Enterobacter cloacae E. coli and Klebs. pneumo., Serratia marcescenes and Strep. viridans, faster in equivalent time to the aerobic bottle. I will just call your attention, this is Strep. viridans. With the aerobic bottle it took on average of 23 hours to be positive. By that time most of the bags have already been issued. However, using the anaerobic bottle, it only took 21.4 hours to be positive.

So, with strep., and we have seen this in multiple studies, the anaerobic bottle is much faster than the aerobic bottle, and we have seen this both for Strep. pyogenes and for Strep. viridans. We did go on and publish this a few months ago in Transfusion and a copy of this paper was in the CD that was distributed for the committee members prior to this meeting.

However, further discussions with the FDA--the FDA had done a little more thinking about this and now they came back and said they wanted to see the detection of 10 CFU in just one bag that is then pooled with five others. So, we went back and redid this experiment following this study design, which actually would give you a much greater

sensitivity than is currently available for 200-300 mL of an apheresis pack.

We did this now in replicates of 10, again 4 mL per bottle into aerobic and anaerobic bottles and 0.5 mL onto two plates for every pool that we took out of these bags.

Again, a busy slide. This is at 100 CFU/mL, and all bottles that were expected to be positive were positive. There were a couple of strict anaerobes that were not positive in the aerobe bottles. That would have been expected. In general, the mean pickup time was on the order of about 12 hours. Again, the little numbers down here which you can hardly see show that the anaerobic bottle was about 10 hours faster than the aerobic bottle with Strep. viridans.

Now, when we went to the 10 CFU/mL single, that got a little more complicated because you are starting with a low inoculum in a single bag and then you are diluting it. So, if you have missed your target by a little bit, you wind up having very few organisms in the pool bag per mL.

So, we ran into trouble with Clostridium perfringens where we actually wound up with probably less

than 0.2 organisms per mL--Klebs. pneumo, Serratia marcescenes and Strep. viridans. However, overall it picked up the majority of cases, and the mean concentration in the single back was 4.9 CFU/mL. But we didn't pick them all up. So, we could re-juggle this data set a little bit. One of the reasons we did 100 CFU/mL is that we anticipated that we weren't going to hit the 10 CFU/mL exactly in any case.

So, if we look at what concentration were all respective bottles reactive, anaerobic bottles only for strict anaerobes, at this point the single concentration average was 16.8 CFU/mL, which is in that 10-100 CFU/mL range. So, we thought that was pretty good.

Alternatively, we could ask the question at what concentration in this data set did we pick up all the bacteria using a two-bottle set? Requiring all bottles to be reactive, the mean concentration was 16.8. But if we said just one of the bottles of the two-bottle set will be positive, the concentration in that single bag drops down to 7.2 CFU/mL.

This gets to the question of is greater volume better for very low inoculum concentrations? So, in this slide I have pulled out the low inoculum concentrations,

Klebs. pneumoniae, Serratia marcescenes and Strep. viridans where the concentrations were 3 CFU/mL were lower in the single bag prior to being pooled. So, the final concentration was probably 0.6 CFU/mL or lower.

What you can see from this is that in each of these low concentrations there are examples--this is the aerobic bottle, anaerobic bottle; aerobic bottle, anaerobic bottle; aerobic, anaerobic--ten different setups in yellow. There are many examples where either the aerobic bottle would pick this up or the anaerobic bottle would pick this up. This is particularly relevant I think to the breakthrough cases that were presented earlier this morning. We heard about Serratia marcescenes and had we only been doing one bottle with Serratia marcescenes with less than 2 CFU/mL we would have only picked it up in 40 percent of the cases. However, going to a two-bottle set we would have picked it up in 70 percent of cases. So, at very low concentrations greater volume does seem to make a difference.

We conclude that the BacT/Alert reliably detects the concentration level of 10 CFU/mL in a single unit even after pooling dilution with five other units. Such

detection may facilitate FDA approval of pre-pooled whole blood derived platelets. Any questions? Perhaps any burning questions?

MR. SKINNER: Any questions for Dr. Brecher? Dr. Kuehnert?

DR. KUEHNERT: That is very, very nice data. It gives us some insight into the possible effect of volume, but it still doesn't tease out between the effect of the anaerobic bottle versus just increasing the volume in the aerobic bottle. So, I wondered if you had any insight in how we could tease that out.

DR. BRECHER: We didn't set it up where we put 8 mL into a bottle. I think in our next iteration of experiments we are going to try that.

DR. KUEHNERT: Great!

MR. SKINNER: Celso?

DR. BIANCO: How much time, Mark, was it between inoculation? You went directly after you inoculated that amount?

DR. BRECHER: We inoculated into the single bag and we put it on a shaker for 10 minutes. Then we pooled

it; put it back on the shaker for 10 minutes. So, within 20 or 30 minutes after inoculation they were set up.

DR. BIANCO: But it didn't get any help?

DR. BRECHER: Any help?

DR. BIANCO: From time, that is to expand whatever you do.

DR. BRECHER: No, we wanted to know exactly what was in the bags.

MR. SKINNER: Dr. Sandler?

DR. SANDLER: Dr. Brecher, you work with both systems and you presented a lot of very, very interesting data. If the FDA were to approve all of the systems just with the data that is there, what would you do at the University of North Carolina? Would you use pooled randoms? Would you go to apheresis? And, why would you pick one over the other?

DR. BRECHER: Right now at the University of North Carolina we are virtually 100 percent apheresis platelets, and we did that as a conscious decision about ten years ago because of the higher risk of bacterial contamination with a six-donor pack, and we did that shortly after a death in our facility from a bacterially contaminated platelet.

If we had pre-pooling with bacterial testing, I think the argument for using single apheresis platelets is a lot less. There will be occasional breakthroughs. We won't be able to prevent them all. Presumably, the breakthroughs would occur more commonly in the random platelets, but I don't know whether that would be a strong enough argument to make me stay with apheresis platelets. So, I can't answer that right now. I would have to think about that.

MR. SKINNER: Thank you. Next we will hear from Dr. Holme.

DR. HOLME: First, thanks for the invitation and the opportunity to present where we are with Pall bacterial detection system, the eBDS, and seven days of storage releases, as well as the Pall pre-storage pooling system. I will talk about five days as well as seven days of storage.

Regarding eBDS and seven-day storage releases, as you have heard from Dr. Vostal earlier today, the Pall random color PC has been approved for seven days of storage. Also, the eBDS system has been approved for Q/C use. We intend to submit a 510(k) for eBDS. The target date is a submission in February, 2005. We are going to provide field data on testing conducted in actual use conditions of the

five-day storage, and also will provide a post-marketing protocol.

Approval, as Dr. Vostal was mentioning, for seven days of storage of single products, we are talking about two apheresis products and one whole blood derived product that have already been approved in terms of quality.

Here are the results of the field data that has been performed with the eBDS system. These are 118,000 tests that have been performed at 23 blood centers in the U.S. from March to November, 2004. The results from these tests were sent electronically, and we followed up with phone calls to help get more information about those test results that had resulted in so-called failed results were there was an indication of a contaminated unit.

So, out of the 118,000 tests that were performed, about 118, which is 0.1 percent, failed indicating the presence of bacterial Of those, 23 percent were confirmed to be true positives. That means that there was presence in both the eBDS pouch as well as in the mother bag by culture. There were 76 false positives. There was no presence of bacteria in either the eBDS pouch nor the platelet model by culture. There was one false negative that was confirmed.

This was a sepsis with confirmed presence of bacteria in the mother bag by culture. Finally, there were 18 that were not confirmed false positive. There was no bacteria in the mother bag by culture, however, the eBDS pouch was not tested so there potentially could be cases with early sterilization of the mother bag.

These are the same results shown here in terms of percentages and frequency. Test samples that failed represented approximately 1/1000. Confirmed true positive was 1/5000, very much similar to what was reported earlier today in terms of the survey that was conducted. Confirmed false positive was less than 1/1000.

Switching gears, this is our system for pre-storage leukoreduced pooled product. It shows here to the left the lead that connects the individual PC. We have a storage container, CLX-HP, and also in-line you can see the bacterial detection system. So, after pooling, the pooled units will be tested with our bacterial detection system.

This system is intended to be suitable for pooled leukoreduced PC from whole blood collected with a Pall RCPL system using CP2D as an anticoagulant. It should be able to store four to six units. These units may have leukoreduced

PC and plasma for five days, with total yields in the storage bag ranging from about 2.2 to 5.8 times 10^{11} platelets. This is supposed to be used in approved bacterial detection systems such as eBDS.

What are the concerns and challenges with pre-storage pooling of random donor PC? You heard the risk, as mentioned by Mark Brecher and others, there needs to be a sensitive bacterial detection system. There are also concerns about lymphocyte activation, generation of harmful levels of cytokines, complement clotting factors. Some of the risk may be addressed by pre-storage leukoreduction.

Finally, we have this platelet storage quality in addition to satisfactory in vitro and in vivo quality at five-day storage. The bag, which I think is more critical in this sense, has to be able to handle four to six on a PC with a large variability in both yield and volume.

The bacterial growth and final CFU level may be higher on a pre-storage pooled product as compared to post-pooled product at the time of infusion. Also as mentioned by Mark Brecher, at the time of the pooling a potentially contaminated individual PC can be diluted in the pooled product, thus resulting in a lower CFU level. This may thus

challenge the sensitivity of detection with immediate sampling.

In terms of growth in a pooled product, we have done several growth studies and this slide shows an illustration which demonstrates basically the generation doubling time in PC with its organisms, very similar for individual PC as well as for pooled PC. The doubling time means that the doubling time was 135 for individual PC and for pooled PC the doubling time was 144. These were studies that were presented by Young and co-workers at the last AABB meeting.

In terms of the effect of dilution at pooling, here is a table that shows the probability of obtaining no organisms in a 3 mL sample, which is similar to what is used for eBDS. And, we can see here that, for instance, we are having a CFU level of 2/mL. With one PC undiluted there is high probability of not detecting it as low as 0.002. However, if you pool, then the likelihood of not detecting becomes higher, about 0.3 which is 30 percent. As the CFU level becomes lower, there are certain differences between one PC and a pooled PC in terms of a probability. But this is within a very low range of CFU, and also with the range

that is shown on this table the probability will be the same.

In terms of in vivo and in vitro quality and lymphocyte activation levels at five days of storage, using pooled leukoreduced on rendered on a platelet storage with CLX-HP, several studies have demonstrated that there is no effect on either lymphocyte activation and that the in vitro as well as in vivo quality of the platelets is satisfactory.

Coming finally to bag capacity, this histogram shows yield distribution of individual processed PC using the Pall RCPL system and you can see here--this is from field data--about 700 measurements were done. The yield of the individual PC is ranging from about 5, almost as much as 15 times 10^{10} platelets.

So, in terms of the expected platelet yield distribution with a pool of 4 PC, this is a histogram, that was done in a randomized manner using computer simulation, a sample of 4, and you can see here that the expected yield with a pool of 4 PC will range from about 20 to about 50 times 10^{10} platelets. The percentage of yield that will be more than 30 times 10^{10}--this is the minimum requirement for apheresis platelet--will be 84.6 percent. The percentages

that will have more than 22 times 10^{10}--this is 4 times 5.5, which is the minimum requirement for individual PC, will be 99.4 percent. There will be zero percent that will be expected to have a yield more than 58 times 10^{10}, which will be the maximum target capacity of the CLX-HP bag.

Here is the expected platelet yield distribution with a pool of 5 PC. Here we have a 99 percent chance of getting a yield more than 30 times 10^{10}, and in this case there is a small risk of overloading the capacity of the bag with 1.4 percent having a platelet yield more than 5.5 times 10^{10}.

Here is the actual data we have from platelet capacity studies done through the last two years. This represents 150 data points with yield ranging from about 2-6 times 10^{11}, and we can that the pH in all cases is maintained about approximately 6.6 after five days of storage. The lowest ones, those with the pH below 6.8, are cases where the platelet was highly concentrated by using 40 mL volumes of the individual PC.

Where are we with our pooling for five days of storage? I am talking about the already leukoreduced platelets. We have completed lymphocyte plasma activation

studies. In vitro and in vivo storage quality studies have been completed. The CLX-HP storage capacity study where we are talking about low and high yield, low and high volumes have been completed. And, we are in the process of completing our studies on the eBDS bacterial testing in pooled PC which should be completed next month. So, our plan is to submit this to the FDA in March, 005.

Coming then with a pooling set, both pooling set number one as well as pooling set number two with seven days of storage, this is a drawing of our pooling set that will be used for non-leukoreduced PC. You see the leads that lead into the pooling bag which will then be leukoreduced and stored in the platelet storage bag which have an eBDS line connected.

We are in the process of drafting an IDE for clinical studies with seven days of storage for pooling set number one as well as pooling set number two, which will be submitted to the FDA sometime in March. And, we hope to start then the patient studies later this spring.

So, just to summarize, with having a pre-storage pooling system with an in-line sensitivity bacterial detection system in place, what are then the advantages in

terms of blood safety and availability? Having just one bacterial test for four to six random donor platelets ensures simplicity and affordability and it also enables continuous use of random donor platelets as an important source of platelets. Also, I want to stress that again, enables improved bacterial detection compared to the current practice using pH dip-stick with random donor platelets. Thank you.

MR. SKINNER: Questions for Dr. Holme?

MR. HEATON: Stein, what is the Cmax for your storage container? What is the maximum platelet content?

DR. HOLME: We have tested as much as 6 times 10^{11} and still find that the pH is maintained. But, to be on the safe side, we potentially go to 5.8 but we haven't decided that yet.

MR. SKINNER: Dr. Epstein?

DR. EPSTEIN: Can you just clarify for me what time of storage is being considered to be recommended before sampling?

DR. HOLME: For?

DR. EPSTEIN: For post-pooling and prior to culture sampling.

DR. HOLME: We are going to recommend that immediately after pooling you are able to take a sample for eBDS, immediately after pooling. So, we pool the individual PC. After the individual PC has been stored for 24 hours, and then can sample directly.

DR. EPSTEIN: Well, just to pursue that point though, your own data suggests that on the model if there were 5 CFU/mL in one of the units to be pooled--I forget how many, 5 per pool--you had a 5 percent false negative rate.

DR. HOLME: Yes, there will always be a risk with pooling, a small risk with pooling, depending where the actual CFU levels are. Within a certain range of CFU you will find a difference between pooling and not pooled product. With more than, let's say, 5 CFU it will be detected in both cases. If you have levels less than 0.2 CFU/mL you will have no detection in any of those cases. So, we are talking about a very narrow range that could potentially be a difference. So, whether that will be something that will happen in clinical practice is uncertain. It is uncertain that when a unit is contaminated initially that it will end up inside a very narrow range of CFU level. Probably if it starts growing and you are

getting more than 5 CFU/mL, there will be no problem in detection in any case, and if it is not growing it will not be detecting in any case.

MR. SKINNER: Go ahead, continue.

DR. EPSTEIN: Well, just to pursue this a little further, it is self-evident that the problem of dilution with pooling only matters at low CFU initially. The clinical problem is that we don't know what the contamination rate level is in contaminated units.

DR. HOLME: That is correct.

DR. EPSTEIN: And we are flying in the dark. Nor do we know how to correlate that with ultimate clinical outcomes, and that has been the driver for trying to optimize the analytical sensitivity of this system based on a presumed low inoculum. So, you know, faced with the uncertainty, which way would we rather go?

DR. HOLME: But I think that using Q/C for a pooled product will tell us whether we are going to miss or not miss. So, my point is we really need to have it tested out in the field to see whether it is going to miss or not miss because we don't know what the initial levels are.

DR. EPSTEIN: I certainly concur with that point. The FDA has been advocating that for years.

MR. HEATON: Stein, could you give us some estimate as to when you think you will have completed the clinical trials, the CCI trials? It is obviously most impressive having the opportunity for the customers to have a choice between pooled randoms as opposed to apheresis. So, when do you think you will be through the clinical trials and ready to submit?

DR. HOLME: With five days of storage, we have already completed the clinical trials and we plan to submit a 510(k) by the end of February with clinical data, with bacterial testing on the pooled product, with bag capacity studies, with lymphocyte activation test. So, the submission will be at the end of February and it is then up to the FDA.

MR. HEALEY: For seven days?

DR. HOLME: For seven days, we will start by the end of this spring and we probably want to take at least a year to conduct the clinical studies.

MR. SKINNER: Dr. Kuehnert?

DR. KUEHNERT: Maybe I missed this when you were answering Jay's question, but what was the organism associated with the confirmed false negative?

DR. HOLME: This was a Staph. epi. and we investigated that case very thoroughly of our equipment, our disposable set. We got bacteria sent to us for further looking at growth studies, as well detection with eBDS and we didn't find anything abnormal with the organisms. It grew normally and we were also able to detect this organism at the level of about 2-3 CFU/mL. So, the only explanation we have is that it could be a sampling error but the levels were so low that it was missed. That was indicated by the level or percent in the eBDS port, which is what you would have expected with a non-contaminated control product.

MR. SKINNER: Dr. Bianco?

DR. BIANCO: I wanted to know your feelings, that is, we just came out from a presentation by Dr. Brecher where the advantages of the anaerobic bottle are discussed, and the possibility that--there are several possibilities about the way they contribute. How do you feel about your system that is focused on aerobic only?

DR. HOLME: Well, strictly anaerobic organisms are unlikely to grow in a platelet product which is a very rich oxygen environment, so potentially would stay at very, very low levels. Then, I guess the survey indicated that the contamination rate using both an aerobic and anaerobic bottle was approximately 1/5000. Our system which has a marker for the presence of bacteria has very much the same contamination rate, 1/5000. So, if there is an issue with anaerobic bottles, it has to be very, very low. You know, if BacT/Alert wanted to conduct studies where they are looking at both an anaerobic as well as aerobic bottle, they can conduct that study and see if there is any significance or not, is it going to be worthwhile doing both an aerobic as well as anaerobic and base it on that. They need to do the studies.

MR. SKINNER: Dr. Brecher?

DR. BRECHER: Yes, I think you have to be careful here, comparing apples to apples. The 1/5000 is based on a data set that is 90 percent just aerobic bottles. See, we are only comparing aerobic to aerobic so I think what you can say is that the detection pickup for aerobic cultures seems comparable, if not identical.

DR. HOLME: But that includes both aerobic as well as anaerobic, doesn't it?

DR. BRECHER: No, because there is probably 10 percent, if that, of centers that use anaerobic bottles.

DR. HOLME: So, they were able to identify anaerobic organisms?

DR. BRECHER: They do, but that data is not readily available.

MR. SKINNER: Seeing no other questions, thank you. At this point the committee has about 15 minutes or so--we can go longer into lunch if needed--for committee discussion. I think the question before the committee is we have heard basically that the AABB task force has completed their work and a number of other presentations. So, the question really is where do we go from here? Are there any additional recommendations that we want to make?

The plan would not be to wordsmith and adopt recommendations at this point but if, in fact, somebody has a recommendation or proposal to put forward, it would be good to at least bring it up at this time so people can think about it and then we will come back to actually

discuss it and act on it at a later time. Any discussion from the committee?

DR. KLEIN: I must say I feel much more comfortable now that studies are under way or about to be under way in both areas, in the area of the single donor and the area of the pooled whole blood derived platelets, than I was the last time this committee met. And, I think that at this point in time I don't feel that there is any need to push very hard.

MR. SKINNER: Dr. Brecher?

DR. BRECHER: I agree with that, Harvey, but I think what the committee might do is to commend industry for having made attempts to move forward and recommend that any resources that HHS might be able to provide to facilitate that should be made available.

DR. BIANCO: And I would like to add to your suggestion, Mark, that we see what is happening in six months.

MR. SKINNER: Dr. Kuehnert?

DR. KUEHNERT: Yes, I want to follow on Dr. Bianco's comment. I mean, I think there is a bit of insight into what is happening with the task force survey, but that

work really needs to be continued somehow and I don't see right now a mechanism for that to happen. That is very concerning to me because I think as the methods start to become standardized, I think the questions are going to be able to be answered. I think right now it is so difficult, because of so many variables, to try to tease any answer out of what we have right now, although I think we need to try. But I think as the methods become more standardized those answers will be able to be obtained, and I think we really need to evaluate these systems. I mean, Dr. Sandler brought up a very good question about, you know, if you have a comparable culture system between apheresis and whole blood derived platelets which would you choose, well, if you don't know what the safety profile is of each system, how are you going to choose? And the only way we are going to get there is by having a system for evaluation. I think the task force has started a baseline and a template to start to do this but it really needs to be carried forward.

MR. SKINNER: Dr. Heaton?

DR. HEATON: First of all, I would like to commend the FDA I think for displaying impressive regulatory nimbleness in facilitating the approval process. We

wouldn't have got to this point had we not had a very significant degree of flexibility and interaction with the agency, and I would very much like to commend the FDA for that.

As we go forward, a key issue here is monitoring the outcome. We have all observed that data collection is going to be critical, and we don't have the world's strongest public health reporting mechanism to follow these cases. So, my suggestion would be that the advisory committee consider recommending to the Center for Disease Control that they assign resources to participate in monitoring reports of bacterial assay and facilitate the compilation of this information so that in a year or two, after the products have been approved, we can adequately assess the safety and efficacy.

MR. SKINNER: Dr. Bianco?

DR. BIANCO: Maybe Jay can help us, but from what I heard, there will be possible marketing surveillance so that data will become available. Is that correct or am I too optimistic?

DR. EPSTEIN: Well, the concept being put forward is to permit extension of dating if the use of an adequately

sensitive quality control test is coupled with culturing at outdate. I think that what we are circling around is how will the national data get compiled because there is a subtle issue about who is accountable, and that is not completely resolved. We think that there is a shared accountability here between the providers of the product who are seeking product claims and the users of the product who, if they are licensed, will be in need of some regulatory approval to amend their license. But I think it is not entirely clear at the moment who will compile the data and how it will come forward, and I think that that is somewhat related to the issue that Mat is raising, but the basic concept is to permit generation of the data in Phase IV, and we need to be sure that we have an effective mechanism.

DR. BIANCO: So, we have to support the recommendation that you just made.

MR. SKINNER: Any other comments from the committee? Dr. Heaton, would you have any interest in wordsmithing that and having it for the committee at a later time?

DR. HEATON: I would, I will be glad to.

MR. SKINNER: Thank you. We will come back to it later in the meeting. Amazingly, we are ahead of schedule so the committee will adjourn at this time and return from lunch at two o'clock. Thank you.

[Whereupon, at 12:55 p.m., a luncheon recess was taken to reconvene at 2:00 p.m., this same day.]

AFTERNOON SESSION

[2:08 p.m.]

DR. BRECHER: Can we have everybody to the table. We are going to begin again. We are going to move on to the second topic of the day, which is the Identification of Reimbursement Issues Associated with Plasma and Recombinant Analogs.

We are first going to hear a report of the Subcommittee on Reimbursement by Dr. Jerry Sandler, who is chair of that committee, and he is a member of our committee.

Jerry.

DR. SANDLER: Thank you, Mr. Chairman.

On November 29, the subcommittee had an informal telephone conference call. We had no votes. Not all the members were present on the call, and what I am going to be communicating to you represents my own representation of that, and not a committee statement.

At several prior meetings of this committee, we heard that some persons with life-long requirements for plasma therapies are not receiving what they feel is fair reimbursement for necessary health care.

We propose that this subcommittee develop a list of specific plasma therapies and procedures that are being proposed for reimbursement, that we estimate the number of persons and events per year related to these, and then calculate the annual costs.

In other words, we are looking for a catalog of what are the issue and is there a specific price tag, and the answers to many of those questions I think could come from representatives of industry, of patients, and from CMS.

The other, bigger topic I think is a second topic. There are several new blood products and technical methods that are being developed by industry, academia, and others with the goal of increasing transfusion safety and availability.

These items include, but aren't limited to, hemoglobin-based oxygen carriers, pathogen inactivation methods, bar code and RFID identification methods. We heard about bacterial testing this morning and new tests for transmissible diseases.

Recent experience has shown that the absence of a mechanism for timely and additional reimbursement, what we

call "new money," for hospitals is an impediment to prompt implementation of such advances when they become available.

What we propose is making a list of what that pipeline is, trying to put some time lines on it, and try and put some price tags on it. Some of these items, like a new test for chagas or something, is pocket change. It is going be a 100 million, whatever it is going to be, in terms of health care, but if you look at pathogen inactivation, with maybe $100 per product times 27 million products, we are looking a couple of billion dollars and a two-year lag between the time when there may be an announcement that it's available for the American public, and when our government is ready to start paying back the cost of that.

So, we think that it would be very helpful to make a catalog of these things, the price tags, and provide the Secretary of Health with a picture of some of the small icebergs and some of the bigger icebergs that are up ahead of us.

Thank you, Mr. Chairman.

DR. BRECHER: Thank you, Dr. Sandler.

Any questions for Dr. Sandler?

[No response.]

DR. BRECHER: If not, we are going move on to the agenda that this committee contributed to.

We are first going to hear from Dr. Bowman, who is a member of our committee, is the Medical Officer, Chronic Care Policy Group, and he will present an overview of the 2005 Rule for the Hospital Outpatient Payment System and Medicare Part B.

DR. BOWMAN: Thanks, Dr. Brecher and the committee. We certainly appreciate the opportunity to participate in getting this allotment of time on the Advisory Committee's agenda.

For those of you in the audience, my apologies for turning my back to you. It is not meant out of disrespect or not any inconsideration. It is actually a lot of this discussion material was just as important to you I think, as it is to the committee.

I know many of you probably don't have the handouts, but if you e-mail me afterwards, I can just e-mail them to you. That way, we don't have to furiously scribble to take notes. There is going to be a lot of gobbledegook on the slides and I would just try to discourage you from

trying to take notes. It is much easier to e-mail it to you.

Also, there is a one-pager handout at the table outside the door. The committee members already have that. That is just a fact sheet resource of web sites with CMS and some other government agencies of easy web sites to find some of the answers to some of the questions that we will be discussing this afternoon.

One little minor housekeeping thing is that nowadays when you type on your computer, and it is not like the olden days with WordPerfect or even a Royal typewriter, when you type a website address and you hit Return or Enter, you get all this underlining on your URL web address, so what may look like a space in the listing of the URL web address, it is not really a space, it's an underscore on that one-page handout.

You will see that it looks like somebody just took a line with a marker and just ran right underneath it. So, that is not what it really is. If you have any questions, you can always e-mail me again, and I will e-mail you a clean copy that is so-called rich text format that Bill

Gates has made available to us that will link it in automatically to you when you punch it up on your computer.

So, with that little bit behind me, hopefully, it won't be like the situation with I think it was a cowboy out west, Wild Bill Hickok with his back to the saloon door playing poker, and he met his early demise that way, so like I say, I usually don't like my back to the audience.

At any rate, again, just to put a little perspective on things, in general, the Medicare payment system starting back around 1984 with the introduction with the DRG inpatient prospective payment system, which I can tell that some of you probably remember that, and then there are others of you who probably don't remember that, but the Medicare program has incrementally over the years evolved into a prospective payment system, and this is in contradistinction to a fee-for-service payment system.

That means instead of submitting a line item laundry list of charges on a bill, the physicians and providers and others in the community will get paid what is called prospectively a bundled amount based on the diagnosis and other factors.

So, the physician's payment system is one of the last holdouts of the old fee-for-service system, so the Medicare physician payment schedule is still a fee-for-service system, but by and large, many of the other types of health care that are rendered within the Medicare scope of benefits is under a prospective payment system.

What that means is actually very few items and services and a very small proportion of the entire Medicare budget is paid outside of that prospective payment system, and the reason Congress set that up is to allow for just what Dr. Sandler was talking about, for medical innovation and introduction of new technologies and advancement into the health care system.

If you had a static prospective payment system and you never introduced any new payments for new technology, then, medicine, of course, would never advance at least within the Medicare system, and since Medicare makes up a good portion of the health care dollar in this country, it does drive a lot of what happens in our health care system.

Having said that, Congress, in its wisdom, actually did carve out, if you will, certain parts of the Medicare program that would be not under the prospective

payment system. As you know, of course, blood products do fall out of that for some settings, of course, not for all settings, as we will get into and we will see.

But certainly that is one component along with new technology and medical innovation, so that you find there are what they call new technology add-on payments into the inpatient prospective payment system under DRGs, and you will also find there are new technology add-on patients under the outpatient prospective payment system, which is a similar DRG system for the outpatient clinic setting.

I just wanted to kind of set the stage here because although there are new technologies and new advances within the blood community and the blood science, some of what is done in the blood community is still old-fashioned, if you will, it's not all new, but be that as it may, Congress did set apart parts of the payment system for blood and blood products outside the prospective payment system.

That is why we have a mix, if you will, and a lot depends on the setting.

Having said that, let me see if I can advance this slide a little bit. Some of the focus as we go along this afternoon will be on the intravenous immunoglobulins portion

of the plasma-derived therapies. This comes out of what Dr. Sandler's subcommittee thought the focus should be, however, I am going to present this in the context of the updated 2005 payment schedules for the inpatient and outpatient physician fee schedules.

There are two IVIG, what they call HCPCS codes, which are just simply HIPAA-compliant identifier codes that are used for reporting and billing and payment purposes. J-1563 is the 1 gram version and J-1564 is the 10 milligram version of that.

As I alluded to earlier, payment in the Medicare program for nearly all services, a lot depends on the treatment in terms of where that health care service is provided.

For our purposes this afternoon, it would be most convenient to think of it as three different settings and then a little special setting we will talk about later, which is the primary immune deficiency home infusion benefit for intravenous immunoglobulins that came about as a result of Section 642 of the Medicare Modernization Act, which is abbreviated as MMA in the rest of these slides, and we will talk about that a little bit later.

But by and large, health care services delivered primarily in three different settings. The first, of course, is inpatient hospital setting, which primarily is based on payment of DRGs, which I spoke about earlier, were introduced in 1984.

The outpatient hospital system in the late '90s came under the outpatient prospective payment system, and those are based on ambulatory payment classification groups which are, in the Medicare lingo, are called APCs.

The physician office setting is based basically on the Medicare physician fee schedule, which is still a fee-for-service for the most part. Then, we will talk about the home infusion just a little bit later.

Now, for each of these three payment settings, to put it in broad perspective, we really are talking this afternoon about three different types of products. The first is what I call blood products and whole blood, so it is whole blood and packed red cells and platelets.

The second is plasma-derived therapies. Primarily, we are looking at IVIG this afternoon although there are obviously other plasma-derived therapies, and then there is a special case for clotting factors that Congress

set special legislation for, and that includes both clotting factors that are derived from blood and also recombinant clotting factors.

So, when you think of the rules that Medicare uses to make its payment, the way Congress set this up, you have three different payment settings or treatment settings, and you have three different types of products or services for our discussion within the Advisory Committee here.

So, it's like a 3 by 3 table, if you will, with inpatient, outpatient, physician office down along the rows, and then across the columns, you will have whole blood and packed cells, platelets, and then you will have intravenous immunoglobulins and plasma-derived therapies and then the special case of clotting factors.

Unfortunately, my computer skills aren't quite adept enough to create a 3 by 3 table, so you will just have to imagine it as we go along.

Just to take care of again a few little housekeeping things. We are in the early stages of the implementation of a massive Medicare reform bill that Congress passed, that we call the Medicare Modernization Act, that the President signed on December 8, 2003.

Some of those changes came about during 2004, quite quickly, and we are in the 2005 cycle now of changes, and then there will be further changes in 2006. For this afternoon, I am going to primarily focus on 2005. There is enough just to talk about this year instead of hashing over stuff from last year and predicting future stuff for 2006 and beyond.

There are huge, big changes involved with this bill. One of the biggest, of course, is the implementation in January 1st, 2006, of the so-called Part D, as in dog or drug, Part D Medicare Drug Benefit Program, which again Part A, of course, is the hospital insurance program. Part B is the optional primarily outpatient services program.

Part C is what we have in the past referred to as Medicare Choice, but now has been renamed Medicare Advantage, and is basically the managed care version of the medicare, and that is primarily around 4 to 5 million beneficiaries enrolled in those plans right now.

So, Part D is one of the biggest changes of the MMA that was passed. Some of those changes, they may affect some of the blood community, but we are not going to get into those today. They will be implemented in January 1st,

2006, and it is primarily a prescription drug benefit for outpatient oral drugs.

Finally, the MMA also added a benefit for intravenous immunoglobulin home infusions for beneficiaries with primary immune deficiency, and we will get into that just in a little bit later.

Again, I would encourage you not to try to take a whole lot of notes, because all of this I can e-mail to you, and I will have my e-mail contact information at the end of this slide.

Now, as far as outpatient, which is called OPPS in the Medicare abbreviations is concerned, when you look at--let me back up just a second--I would like to go through this just very quickly.

Under the different treatment settings, the inpatient is primarily for blood under the DRGs, and that is not unusual. Most all of the inpatient services are covered and bundled into what we call DRGs, which are various categories of groups.

The plasma-derived therapies are also covered in the inpatient setting under DRGs, and then the clotting factors are a special case where not only is the DRG is paid

to the hospital for that particular medical diagnosis, but there is also a special payment prescribed by legislation in addition to that for the clotting factors themselves.

Now, under the outpatient OPPS system, blood products, meaning primarily whole blood and packed cells, have special versions of the DRGs for outpatients, which are called APCs, and they have special assigned APCs, that are fixed by law.

Under the plasma-derived therapies in the outpatient setting, are prescribed by the MMA statute, and there will be some changes from 2004 to 2005 and 2006 and beyond. The clotting factors again are also prescribed by changes in MMA. For the most part, those are based on what we will call the average sale price plus 6 percent, and we will come back to that in a bit.

Finally, in the physician's office, the payment for blood and blood products in terms of whole blood and packed cells is unchanged by the MMA, but certainly for the plasma and the clotting factors, the MMA does change that, and that again is based on the average sales price plus 6 percent with additional provision that in the physician's office and under incident 2 services under the physician fee

schedule, the clotting factors also be reimbursed at administration fee or dispensing fee based on the number of units of clotting factors that are administered, and we will get to that shortly also, but that is currently at 14 cents per unit.

That is based on a GAO study and some updated information that the CMS took into account to arrive at that. The GAO study suggested somewhere in the range of 3 to 8 cents per unit, but the updated information that CMS received, actually CMS felt was more reflective to use a number of 14 cents per unit for that.

Now, this gets a little bit into the nuts and bolts of the outpatient prospective payment system for the blood products. As I noted before, for whole blood and packed cells, this is specified by inventory payment category groups, or APCs, and there is a statutory way that those are computed, just like it is for all the other services in the OPPS system.

Now, for 2005, the MMA made some very significant changes in the payment rates for drugs and biologics in the outpatient system. In 2005, the payment will be no lower

than 83 percent of the AWP, which is the traditional average wholesale price, and it will be no higher than 95 percent.

Now, going forward, in 2006 and beyond, that is going to be based on a combination of the average sales price, and if that is not available, what is called the wholesale acquisition cost, and we will talk about that in just a little bit. It was an input from a GAO survey for that.

The 2005 proposed rule is listed in the Federal Register, and that is available on the one-page handout. This is just for your reference purposes. The final rule was November 15th. There was a technical correction that was issued again in the Federal Register on December 30th.

Under the Physician Fee Schedule, again, payment for blood and blood products was unchanged, and we will talk about the intravenous immune globulin in just a minute, but for the drugs and biologics, again, some significant changes were made by the MMA in the way this is going to be paid.

There were some changes to what we call the Social Security Act. I have abbreviated that SSA up there, and you will typically hear that referred to as "The Act" as an abbreviation.

There are two ways that drugs and biologics will be paid under the Physician Fee Schedule. One is average sales price, and the other is the wholesale acquisition cost. For sole source drugs, which include the biologics and plasma-derived therapies, this is going to be based on the lesser of that average sales price or the wholesale acquisition cost. This is based on the external data that is provided to CMS by drug manufacturers.

The physician payment in general will be 106 percent of that basis amount that is calculated, and that is basically ASP plus 6 percent is the way it is often referred to.

There are two methods that will be used, that are being used actually. One is the average sales price. This basically is an aggregate number. It takes all the manufacturer sales and divides by the total number of units sold.

If there are multiple manufacturers for the same product, such as generics, then, those a volume weighted average to come up with the average sales price. If it's a sole source, then, of course, it is based on just that one manufacturer's sales.

There are certain sales that are exempted from the calculations. That is primarily to Medicaid programs and some others that are what they call "trivial" sales where the sales price is not really relevant. The sales price calculation is net of discounts and rebates for this method.

Now, if the ASP data is not available--and I forgot to mention that the ASP will be updated every quarter by CMS, so this is a little more timely than the traditional updating of one year on these types of payments--if the information is not provided to CMS on certain types of drugs and biologics, then, a different method is called the "wholesale acquisition cost," or WAC is the abbreviation.

Again, the statute reference is listed there. This where the manufacturer supplies CMS, actually, the manufacturer list in reference catalogs the price of a particular drug or biologic, and this information is used as what is considered the available market price, just like you would in the old-fashioned days go to the Sears catalog and look to see how much a bicycle or a washer would cost.

Again, this is used when the ASP is not available. For this method, it does exclude the prompt pay discounts

and other types of rebates and reduction in price, and this is again based on the statute in the MMA passed by Congress.

Now, just to give you a sneak preview, in 2006, you may have heard of competitive bidding for drugs and biologics. The beginning of competitive bidding will start in 2006, January 1st, 2006. Not every drug and biologic will be put on the competitive bidding schedule, certainly not initially. There will be a phased type of rollout of this and it is going to occur over several years.

There are certain exclusions to the competitive bidding method. Certain of those exclusions are actually based in statute, and that includes blood and blood products, DME infusion drugs, and certain vaccines.

In addition, there are certain exclusions that the Secretary may make at his or her discretion, and the primary criteria specified in the MMA for these exclusions are either no significant savings to the Medicare program by using the competitive bidding process, or it may have adverse impact on access to care and services or products if the competitive bidding process is implemented for that particular category of drugs.

Now, physicians will have a choice. Nobody is going to shove this down the physician's throat. If they want to use the ASP method and get reimbursed directly, and they can go out and buy the drugs or biologics and the provide them to the patients, then, get reimbursed under the ASP method, which is a fee schedule that will be updated every quarter, that is their option.

Each year they can choose. If they would rather have the competitive bidding process, then, it sort of takes the physician out of the loop on this, because actually, the Medicare program will directly reimburse the provider of that produce or drug, and the physician is sort of out of the financial loop on that, but again, physicians will have a choice under this type of system.

Now, as I mentioned earlier, Section 642 of the MMA amends the Social Security Act in a certain section there, you know, Section 1861(s) blah-blah-blah, and adds another section 1861(zz).

This is a benefit that actually started January 1st, 2004. it is for intravenous immune globulin for primary immune deficiency disorders, and it is for use in the home setting.

The Social Security Act, under Section 642, has very specific language that does exclude from the benefit, administration items and services. It is a very short section of the MMA and takes up less than a page and a half. If anybody is interested, I will be happy to fax them a copy of that.

The pharmacies and hospitals and physicians who provide this can bill durable medical equipment regional carriers. There are four, what we call DMERCs, in the country, which are analogous to the fiscal intermediaries under the Part A program or the carriers under the Part B program, and they are generally referred to as "contractors" under the Medicare program.

So, pharmacies, hospitals, physicians may bill the DMERCs. The home health agencies can bill the regional home health intermediaries that they are accustomed to dealing with for all the other home health services that they provide.

Finally, in addition to the one-page fact sheet that I left at the doorway just outside in the foyer, there are several websites that are useful. Those are all written down on the one-page fact sheet, and I can certainly e-mail

you that. Like I said earlier, it has all the rich text format.

I checked all these websites last night, and they are still active. Six months from now, some of the little characters may change or the little forward slashes and things like that may change, but at least right now they are still active.

For the most part, the CMS website is fairly easy to get into and find information on. It may take a few clicks to get deep into the website links to find what you are exactly looking for, but it is fairly intuitive. I have been able to get into it, so as technically challenged as I am, I suspect most of any of you will not have any trouble at all.

I would mention that the Federal Register links are available on that one-page sheet for the specific dates that these rules appear. I didn't put the link for the actual PDF file or the HTML type of word file, which would be kind of cumbersome, but when you go to the Federal Register for any particular day of the year, it will have a whole laundry list of every federal agency that has issued

anything of importance or official type of notice for that particular day.

You can either pull it up as a PDF file, which is kind of a condensed sort of document that makes very easy printing, but you can also pull it up in an HTML type of a word format, and that makes it very easy to search for particular words or topics you are looking for. To the best of my knowledge, you can't search under PDF files. If you can, I don't know how to do it.

So, I put the links there just for the particular days of those particular rules, and then you scroll down to where you see centers for Medicare and Medicaid services, and it will list every regulation on that particular day that CMS issued.

If you are looking for the inpatient rule or the outpatient rule or the Physician Fee Schedule for those particular dates that are listed, it will be listed there in both formats.

Now, I would like to just conclude and mention that I have with me a knowledgeable colleague of mine. Both of us are staff physicians here at CMS, Carol Bazell, who is

hiding over there in the second row. She will be assisting me after we listed to the next portion of the program.

I have asked her to correct any inaccuracies that I may have mentioned so far along in this program, because she is a lot more knowledgeable than I am about some of these issues with the regulations and the most recent updates.

Again, I will be happy to e-mail any of this information to you. In addition, there is a very useful three pager from the Medicare program's website that I can e-mail you. I have extracted it out, and it will make a very easy e-mail on the deductibles and the co-insurance amounts that have been updated for 2005 based on statute.

The Medicare program has always had deductibles and co-insurance amounts especially in the Part B program, and those get updated every year based on calculations that are written in the statute. I will be happy to e-mail that to you. We didn't xerox that off and pass it out here, but it is actually available on the CMS website.

It is not quite as easy to find, because you actually have to go to Medicare.gov, which is the sort of the Medicare website that is open to the general public.

Actually, the CMS website is open to the general public also, but it is sometimes hard to understand even for those of us in CMS.

With that, let me first ask Carol if she has any comments on any glaring discrepancies or inaccuracies I may have presented. Okay. She might clarify some things in a little bit, but for right now I think this will suffice.

Again, I would like to let you know that we can make some of this information available just by e-mail that might help answer some of the questions.

Some of the committee members had questions the last meeting, and there have been other questions that have been raised during that time period that Dr. Holmberg has referred to us, but first, we would like to listen to the other presenters that are going to present before we go specifically into some of those questions.

DR. BRECHER: Dr. Epstein.

DR. EPSTEIN: Thank you very much, Jim.

It is very helpful to hear such a clear and coherent description of how the reimbursement system works, but I wonder if you could also comment on Jerry Sandler's question, which is how do the reimbursements get adjusted in

the face of practice or technology change, and, in particular, how quickly can the current system adapt if there is a need and desire to introduce new blood safeguards.

DR. BOWMAN: That is an excellent question and actually, I meant to address that, Dr. Sandler, and I got so excited and nervous up here with the little presentation that I forgot all about that, but that is actually a very important question.

I would like to put that in context. That has been--let's just put it sort of bluntly--that has been sort of a perennial, if you want to call it, a problem or an issue with the Medicare program probably since its inception even back in the old fee-for-service days, but I think it is more highlighted and exacerbated by the prospective payment system.

Certainly in the old fee-for-service days, when things were paid under usual, customary, and reasonable type payment systems, those were more or less immediately reflected when any provider updated their payment system to adjust for increased cost, in their "cost" of doing

business. That includes, of course, new technologies and innovations.

The Medicare program and the Administrator of CMS, of course, had to wrestle with that problem in just about every aspect of health care, whether it is a new type of surgical device that is used in the operating room, whether it is new technology that is used in the blood banking community,, whether it is a new drug, for instance, that FDA has approved and then has to go through the sort of arduous process of coverage by the CMS process.

So, that is a problem that is not unique to the blood community. I would say it has become more prominent on the radar screen in most recent years, especially with our new administrator having most recently come from the sister agency, the FDA.

I think he is very much aware that is an issue in some of the initiatives that have not only been brought up today regarding the FDA, but also the Department of HHS, that Dr. Heaton mentioned earlier to me about the--I have forgot the exact name of it now, but it is a medical innovation initiative that is supposed to strengthen, to accelerate some of the process and facilitate the process of

getting appropriate new technology and medical innovation into the marketplace, if you will, and to the beneficiaries who need it the most, and to facilitate reimbursement in a timely fashion.

I don't think the kinks have all been worked about, because some of that is based on statute, some of that is based on a long-standing bureaucratic type of process, and that has not at this point I think received the in-depth attention that would create solutions that you are probably looking for at this time.

So, Dr. Epstein, I don't think that answers your question, but that is the best we can do right now. I would just have to say that it is being recognized as an issue.

DR. BRECHER: Jerry.

DR. HOLMBERG: I just want to comment on the medical innovation document that was recently posted on the website. This document is very fresh off the press. Actually, it was signed by Secretary Thompson, and from what I understand, Secretary Thompson went through and made his final good-byes yesterday, so this really has hit the website.

There is a lot in that medical innovation document and I think that it would be worth maybe our next meeting, for us to really go through and maybe have a good presentation on.

What is very encouraging about that is that there are MOUs, memos of understanding, established between various agencies to address some of these various issues. We have heard the say CMS has in the past grouped things to take care of innovation, and we know that that is not an efficient way of doing things.

So, I think right now the ball game is open and we need to look at how that new innovative document and how the memos of understanding really operate.

DR. BRECHER: Celso.

DR. BIANCO: Just a quick question, Jim, of clarification.

What is in to the competitive bidding and what is out? That is, when you discuss competitive bidding for drugs and biologics, you said blood and blood products are excluded.

DR. BOWMAN: Well, the statute reads certain vaccines, blood and blood products, and drugs that require

DME infusion apparatus and equipment, and then, at the Secretary's discretion, to exclude other products.

The statute doesn't get more specific than that, so let me just say that there is a whole unit within CMS that is actively working right now, as you can imagine, on the competitive bidding process and implementation. A lot of the decisions about the nuts and bolts of the day-to-day operations, how that is going to work and implemented, how it is going to roll out, which drugs and biologics will be included and which will not initially has not been worked out at this point.

DR. BIANCO: Can we help?

DR. BOWMAN: CMS is always open to help.

DR. BIANCO: Who does the bidding?

DR. BRECHER: Celso, why don't we hold on this, we are running behind schedule. He is going to come back for a panel discussion, and we can ask more questions then. One of our speakers has a plane to catch, so we need to move forward.

Thank you.

Let's move on to the Issues Facing the Core Plasma Therapies. We have a series of speakers. The first one is

Ms. Elena Bostick, patient advocate with the Hemophilia Association of New Jersey.

MS. BOSTICK: This is entirely different than the presentation before. I am an advocate and I appreciate the opportunity to be here today.

My name is Elena Bostick. I am the Executive Director of the Hemophilia Association of New Jersey, a position I have held for 25 years.

The HANJ maintains a proactive, hands-on approach to the provision of services for persons with hemophilia. The board of trustees is comprised of business leaders, consumers, and legislators. It excludes representatives from the hemophilia treatment industries, both manufacturing and home care.

Consumers are involved in every function of our organization in a continuing effort to identify unmet needs and failures in the system upon which their lives depend.

Our working relationship with the New Jersey State Department of Health and our comprehensive hemophilia treatment centers is synergistic and has allowed us to accomplish a great deal including legislating standards of care for hemophilia home care.

The organization exists to advocate for persons with hemophilia and related bleeding disorders, and I thank you for this opportunity to do so today.

I imagine my years on the job make me supremely qualified to talk about reimbursement and hemophilia, however, as a result of the state of affairs in this issue, suddenly, retirement seems way too far off.

The payer mix in hemophilia is approximately 60 percent private payers, 35 percent Medicaid, and 8 percent Medicare. I will follow this schedule in addressing the issues of each.

The state of the nation's health care reimbursement systems has reached a very dangerous point with no solution in sight. Gaining access to quality, affordable health insurance has becoming a crisis of unprecedented proportion and it is rapidly getting worse.

Double digit increases in health insurance costs are leading more employees to drop health insurance coverage all together or to pass increases on to workers by way of pay cuts, higher deductible and co-payments, and a higher percentage of premium cost sharing.

Health care expenses are the number one cause of personal bankruptcy in this country. What has evolved is a large class of citizens gainfully employed that are the working poor.

In hemophilia, the high cost of treatment, as well as the high cost of insurance, co-pays, deductibles, cost sharing, et cetera, has made the situation unmanageable. Even if gainfully employed with good coverage, people with hemophilia live in constant fear that if they lose their job, and lose their coverage, they will not be able to afford clotting factor.

With an average cost of treatment of 100 to $150,000 per year, a 20 percent co-pay imposes a financial burden of 20- to $30,000 every year, a cost not many of our families can afford.

Tremendous state disparities exist in access to care and insurance coverage for persons with chronic illness. In New Jersey, a law is in place called Guaranteed Issue. This means that anyone wishing to purchase insurance for themselves or their families may not be denied on the basis of health status. This is in the individual non-group market.

The people with chronic illnesses and other health issues generally purchase insurance in this market, and so the insurance industry has vigorously tried to overturn Guaranteed Issue, but they have been unsuccessful.

Instead, they have reasoned that if they price these policies out of the reach of most individuals, they can accomplish the same goal. I direct your attention to the attachment, Attachment A. It is the most recent notice of rate increase for Horizon Blue Shield of New Jersey.

If you follow this schedule to the asterisk, you will see that in New Jersey, the cost of an indemnity family policy with a $500 deductible is currently $79,200 a year. The cost decreases with higher deductibles and greater cost sharing, but remains out of the reach of most families.

Meanwhile, the CEO of Horizon Blue Cross/Blue Shield of New Jersey earns $2.65 million and his top 10 management people earn a million each. Still, Horizon has been able to amass a surplus of $1 billion.

When I questioned a top Horizon executive regarding the enormous rate increases when their surplus was a billion dollars, his response was, "Well, it didn't come from the individual market."

My subsequent question was, "How much of a surplus is enough?" Of course, I received no reply. But please keep in mind that Horizon Blue Cross/Blue Shield operates only in the State of New Jersey.

The CEO of United Health Care, a nationwide corporation, has earned an average of $15 million annually in each of the last five years, and earns and holds $561 million worth of unexercised stock options.

There is something terribly wrong with a system that allows insurance carriers to hold consumers, physicians, and hospitals hostage by denying, delaying, and randomly questioning long unsettled claims while executive salaries remain so outrageously high, but the tactics are succeeding.

They provide a disincentive because of staff and fiscal constraints to do the never ending follow-up work required in an attempt to collect on these claims.

Approximately 30 states have high-risk pools. These are usually underfunded and not comprehensive in nature. Premiums are high as is the percentage of cost sharing. Generally, these are created when chronically ill people have no access to private insurance.

An example of this is the State of Florida. They have a high-risk pool. They have not accepted new applicants to the pool since 1991 for lack of funding of Medicaid.

Almost every state in the nation has a significant budget deficit. It is a situation that has been described by economists as the worst fiscal crisis in 50 years. Since Medicaid expenditures represent one of the largest single budget items, states are struggling to bring its costs under control. In doing so, drug access has become the target with high-priced therapies flagged for cost containment measures.

While disparities exist in state Medicaid programs, as well, cost containment measures in hemophilia translate into a number of inappropriate changes including prior authorization requirements, increased co-payments, decreased eligibility, restricted access to providers, preferred drug lists, preferred by a numbers cruncher, not by a physician or his patient, and others.

Clotting factors are not therapeutically equivalent and therefore they are not interchangeable. Restrictions on product access are not acceptable.

Interference with clinical decisions made by a physician in consultation with his patient is not acceptable.

Jeopardizing medical outcomes in a desperate attempt to contain costs is simply not acceptable.

Many Americans have some chronic conditions that are not necessarily impairing, and while drug therapies may be prescribed, they very often do not require extraordinary care. However, there is a small group of individuals whose lives and medical outcomes are dependent upon access to treatment modalities deemed necessary and appropriate by the treating physician.

Across-the-board reforms ignore the challenges posed by those individuals with the greatest need and at the greatest risk. Consumers' best interests should be protected by the state in which they reside. Yet, 25 states have restricted eligibility, 18 have reduced benefits, and 17 have increased co-payments so far.

Medicare. Medicare recipients are among our most vulnerable of populations, the elderly and the disabled. In hemophilia, the number of Medicare recipients is lower than one might expect. One reason for this is that we do not have a significant elderly population.

Almost an entire generation of persons with hemophilia became infected with HIV when the blood supply became contaminated. Forty-six percent of those have died. An additional 20 percent of the entire hemophilia population have died of liver disease.

Those remaining of that population are more than likely to be hepatitis C positive or hepatitis C and HIV positive. These are the individuals with hemophilia that may be eligible for Medicare.

As a result, Medicare recipients represent the smallest percentage in the hemophilia payer mix at approximately 8 percent of the population, however, Medicare is viewed as a leader in reimbursement methodology, so we can expect private payers to follow its lead within a year's time.

The Hemophilia Association of New Jersey remains deeply concerned about the impact reimbursement changes will have on access to care. We wish to thank CMS for acknowledging the inadequacy of the originally proposed formula and adjusting the add-on in the final rule, however, it is still too soon to determine whether this adjustment is enough to ensure uninterrupted access.

At issue is the ongoing problem of a yearly 20 percent co-pay of a very expensive therapy from a community that just can't afford it. At the AWP-based reimbursement rate, a home care company could, with appropriate financial documentation, observe the co-pay as bad debt, make less money per patient, but not incur loss. Continuity of care was not threatened.

It is not yet clear what impact the new payment system will have on continued access to these life-sustaining therapies. Close and early monitoring by CMS and by advocates for the bleeding disorders community is essential to prevent any potentially grave consequences.

Clotting factors are not recreational drugs that require higher and higher doses to satisfy the user although that appears to be the perception of some case managers. Factor replacement therapy is not an option for persons with hemophilia, it is an absolute need.

To deny a person with hemophilia the appropriate clotting factor support as determine by his treating physician is analogous to denying a patient with a life-threatening bacterial infection the appropriate antibiotic. It can't be medically justified.

Yet, each day the principles that we have held dear, those that address the needs of our vulnerable chronically ill population, such as functional outcomes, quality of life, comprehensiveness, and continuity of care are being put aside in favor of bottom-line considerations.

There is no question but that hemophilia care is expensive, but it is still a bargain when compared to the long-term medical, rehabilitative, psychosocial, and welfare costs in dollars, as well as human suffering, of improper or inadequate care.

Thank you.

DR. BRECHER: Thank you.

We are running behind. Maybe we have time for one quick comment or question.

[No response.]

DR. BRECHER: If not, we are going to move forward.

MS. BOSTICK: Thank you.

DR. BRECHER: Our next speaker is Dr. Richard Metz. He is the Advocacy Committee Chair of the National Hemophilia Foundation. Dr. Metz is not only a provider, but a parent of a child with hemophilia.

DR. METZ: I want to go ahead and thank the committee for allowing me to come today to speak on this very important topic, that I share the kind of passion that Elena just shared with you.

My son, who is now 17 years old, has severe hemophilia A. In the beginning, when my son was born, we were faced with the issues of how we were going to deal with this disease and how our family was going to get along, but we never imagined that we would also have to deal with reimbursement issues.

At the time, we were insured by a private insurance company through individual family insurance, and we found that our premium, which was $600 a month to start, started increasing 130 percent per year when they got wind of our diagnosis, such that before we were able to switch, our bill was approximately $4,000 a month for the premium.

Only by the grace of God were we allowed to switch because our medical association had an open enrollment period whereas if you were under 45 years of age at the time, they did not ask any questions about pre-existing conditions. So, we were very fortunate, but others may not be.

Today, I would like to talk a little bit about general reimbursement issues facing the bleeding disorders community and then get into specifically the Medicare issues and, in particular, the Medicare 20 percent co-payment.

Reimbursement for clotting factor is an extremely complex issue within the bleeding disorder community. Hemophilia is a potentially life-threatening and serious disabling disorder. We have so many different insurance plans, it is hard to keep track.

We have PPOs, we have Medicare, we have Medicaid, we have HMOs, we have high-risk pools in the states, we have individual policies, and the shrinking indemnity market. There are so many plans, everyone has a different idea how they are going to treat a high-cost condition.

Most have a different idea except for one central them, and that one central theme is that with the changes in the marketplace which are occurring, all the payers are seeking to lower their costs.

In particular, in hemophilia, the manufacturers and providers have been aggressive in seeking contracts for their services and their products.

Such agreements and changes in reimbursement potentially affect which products that are available that we can have and which providers we can get our products and services. For instance, those providers would home care companies or hemophilia treatment centers or others, and then the products would be available from one of these companies.

This gets into the basic issue of choice and access. All of us in the community feel that for such a disabling and potentially life-threatening disease, if the physician who is treatment the patient feels that an appropriate treatment regimen is the way to go, then, the consumer or patient should have the right to choose that product which the physician recommends and to have access to seeing that physician as a specialist or to the treatment center.

It is well known that patients who get their care in treatment centers have substantially lower mortality and substantially lower costs in their care over their lifetime. In fact, a figure of about 40 percent has been quoted.

These agreements have assumed one essential fact, that is, these agreements have assumed that clotting factor

products are interchangeable and equivalent, but actually they are not.

Clotting factor products are biologicals and are not considered prescription drugs. The FDA does not recognize them as being functionally equivalent.

Why is this? Each product is manufactured using different fractionation and viral inactivation products. Each product may also react differently in each consumer.

Let's talk for a minute about inhibitors. One patient may be prone to developing an inhibitor from one product, but have no propensity for developing an inhibitor to another product.

We can talk about safety issues. Yes, there may be a theoretical risk now that we talk about, but we all about variant CJD, which is in the news, and how it has been shown to now be transmitted by blood transfusion.

So, even though no cases have developed at this time in patients who are transfused with plasma products, there is a always a theoretical risk, and we know what has happened to this community in the past before we actually had the data and the outcomes, and I am referring to the HIV epidemic and also hepatitis C.

Then, there are some people that just do better with one product than another. They just get higher factor levels, they just have less bleeds. I am not sure why that is, but that does occur.

In general, we have to balance the desire for choice of products and providers with the desire for lower costs. This is an issue that really is dear to the heart of the consumer, really hurts the consumer, because we don't want to feel that any quality of care or quality of life is going to be sacrificed when it comes to costs, yet, we understand also that these treatments are very expensive.

This balancing act is made complex by the issues of product safety and availability. Product safety, I have already alluded to before, but product availability, we know that just perhaps a few years ago, there was a shortage of recombinant factor 8 products, so we had to rely on plasma products.

Supposing that it was decided to do away with certain products because they were too expensive or not appropriate, and suddenly we were left with just a few products. What if, for an example, an earthquake were to occur in California, my own home state, so I am aware of

earthquakes, and suddenly, certain plants were to be shut down that produced certain factor products in California, what would then happen if we didn't have a whole spectrum of products available?

In general, reimbursement concerns fall into five major categories. These reimbursement falls into insurance coverage, to start with. I told you a little bit about my son's problem with insurance premiums in the beginning, but now that he is 17 years old, once in a great while he opens up to me, and lately he came up with the question, "Well, dad, what am I going to do when I want to get a job and I am done with college, am I going to have to join some big group just to be able to get insurance, or will I be able to start my own business? Or if I wanted to join a small group, what would happen, would the costs be so high that they would fire me after a short amount of time of being there?"

These are all very good questions and I didn't have all the answers to these.

So, we talk about for insurance coverage, getting coverage, getting access in the beginning, of being able to be insured, and also being able to keep coverage if one

changes jobs or has to go an individual policy, decides to have one's own business, these are the issues there.

Product choice, we have already talked about, and provider choice, we have talked about. The out-of-pocket costs are enormous for this condition.

In the talk about Medicare, the 20 percent co-pay, which I am going to get into in just a minute, there are some people that use more than the 100 to $150,000 that Elena quoted earlier. I can tell you that my son uses about $300,000 a product per year in the last year.

If we look at what 20 percent of that is, you can see that that is an enormous figure. Fortunately, in most of the private market, there is a stop gap loss to most policies where if you have $5,000, say, on an average out of pocket, the insurance then picks up the 100 percent after that for the rest of that year. Unfortunately, there is no such provision in Medicare for the 20 percent.

Then, finally, lifetime caps, which is an issue that we will be addressing this year during our Washington day on the Hill. In general, lifetime caps that were set at approximately $1 million for private insurance policies were set 30 years ago.

No readjustment for inflation has been taken into effect or to cover some of the costs of these very, very high-cost conditions, and we think that it is time that there be some legislation in order to get the lifetime caps raised to an acceptable level today especially for certain chronic conditions or perhaps eliminated.

The cost of doing that would actually not be that high given the small number of conditions that have these very high lifetime costs.

Now, I would like to focus in particularly on concerns with new Part B Medicare reimbursement. We know that there is a 20 percent co-payment responsibility for this.

Because the cost of this is so high, if the fee that is paid to the home care company or treatment center that is providing the product is not adequate to cover their acquisition costs, there may be a problem in terms of access to product of choice, because they may not be able to provide all those products.

As I mentioned before, the co-payment responsibility can be enormous, equal to $40,000-plus annually. However, I should say that up until now, if a

beneficiary is not able to afford the co-payment, and the company can demonstrate that this is a bad debt, that is to say bills have been sent out to that patient, and that patient just can't pay it, then, oftentimes this is waived or written off.

The problem is when it is waived or written off--I will show you the data in a minute, then the acquisition cost becomes greater than the reimbursement minus the 20 percent for most of the companies.

This, I just discussed, how because of the change in reimbursement, which is now ASP plus 6 percent, and then the 14-cent add-on, the new drug payment levels are much closer to acquisition, making that absorption of the co-payment much more difficult.

I purposely tried to put into red on this slide to show where there may be a deficit that a home care provider may have. Now, if we go from left to right, the J codes for the various products are listed.

Then, we have the various products that are used for the care of bleeding disorders. Then, we have estimated acquisition costs. I cannot tell you what the exact acquisition costs are due to issues with the anti-trust

laws, but in surveys that have been taken, these are the estimated acquisition costs.

The Medicare approved charge, which is listed here, is the ASP plus 6 percent, plus the 14-cent add-on, however, the Medicare payment is 80 percent of this.

So, if we look at the Medicare approved charge, the Medicare approved charge is adequate for most or all of these conditions in terms of getting the acquisition costs covered or perhaps a little bit more than the acquisition costs, but if we look at the actual Medicare payment, we take the 20 percent away, the Medicare payment is insufficient to cover the acquisition costs.

This, in our mind, puts the access to various products in jeopardy.

So, in summary, this new payment formula creates clear winners and losers that could affect access to certain brands, however, in looking at the data, there were actually more potential losers than a few of the winners.

There is also concern that beneficiaries that don't have supplemental coverage may be forced to switch products to less expensive products even though those less expensive products would not be in their best interests as

determined by their treating physician, or seek care in other settings.

In the emergency room in the hospital, for instance, there is a different payment schedule, and 100 percent will be covered for that patient. This could potentially result in many more emergency room visits for the patients to receive their treatment rather than being able to do their treatment at home, and actually, therefore, increase the cost of care.

Yesterday, I am pleased to say we had a group meeting of all the people from the hemophilia community that were very concerned about this issue. We had the National Hemophilia Foundation there. We had members from the Hemophilia Federation of America, from COT, we had home care providers.

We also had manufacturers in the room, and we wanted to really discuss this in detail to see if we could come to the meeting today and come up with some possible solutions, and then perhaps a recommendation or a solution that we would feel would be most appropriate.

We spent a couple hours yesterday doing this. All of us really got along quite well at this meeting and were able to achieve consensus.

Some of the possible solutions that we talked about are listed on the next slide, and I apologize to everyone for not getting these slides all to you in advance, but I wasn't able to put these slides together until the last minute, because I didn't know what the results of this meeting would be.

The possible solutions that were discussed included getting legislation passed to have clotting factor reimbursement at 100 percent of the Medicare approved charge. Apparently, there are a few other chronic conditions which are paid at 100 percent. I understand end-stage renal disease is one of them.

This would certainly be a way of improving access. We talked also about co-payment subsidy for beneficiaries with bleeding disorders who would not afford it.

Perhaps this would be an income-based type of subsidy, but on the other hand, you couldn't only do this for people who are close to the poverty level, because as you can see, with the $40,000 co-payment, even families that

are middle income families or high middle income families would be substantially hit with a $40,000 co-payment. Yet, some sort of sliding scale based on income level might be practical with some subsidies.

We also talked about doing something to change the supplemental insurance coverage options for disability-qualified beneficiaries.

At the present time, people that go on Medicare, my understanding is, due to a disability do not have that six-month period where they can automatically enroll with no questions asked in a supplemental plan, and can be denied access to the supplemental insurance, or the supplemental insurance premiums can be made again so great that nobody can afford them or very few people can afford them.

Finally, you can't see the last issue on the slide so clearly. Thank you. But we talked about re-insurance, which is an option where insurance companies actually get insurance for themselves to cover the risk of very high cost conditions.

Whether this would be something that could be applicable to Medicare, it was discussed, and I will leave it to you to possibly discuss further.

After a couple hours of discussion of these issues, we felt, though, the best solution to really take care of this problem would be to pursue legislation seeking payment for clotting factor at 100 percent of the Medicare approved amount.

Now, we realize that this is going to take a little bit of time. We feel that we need to get some data together before we can go to the Hill and actually get this accomplished. Some data that we were missing at the time that we had the discussion was some provider data on supplemental coverage.

That is, the home care companies have agreed to aggregate their data, so we can see how many patients does this really include, how many are not covered by supplemental insurance at the present time, therefore, what would be the cost of offering 100 percent insurance to those who are not covered at this time.

Finally, we need to do some data collection on utilization patterns, because we believe that this will disprove the myth of excess use of product patterns. Some people have alleged that if a person didn't have to bear the

responsibility of paying for part of their treatment, that they would tend to use more factor or use more treatment.

We don't believe that that is true, we don't have any data that shows that. We don't have any information to that effect in terms of talking to home care providers and physicians in treatment centers, but we want to actually collect data to be able to show that, which I think is important.

Finally, I want to move away from the Medicare co-payment to discuss just a few other Medicare concerns. As we have heard about earlier, the Part D prescription drug plan has come out, and there is certainly some concern as what could happen to clotting factor products.

Right now we are covered under Part B, but there is some fear about any change that could be made to Part D. Part of this fear has to do with the fact that supplemental insurance coverage would not then cover clotting factor products.

So, for the people that are covered with supplemental insurance right now, they would run into a huge co-payment effect. Also, there is a lack of coverage of

clotting factor in short- and long-term health care facilities.

In the hospital, clotting factor is covered through a passthrough mechanism, but say a person needs to go to an acute rehab unit, they have had orthopedic surgery on their joint, or say they need to go into a skilled nursing facility to get additional physical and occupational therapy, the problem is clotting factor is not covered as an extra entity there, that these facilities are reimbursed a set amount, similar I guess to the DRG amount.

So, these facilities simply do not want patients that are going to have costs of thousands of dollars a week in clotting factor because they are going to be losing money from the time the person steps in the door.

I wanted to just digress for just one moment and talk for a moment about Medicaid concerns. There seems to be a lack of separate inpatient hospital payment for clotting factor.

Just a moment ago, I talked to the fact that there is a passthrough mechanism for patients on Medicare for extra payment for clotting factor in the hospital setting. Medicaid does not have that. So, here, in an acute hospital

setting, right away the hospital is going to take an enormous loss when the persons walks in the door.

There are changes in trying to restrict enrollment. Some of the contracts that are occurring with providers may have little or no hemophilia experience, and even the ones that are coming up with providers that have a great deal of hemophilia experience are somewhat suspect.

I just want to give you a few examples of what has occurred recently. One example was in the State of Florida where the Medicaid program there went ahead with a sole source providing contract and had an RFP that came out, various companies responded.

One company responded to this RFP and was selected as the sole source contract provider. We fortunately had a very good cooperative effort among all people in the hemophilia community.

Eventually, for purposes of right now, we understand that this is off the table, but there was certainly a suggestion, if you read the RFP, that the company was going to try to restrict access to product in the long run, that there really was quite a push to contain

costs, and that we could see that the patients would be sacrificed in the long run.

We strongly believe that sole sourcing contracts are not the right way to go. There is no competition left, and, hence, one company can make a decision to select their product or not to select their product.

In Pennsylvania, there was a problem recently where there was a management company that was contracted with that was going to seek stepwise therapy for factor therapy, and that is to say they had their preferred product listed as number one, and then only if you could demonstrate that there was a problem with that preferred product, you could then move to step 2 and then move to step 3.

Prior authorization would be required to move ahead. Again, we thought that this was really restrictive of choice and access, and fortunately, our Delaware Valley Chapter is very, very active in Pennsylvania, and they have been able to get this reversed.

We are very thankful to all members in our community for the advocacy efforts that we have shared together, but we all have one common goal in mind, and that one common goal is to protect the quality of life for all

the people with bleeding disorders and hemophilia, but in order to protect that quality of life, we need to protect access to choice and provider, and you can really help us with that.

I thank you very much.

DR. BRECHER: Thank you, Dr. Metz. We have time for maybe one or two questions or comments. We are a little behind.

[No response.]

DR. BRECHER: If not, we are going to move on to the next speaker. This will be Julie Birkhofer, who is the Executive Director, North American Plasma Protein Therapeutics Association.

MS. BIRKHOFER: Thank you, Dr. Brecher, Dr. Holmberg, and members of the Advisory Committee for once again having PPTA before you to talk about critical access to care issues reimbursement.

As I have spoken to you in the past, the Advisory Committee on Blood Safety and Availability has acknowledged that availability and supply are access to care issues and that reimbursement, adequate reimbursement is the key to sustaining access.

I would like to thank Dr. Bowman and Dr. Bazell at CMS for their openness and their willingness to meet and to discuss these critical issues. I would like to also thank them for acknowledging support reimbursement for innovation to new therapies.

I would like to acknowledge Dr. Metz' remarks, his stressing that blood clotting factors are not interchangeable, the need to have all brands on the market, a robust supply, that translates to choice, choice of therapy, choice of provider that is critical, and that is why, with regard to Medicare Part B, as in boy, physician office, PPTA has been working with the hemophilia community to exempt clotting factors from competitive acquisition, and i will talk about that more in my remarks.

I would like to share with you PPTA, Plasma Protein Therapeutics Association. We are a global association. We represent manufacturers of both plasma-derived and recombinant analog therapies. We represent manufacturers of life-saving therapies that treat individuals with coagulation disorders, primary immune deficiency disorders, alpha-1. Our companies, those are the core therapies, also manufacture albumin and other

hyperimmunes used to treat tropical diseases, rabies, and other things. Many of you are familiar with those therapies.

I would like in my remarks to address publicly-funded programs. CMS has jurisdiction over federal Medicare and state Medicaid, share with you some of PPTA's work plan with regard to 2005, and then offer some conclusions.

As I have come before you in the past, not to be repetitive, but we have talked about the differentiation between plasma-derived and recombinant analog therapies and chemical or synthetic pharmaceuticals, keeping in the back of your mind that PPTA member company therapies are a unique niche in the biotech sector.

Our therapies treat fragile populations, otherwise most often known as orphan populations. The cost of the starting material is very expensive. It has been discussed by the consumer organizations that these are expensive therapies. We acknowledge that. There is a lot of time it takes to manufacture and to bring these therapies to market, six to eight months, and this is a constantly evolving manufacturing process.

So, if you can just in the back of your mind as we move forward keep in mind this unique niche in the biotech sector that PPTA represents.

Again talking about Medicare, as Dr. Bowman broke down in terms of site of service, physician office Part B, PPTA is concerned, as are the consumer organizations, about the impact of the new payment methodologies, the move towards ASP plus 6 from AWP, and is this enough to sustain access.

2005 will be a benchmark year for that discussion. We are watching, we are monitoring, we are closely working with the consumer groups. You will hear from the next presenter, Michelle Vogel, her sharing with you some access to care issues that have already percolated up to the Immune Deficiency Foundation.

With regard to blood clotting factors, the issue of the add-on, the 14 cents in the Final Rule, is that sufficient to sustain care. The consumers have brought forward issues of co-pay. PPTA stands firm to work with them and provide resources to advance that through whatever strategies the consumers put forth, be it legislative or regulatory.

With regard to IVIG, we have major concerns about access. We have heard from providers, we have heard from patients. We also have concerns that the home infusion benefit covers the drug only, but not the administration and the supplies. That is a problem. It's half a benefit. Again, I know Michelle will address those issues in her remarks.

With regard to alpha-1 proteinase inhibitor, A1PI, we have had two new entrants to the market in 2003, and we are concerned that the rate is sufficient to sustain access to the new entrants.

Looking ahead to 2006, Dr. Bowman made some remarks about the competitive acquisition program commonly known as competitive bidding. Section 303.1847(b) does specifically exempt IVIG from competitive acquisition, and initially, the original version of the bill, the House bill HR-1, as a matter of fact, exempted blood clotting factor.

As you members of the Advisory Committee recall, you issued a recommendation at the last meeting urging the Secretary to exempt blood clotting factor from competitive acquisition. This is a crucial access to care issue.

Plasma users of IVIG and the recombinant and plasma users of recombinant have the same access to care concerns that IVIG users have and that alpha-1 users have. We have since expanded our position and are working with the alpha-1 community and the hemophilia community both with Congress. We have had report language in the Omnibus Appropriations bill calling on the Secretary to exempt.

We are conducting outreach to the HHS nominee Levitt, and we are hopeful that the Secretary will, in writing, exempt blood clotting factor and alpha-1 from competitive acquisition. This is an access to care issue.

With regard to our companies, ASP requires several new reporting mechanisms. We would hope that timely instructions would be issued. The ASP is reported quarterly, the rates change quarterly.

You can imagine the impact on providers. There is no predictability, there is no quantifiable rate that is annual. It is a constantly evolving process. That will impact access.

We would like that these rates, when they are released, are confirmed by an independent auditor. I am not a mathematician, I don't like numbers, you know, no one is

perfect, so we would ask that before these rates are public and final, that an outside auditor does confirm them.

With regard to Title 1, Part D, the new benefit, the intent of Part D is to fill in any gaps to provide wraparound coverage, and we are curious with the impact that will have on Part B.

We also are curious, could that be used to cover the ancillary supplies and services for the IVIG home infusion benefit with regard to the use of durable medical equipment, and these are issues that are on our radar for 05 and moving forward as that benefit gets implemented.

With regard to the Hospital Outpatient Prospective Payment System, the other site of service, hospitals have unique regulatory requirements that increase their overhead costs. We firmly believe that reimbursement should be based on all brands currently on the market to support innovation.

This issue, as you know, under a J code--and Dr. Bowman used J-1563, IVIG--all of the branded therapies which are not generic under that J code, so we have a clustering or a bundling of brand name drugs under a J code.

We are looking ahead to 2006. The GAO is conducting a hospital acquisition cost survey. We are

working with GAO. We are providing them data, and we are hoping that they will recommend that the outpatient system be reimbursed on a brand-specific or NDC-based approach that would reflect the cyclical price trends in the market and would be a more accurate sustainable rate in terms of access.

In 2005, immediate concerns. Alpha-1 proteinase inhibitor has been deemed as a single indication orphan drug. We still have concerns, is the rate of ASP plus 6, or 88 percent of AWP, is that enough when you have such a fragile small population dependent upon a life-saving therapy where there are no alternatives.

So, moving forward in the 109th Congress, we will continue to work in coalition with our stakeholders. We are, as Dr. Metz indicated, looking at the co-pay issue and all believe that working together, we can hopefully address this issue.

We are looking particularly strong at ensuring coverage in all sites of service. We want to eliminate coverage gaps. We are very strongly focused, with support from the Advisory Committee and Congress, on urging the Secretary to use his exclusion authority to exempt blood

clotting factor and alpha-1 from competitive acquisition just as IVIG is, and Medicaid reform is on the horizon for the 109th.

I would like to quickly move to PPTA's initiatives in the states since CMS has jurisdiction over Medicaid, as well.

Standards of care legislation is very pivotal and important. It is one of our key focuses in the states. It would require that private insurers contract with providers that are familiar with the disease states. This percolated from New Jersey, no surprise there. Elena Bostick has a lot going on in her state, but she led the effort in New Jersey, spearheaded it.

We are working with other groups across the country. We have had this adopted as model legislation. We are working very strongly with consumers and experts in California, Florida, Minnesota, and Pennsylvania to pass standards of care legislation.

The focal point of this legislation currently is hemophilia coagulation therapies. We would like, as our resources allow, to extend it to IVIG and alpha-1.

Again, I would like to make the point here that our focus is on public payers. When you look at private insurers in terms of resources and what dragon we can slay, right now we are limited by our ability to impact beyond the publicly funded programs, but the private insurers are on our radar, and we all know that these public programs are a model.

Prior authorization for drug lists. This is another tactic that has been employed by state Medicaid to control the budget. We are working in Illinois, Minnesota, Nevada, and North Carolina, South Carolina, Texas. We are working to expand the exemptions from prior authorization to include immune globulins.

We are very heavily engaged right now in Minnesota. It is our precedent state. They have exempted blood clotting factor. The provision is up in 05, and we are working hard to preserve that exemption.

Single source provider contracts. Again, states are desperately trying to control their expense, control their budgets by contracting with a single provider. The states Arizona, Florida, Massachusetts, Minnesota, that is

where we are engaged. Our concern is that this type of tactic could lead to limitations on choice of therapy.

Formularies. Limits on brand name drugs already happening in the private market, already underway in Medicaid. Beneficiaries could be forced to prioritize drug usage. It could result in limitations to access, and we are working to enact exemptions for "high risk" disease states.

In conclusion, working in coalition and conducting outreach to providers and policymakers is the key to success to assure sustained access to care for these life-saving therapies.

We, to date, have had some successes. There is a lot of work to be done. It's evolving, these issues are here to stay, they are growing. We are looking at federal legislation with regard to Medicaid, prior authorization that wold preempt state action.

We have developed some questions for the record that we would hope would be submitted to CMS and that the answers to these questions would be made public and part of the record.

That's it.

DR. BRECHER: Questions, comments? Jerry.

DR. HOLMBERG: Julie, you have made reference to the bundling of the therapies under a J code. Is that the J-0256?

MS. BIRKHOFER: We have several J codes that plasma-derived and recombinant analog therapies are included under. J-0256 is the code for alpha-1 proteinase inhibitor, A1PI, and within that code are three brands, Zemaira, Erolast, and Prolastin are included.

J-1563 and J-1564 are the codes that IVIG, all of the companies' brands of IVIG are within those codes, both liquid and lyophilized. Again, obviously, these are not generics, they are not interchangeable.

With regard to recombinant, I believe it is J-7190 and 7192 for the plasma-derived and recombinant. There are others. I can supply the codes and the therapies that they fall under.

DR. HOLMBERG: So, the bottom line is that there is more than just one J code that has bundling?

MS. BIRKHOFER: Yes, for our therapies, yes, that is the way it was handled.

DR. BRECHER: We are going to move on to our last speaker of this section. That is Ms. Michelle Vogel,

Director of Government Affairs at Immune Deficiency Foundation.

MS. VOGEL: Thank you, Dr. Brecher and Dr. Holmberg, for inviting me again to come back and talk about reimbursement issues and address the committee today.

I want to start by my title here, patients need access to all brands of IVIG and all sites of service. What happened to the primary immune deficiency community on January 1st, 2005, was pretty major, and Dr. Holmberg knows a lot because we were e-mailing each other, but the new lower Medicare reimbursement rates for IVIG went into effect and basically, the new ASP rate brought IVIG down from $66 a gram to $40 a gram.

A lot of people, and I was included in this, compared it to the hospital rate even though these are two different formulas, but the hospital rate hasn't been switched over, it will be in 2006, but it's at $80 a gram, so coming from a provider standpoint, the physicians were looking at here you are at the hospital at $80, and in the physician's office at $40, what is going on even though you are two different formulas.

What happened to patients at this point, there wasn't a product that could be purchased at $40, not one IVIG product. So, all the patients were being shifted out of the physicians' offices, out of the home care settings, into the hospitals.

Now, looking at that, I could have predicted that would have happened and thought, okay, we are going to have a problem in the rural hospitals and we are going to have a problem in the small hospitals, but thought, well, the urban hospitals will have infusion centers, so we will be okay.

It wasn't the case because a lot of these infusion suites were actually owned by physicians in the hospitals and were billed under the physician payment fee schedule, so weren't under HOPPS. So, all of a sudden we had massive numbers and for a rare disease group, these were massive numbers of patients who had absolutely nowhere to go, so we eliminated almost all the sites of service for these patients and eliminated access to all brands of IVIG.

Just to give you some examples, I had 59 patients in southern Florida that had nowhere to go, where the doctors were looking to change them over to antibiotic

therapy, not a good thing to do for immune deficient patients.

I had Texas, 32 patients. In Birmingham, Alabama, there was a three- to six-month waiting period to get into a hospital, and reports from Atlanta and Ohio, so the doctors started saying, okay, if we can't put them into an infusion center, we will admit them as an inpatient.

Medicare said no, you can't do that because it is medically unnecessary to admit a patient for an infusion, which is true, but where else are they going to go, especially during flu and pneumonia season, this is not the best thing for the immune deficient community.

So, we really truly had patient lives in jeopardy, and it was really based on reimbursement that this was happening.

So, patients need access again to all brands of IVIG and all sites of service, and reimbursement should never dictate where a patient receives their infusion.

Now, moving forward, I just say, and I want to compliment CMS did an outstanding job, absolutely an outstanding job, started working with them once we saw what the rates were going to, and within two weeks of the new

regulations going into effect, we came up with a solution, and their hands were tied to a degree, because Congress gave them this new formula to work with.

What is happening in the marketplace right now in IVIG, you have your lyophilized products and your liquid products, and they saw two big difference in prices, so we were trying to figure out what can be done.

In the meantime, the lyophilized products are on allocation, so there is a shortage of product and the products are going to the hospital first, so they are really not going to the physicians' offices, so the more expensive products are going to the physicians.

CMS was able to be a little bit more creative since IVIG wasn't accessible to all providers, and took out of the formula, the lyophilized products and used just the liquid products in the ASP and brought the reimbursement up from $40 to $56.72 per gram.

Is this adequate? Not really, but will it do the job right now? Yes. Are we seeing patients getting back into the doctors' offices? Yes, we are. If a patient has a secondary insurance picking up that 20 percent co-pay, most

products can be purchased for that price. If they don't have that 20 percent, it gets kind of tricky there.

So, this has definitely helped tremendously, but more has to be done.

I want to go into the talk about all IVIG products are not the same and the perception that they are equivalent is not true, and you see sometimes in my presentation, and I am sure you all know this, but it may be for the audience, too, that it may switch IVIG and IGIV, and they are both comparable to each other.

But going into the features, IVIG product features potentially affecting tolerability, finding that right match for a patient is of critical concern. We look at the volume load, which is the rate of infusion, osmolality versus osmolarity, sodium content, sugar content, immunoglobulin A, the IgA content, and pH, this is all different in all the different formulas, and that causes a different reaction in these products for patients.

Tolerability is a critical concern for IVIG selection, and in the incident rates of IVIG, adverse events vary widely, and some of the serious adverse events may account for up to 5 percent of reactions. Those include

cerebral infarction, myocardial infarction, aseptic meningitis, renal failure, and then we go into other adverse impact of IVIG therapy. It could be 16 percent of patients experience an interruption of therapy, that will have an impact on their adverse events, and 7 percent of patients having therapy permanently discontinued.

Again, this comes from IDF surveys, and we don't like to see any of these things happen. This is a chart that really goes into some of the considerations of finding the right therapy for the right patient. Really, just to kind of sum this up, patients with congestive heart failure or compromised renal function may fare better if they receive a product with low osmolality and low volume, patients who are diabetic should receive a product containing no sugars.

Patients receiving products with sucrose may be at a higher risk for renal failure. Patients with an IgA deficiency should only receive products with the lowest amount of IgA, or they could have an anaphylactic reaction, and patients with small peripheral vascular access or a tendency towards phlebitis may want to avoid preparations with a low pH.

So, why this is important is to really show that these products really are truly different, and when working with CMS, one of the alternatives that I offered to them was really separating these J codes out. As we talked about bundling products, these products are different and when you try to price them all together under one category, you see how the product's price drops dramatically.

Congress understood that IVIG should be exempted from competitive bidding because patients react differently to these products, need access to all of them. One way to help ensure this is to separate out these J codes, so we make sure that all these brands are accessible.

So, one of the things that CMS wanted me to do, while we were going through these number of weeks trying to come up with a solution, they were looking at putting a category of lyophilized together and liquid together, because they saw the price difference of the two categories.

They were stuck because there had never been a clinical trial of liquid versus lyophilized. Well, there really hasn't been a reason to do that, but I was asked to pull together the clinical differences.

So, this slide really shows you that the only major difference that IDF was really able to come up with was the clinical trial design has been changed with the newer liquid products that have come out where we show now what the infection rates for these new recently licensed liquid products have been reported and we have it validated, and the three newest, Gamunex, Flebogamma, and Octagam, does that mean that they are better products than the lyophilized? No, it is just that these are quantified and the new clinical data.

So, that is one of the reasons why CMS was unable to go into that category of liquid versus lyophilized, but I think they are still spinning the idea of these separate J codes, or I hope they are, and we will continue to work with them on that.

In preference for IVIG formulation type, this was another question that came to me from CMS. Right here, this slide that was done by infusion nurses, 87 percent prefer liquid formulation, and one of the questions that came to me was why do physicians' offices tend to use liquid products and everybody else uses lyophilized.

So, reviewing that, the issue really is safety, and that is, physicians don't have a sterile environment with the pharmacists to reconstitute the products like hospitals do. So, I was able to give that information to CMS with them trying to understand more about these products.

Moving on, I just want to go quickly through some of the IDF treatment experiences and preferences of patients with primary immune deficiency diseases because I think it is important for you to understand what our patients are going through and how important access to IVIG is and all sites of service.

This chart just shows you--right now I am focusing on Medicare--so 19 percent of our population is on Medicare. For being infused, if you look at this, really, 67 percent of our patients are infused in a physician outpatient setting including home care, and 32 percent is under a hospital outpatient setting.

Patients' perceptions, really, efficacy is one of the most important factors in switching to another IVIG product, and 68 percent feel the effect wears off within two weeks of IVIG, and tolerability, 58 percent have preferences

for specific products, primarily due to side effects, and 34 percent will avoid a specific product due to a side effect.

In this slide, it is important to show again here, this is based on population, showing you that some or a lot of these patients will prefer a certain product over another based on tolerability, infusion rates, and keeping you healthy.

If you look at the overall numbers, 55 percent on tolerability, 44 percent on infusion rate, and 43 percent on keeping you healthy.

Concern on safety, 90 percent of our community is concerned to some level about safety of IVIG. On serious side effects of IVIG, 44 percent have had some type of serious side effect, and tolerating IVIG products differently, 39 percent.

This is important. On the number of IVIG products that ever used, you can see, looking at this, I mean the highest is two products, but we go all the way down to five or more products. So, really, when going to the physician's office, patients are going through a trial and error period, going through one product after another until they find the right product that has the least side effects, and that is

the brand they really need to be on for the rest of their lives.

So, through these changes in reimbursement, changing them from their site of service to another site of service, and changing the reimbursement rates where a product may not be affordable is causing problems for patients' safety and tolerability and putting people's lives in jeopardy.

Now, in terms of most important differences among products, you have this in your handouts, but if you go down to the bottom, you are going from side effects, going up through purity and production methods and tolerability, so I am not going to go through all of this.

Preferences for specific products, you can see that 58 percent prefer a certain product. I am going to keep on going through here.

The most important factors in switching products, again, the same thing with effectiveness of product. Now, this was very interesting, this slide, because we talked about prices and price of products have been going up.

So, if a product would cost a patient more, would they be willing to switch to a new product? They said yes,

if it would cause fewer infections, fewer side effects, faster to infuse, greater purity, safer, better tolerability, and guaranteed availability. So, price is not really an issue to the patient.

Now, going into the influences on total cost. Cost is an important consideration in selection of an IVIG product, and what you need to take into consideration besides just the acquisition costs of the drug is the cost of IVIG to the provider.

This is what is very important, and I think this is a part that really Congress missed in this ASP formula. They looked at what the cost of the manufacture price was, but didn't look at what the end user was.

In IVIG, you have the cost of IVIG goes to a distributor, and then you have the distributor selling to the provider, and you miss that middle man in this formula, so you don't have most of the end users, these physicians, purchasing directly from the manufacturers.

So, when you come up with this ASP number plus 6 percent, it is way off, you don't have the middle man included in all of this formula. So, it needs to be recalculated to include the distributor's cost in this.

You need to also include the staff cost in handling the product, the infusion time impact, reimbursement, and cost of adverse event management.

In summary, all IVIG therapies are not the same based on clinical evidence, manufacture, and final formulation. Patients perceive differences in various brands of IVIG based on effectiveness and tolerability.

Congress intended patients to have access to all brands of IVIG by exempting them from competitive bidding, and reimbursement should never dictate site of service.

Some of the recommendations that I have separating the J codes for each IVIG brand. CMS made an adjustment to the reimbursement of IVIG for the first quarter data, but what happens to the next quarter when it comes out, is the lyophilized products are not on allocation, does the price drop again, and do we have another situation in March where all the patients are out of their physicians' offices and home care settings, and have nowhere to be treated?

It can't keep on going up and down, and up and down on the reimbursement, and have patients all over the place. We have to get to a steady reimbursement level that is adequate and keep it there, and it really needs to be

somewhat equal in these different sites of service because again, reimbursement should not be dictating where the patients should be getting their therapy from.

CMS definitely, and Congress, has to consider the distributor's role in determination of the reimbursement rate for IVIG. Some issues that may want to be considered is, you know, increasing the ASP rate.

I mean you have ASP plus 6 percent, you have the issue of inherent reasonableness, and you could add another 15 percent. You can put an add-on fee, you know, but what that number is, I am not exactly sure, and I know that opens up the flood gate for CMS, if they do it for one therapy, do they have to do it for the rest.

But I think that you have got a situation that you saw what can happen in a two-week period to a whole community, and I am talking from the primary immune deficiency community. This also happened to the neurological community, too, that uses IVIG, that I didn't even address because that is not my specialty area.

So, another area which I know people don't really like to talk about, but you do have, in the MMA, you have

the area of blood products being exempt from ASP and being reimbursed at 95 percent of AWP.

I know it goes further to reimburse IVIG under the ASP model. Maybe that should be re-looked at as a possibility since the committee has recommended for CMS to recognize IVIG as a blood product.

Maybe that is a way to get that reimbursement up as a possibility, but this is just the first step. We go into 2006, the hospital reimbursement is going to drop dramatically, and then Medicaid, they are looking to switch over to an ASP model, so we have got to act proactively to prevent some of these other reimbursement crashes.

On the administrative side of things, IVIG dropped dramatically in the reimbursement. Last year, we were reimbursing physicians for administering IVIG at $117. It dropped this year for the first hour to $76.

So, where Congress came in thinking that we wouldn't let physicians be making a huge profit on the drug, but we would give them sufficient money to administering the product, they did that on the oncology side with chemotherapy. They didn't do it on the non-chemotherapy products.

Now, it gets interesting because if you look at the definition of chemotherapy, they expanded it to include biologic response modifiers. In that definition of a biologic response modifier, if you look at the U.S. National Library of Medicine, the definition is the treatment to stimulate or restore the ability of the immune system to fight infection disease.

Well, IVIG meets that definition, I would say it definitely does. So, if we can get IVIG under that category, we would bring reimbursement back up to a level that I think we can get physicians to continue treating our patients in their offices.

So, that, I would like to see CMS, and I have contacted CMS and am working with them, to see if we can't get that into that chemotherapy code.

The last point, and again this is a point that really Congress is going to have to get involved in, is covering the administration of IVIG in the home care setting, because I do agree that CMS hands are tied, but I do want to thank CMS because they did fix the situation that I spoke to you guys about the last time, about the whole administering IVIG through durable medical equipment, and if

they did it through DME, they would no longer cover the drug.

They are coming out with a program memorandum to fix that definition, so I mean I want to say kudos to CMS, you have done a great job, you have responded beautifully, and I am looking forward to continue working with you and Congress.

Thank you.

DR. BRECHER: Thank you, Michelle.

Any questions or comments? Jerry.

DR. SANDLER: When the subcommittee on reimbursement met, we had a sense that there were serious issues in the area of persons who require life-long treatment with plasma therapies.

I think today we heard four very, very expert, concise, and highly focused presentations that just gave us even a window into the serious problems that Americans are facing who have inherited and acquired these diseases.

I want to thank all four speakers for their very excellent presentations. They hit the topics exactly as the subcommittee had hoped they would. Thank you.

MS. VOGEL: Thank you.

DR. BRECHER: I think my take on this is that the reimbursement is very confusing and complicated, but coverage is short, but the need is long.

MS. VOGEL: Definitely.

DR. BRECHER: Jerry.

DR. HOLMBERG: Michelle, can you explain to me how the 95 percent of the AWP would be beneficial compared to the ASP?

MS. VOGEL: Sure. At this point, the hospital reimbursement rate is at 88 percent, 88 or 83 percent--83 percent of AWP, and it is at $80 per gram, so that would bring 95 percent, if we do the math, which I am not a big math person, but that would bring it up much higher reimbursement for all the products.

I mean you get into an issue does it need to be the 95 percent, can it be a certain percentage of AWP, but you are having one certain reimbursement for the whole year, and if you could standardize it, so that you do not keep having these fluctuations, ASP keeps on dropping or going up on a quarterly basis.

If you look at how IVIG is set up, you have lyophilized products and you have the liquid products, so

you have a huge range of products with different prices, and it is a weighted average. So, the more expensive products are new in the marketplace, so they are not weighted as heavily as the older products that are lower.

So, it drops it pretty low. So, $40 a gram, I can tell you there is not one product on the market that you can purchase at that, especially if you are going through a distributor, which all of them go through a distributor.

DR. HOLMBERG: But I guess that is the question that I have really lies. You have pointed out that the ASP does not include the distributor. Does the AWP include the distributor?

MS. VOGEL: Well, if you are talking about over $80 a gram or $85 a gram, definitely, because you are talking about products even at the highest cost of the products through a distributor.

If you are talking close to $60 a gram, you have plenty in there as the products are going up in price, you have got a window there where all products are going to be accessible and reimbursable, and if you are not going to increase the administration side of things for physicians, then, you have some profit in there for physicians.

So, is 95 percent, I mean I would look at this, and I don't want to get killed on the record here, but I mean you may want to look at 95 percent as saying is that the right percentage, could that be a little too high, I am not sure.

That would have to be looked at, figuring out the numbers, and looking at what the products are actually at under the AWP methodology, and looking at what the prices are coming through distributors.

That is the data that I have been supplying to CMS, giving them information of what the products' prices are coming out of the distributors, so that they have that, and being in contact with that.

DR. BRECHER: One last comment before we take a break.

MR. HEALEY: Michelle, based on your presentation, which I thought was excellent, it seems like the most accurate course here was I think your suggestion of the reimbursing on the NDC or separate J codes, because then, you are looking at each of these branded, you are avoiding this whole clustering and bundling problem.

MS. VOGEL: Exactly, you are not averaging anymore, and that is where you are getting into the problem of you are averaging these products that, number one, are very different from each other and patients are reacting differently and need access to all of them, and Congress saw that with exempting from competitive bidding.

So, if you separate them and give them all their own J code, and they are reimbursed on their own, and physicians have access to the right product for the patient, you are not getting into trouble because you could actually reimburse it under the ASP model plus the right percentage going through the distributor, and it is getting reimbursed on its own value, and not through a cluster.

So, I mean that would be the best scenario if CMS can move forward in that direction or Congress gives that order to CMS to separate the J codes, but there is enough evidence to do that.

DR. BRECHER: Thank you. We are going to take a 10-minute break.

[Recess.]

DR. BRECHER: We are going to move into a panel type discussion with the CMS representatives, Carol Bazell

and Dr. James Bowman. So, if they could take a seat at the table or up at the microphones up there, then, we could begin.

I know that several members have had some questions for CMS. Would you like to start with some of those questions? Dr. Wong, I know you had put a question to CMS. Would you like to start?

DR. WONG: I am not sure this is included in the handouts. I think it was included in the CD-ROM that we put through.

First of all, I want to just thank both of you for being here and being able to answer the questions. I echo the concern of the 20 percent co-pay that has been voiced recently by the various other members.

I certainly support the importance of choice in factor replacement, but I do want to bring up just one point that I had echoed to Dr. Holmberg in the last meeting, which is the DRGs and the inpatient reimbursement specifically for Novo-7, which is a very special product.

My question to Dr. Holmberg has been that there is no parity in terms of reimbursement for inpatient use for

this very highly specialized and highly expensive product as opposed to an outpatient reimbursement.

If you look at the slides that were presented earlier, there is a 900 times difference between the cost of one product versus the other factor 8 replacement products, and this product is one that is very crucial to a small group of high-titer inhibitor patients.

It is not a matter of choice in this case, it is a matter of necessity, and most of these products are used in highly specialized centers as mine. We are the largest center on the West Coast, where they have specialized care.

Right now we can't afford to even do surgeries on these patients because of the cost of this product that put us into $3 million in the red last year for the use of this product specifically.

So, is the CMS addressing this specific issue, because it cannot be bundled or lumped into other factor replacement products?

DR. BAZELL: I think one of the presenters made reference to a passthrough payment, which is the term they use with respect to clotting factors for use in the

treatment of patients with hemophilia in the inpatient hospital setting.

Are you talking about an inpatient hospital setting for Medicare patients?

DR. WONG: Specifically, inpatient hospital setting under the DRG system.

DR. BAZELL: I believe that the code for that is Q-0187, is on the list of factors for which there is a 95 percent AWP payment for the use of that in inpatient hospital setting for Medicare patients.

I know in your specific question, you included some charge data, and I wasn't sure, maybe some of those were Medicaid patients?

DR. WONG: This is a pediatric population, and I am not sure if they are Medicaid, but I know they are Medi-Cal.

DR. BAZELL: I am speaking about the additional payment for the use of clotting factor in inpatient hospitalizations is a statutory provision, and it refers to Medicare.

As many of you know, and it has been sort of alluded to around here, Medicaid programs have different

policies, and they may or may not adopt Medicare payment policy.

DR. BOWMAN: Dr. Wong, Medicare does pay $1681.50 on that code, which is 95 percent AWP per 1.2 milligrams for inpatients.

DR. WONG: Say that again, please.

DR. BOWMAN: It is $1681.50 in addition to the DRG, for whatever the patients in the DRG, because that is statutory 95 percent of AWP, and that is in the inpatient IPPS final rule.

DR. BAZELL: But if your patient population is principally a pediatric population, they may likely be Medicaid beneficiaries, not Medicare beneficiaries, and that is Medicare policy that Dr. Bowman just referred to, and not necessarily your state Medicaid policy.

DR. WONG: Doesn't apply to it, yes, so what do we do in our situation?

DR. BOWMAN: As you probably know, CMS has very limited discretion over the various state Medicaid programs. As a matter of fact, the tendency has been to allow these programs in the states to run themselves.

You know, the Federal Government either matches the money or pays 60 percent and 40 percent from the state or whatever the statutory formulas work out to be, but there has been within certain boundaries, some hands-off approach over the last couple of decades to the state programs.

So, that is an issue that probably would have to be addressed to the state Medicaid program that you are practicing with. There are some issues that can be brought up to the Medicaid component of CMS, but I wouldn't want to hold my breath on that.

DR. WONG: Thank you.

DR. BRECHER: Other questions from the committee for CMS? Jerry.

DR. HOLMBERG: We have heard from several people concerning the bundling issues. Is CMS willing to work with the organizations in de-bundling those biological products?

DR. BOWMAN: Well, if you are talking about specifically the IVIGs and getting separate J codes or HCPCS J codes for every product manufactured specific IVIG, that is still currently under discussion at CMS, and I think they are certainly willing to listen and work with the community on that.

DR. HOLMBERG: So, establishing J codes really is at the discretion of CMS, and it is not a statutory requirement?

DR. BOWMAN: That specific question, you are correct in that. I don't think the statute specifically addresses it at that level of specification and detail.

DR. HOLMBERG: I have another question if I can, please. Also, what was mentioned today and it has been mentioned numerous times at these meetings that I have been attending, the fact that--well, let me just go back to the last time that we had a meeting.

We had a very good presentation explaining the manufacturer scheme of things as far as manufacturing the product, the economics of manufacturing the products, and then the cost that goes on from there to the distributor, to the physician or to the hospital.

What I am leading up to is the distributor, and in the formulas that you have, you don't consider the added-on price from the distributor. How do we or how does CMS attempt to, or want, or propose to overcome that, because I mean I think the last suggestion that I heard was going with the AWP, but to me, I don't see the rationale on that, and

the advantage of going to AWP versus the ASP, I would think that it would be better to take in consideration what the distributor may tack on.

DR. BAZELL: I think Congress was very clear in the MMA about what it envisioned in the ASP, moving away from an AWP-based system. I can't speak for whether Congress really considered the role of the distributor, but Congress, I think we believe is quite clear about how we collect ASP data.

So, that latitude for us to say, oh, we don't think 6 percent is enough, I think doesn't really exist, and we really haven't--Congress was very clear--106 percent ASP system.

To the extent that we believe or you believe there are access issues and other things that arise, and things that weren't contemplated or considered at an appropriate level, either for certain drugs or for all drugs, I think that is information that we would share with people we are speaking with, as well as you might share.

I did not that on the presentation from the Immune Deficiency Foundation, some of the things that were associated with the higher costs that were mentioned, such

as the management of adverse reactions and what have you, I think we would consider that we wouldn't be paying for within the drug payment itself, but within the administration payment that we make for the drug.

That could be the administration for the drug, the payment for the drug, or it could be an evaluation in management visit payment that we make for evaluation and management of a drug reaction and/or a critical care payment to the extent the patient had a seriously adverse reaction in a physician office.

So, some dimensions of the increased costs associated with a physician providing the service, we believe there are other ways we would pay for that portion of the services that the patient was receiving.

DR. BRECHER: I have a question. Listening to all the talks, I am struck by how complicated the whole system is. Does it have to be this complicated?

DR. BOWMAN: I ask myself that question a lot, Dr. Brecher, ever since I came here to the first meeting. I think you are probably asking the wrong two people about that.

DR. BAZELL: The fact that these various payment systems you heard about in the inpatient setting and the hospital outpatient setting and the physician setting, most of those are statutory payment systems.

Now, some of the nuances of how they are implemented may be administrative decisions, but the fact that we have really two prospective payment systems and then a physician fee schedule, I mean those are set up that way.

DR. BRECHER: At least we could try to harmonize across the systems, so that they are all relatively equivalent. That would be goal, I think.

DR. BAZELL: I think that all of us believe that might have some merits to it. On the other hand, there are people who argue, for instance, that the resources really associated are costs of delivering certain services in certain settings are really very different, so that is part of the genesis of different payment methodologies.

Some of the differences that were mentioned about the payment this year for IVIG have to do with again statutory provisions about how we pay for those in the hospital outpatient setting for 2005 versus statutory

provisions about how they are to be paid for in the physician office setting.

There may be some more, the law may be less prescriptive for future years about that, and there may be some ability to harmonize those systems.

DR. BRECHER: Thank you. Actually, what I had wanted to say was that it is bloody complicated, but I restrained myself until now.

Are there other questions? Yes, Celso.

DR. BIANCO: I know it is going to get even more complicated, but can you help us understand, you started the competitive bidding clause and what is out there, who does the bidding?

DR. BOWMAN: The details of that, Dr. Bianco, are still being worked out. Now, they will get worked out fairly quickly obviously, because it starts January 1st, 2006, at least for the initial rollout of categories and products and whatever.

But in terms of other than what I mentioned earlier as specifically excluded from competitive bidding, that is still under discussion with the unit at CMS that is working on that.

DR. BAZELL: There will obviously be notice and comment as CMS does on many of its programs that it administers related to aspects of the program, as well.

DR. BRECHER: Jerry.

DR. SANDLER: Dr. Bowman, you have got a couple of hats on at the moment. I would like you to revert back to the hat that you wear across the table as a member of this committee and charged with advising HHS on safety and availability.

Can you help us advise HHS how we can go forward? From the stories that we heard today, I think everyone in the room wants to help on this problem, but as so many people have said, it is so complicated, we don't even know how to ask the questions.

You are technically much more expert than most of us on this committee, and therefore, could be a great resource to us, advising how to go forward. How would you fix what we want to fix?

DR. BOWMAN: Dr. Sandler, that is pretty scary if you think I am technically more expert than you guys. I hate to say it, but it's way above my pay grade to tell you how to fix this system.

You probably should ask Jerry that, because he is closer to the top than I am. To the extent that there are, like Dr. Bazell said, there are discretions available to the Secretary, and through the Secretary to the CMS Administrator, when there are compelling issues of access and availability that those discretions are allowed within certain specific limited things that we have discussed, and the best thing I can say is that I think CMS has demonstrated a willingness to work with anybody, whether it is the patient or beneficiary community, or sub segments of the population or the providers, other stakeholders, manufacturers, because they do want to get it right.

There is no advantage to getting something wrong and then having to redo it. That is kind of a basic of doing business in the business world, and I think it is a basic of doing business in the government.

So, I think they are willing to work to get things right. Very often, I think it is going to take smaller, one on one meetings to approach CMS, and to the extent that myself and Dr. Bazell and Dr. Holmberg can facilitate identifying the right people within the agency to work with,

I think those folks are open and Dr. Holmberg would probably attest to that.

MS. LIPTON: I was just going to say I think perhaps also the issue that you didn't say, but we are finding is so important in terms of being able to change any kind of policy is data. Just as we sit here at this table, is keep asking for data, and I know it puts a burden on all of us to collect these data, but that really is, in the end, what seems to let us sit down, you know, in a group and explain what is going on.

So, it is just a note to ourselves. I was also struck, I know this isn't exactly within our purview, but there has been a lot of discussion of Medicaid today, and I wonder if we couldn't, in the future, talk a little bit more about what is happening in the Medicaid arena to a lot of these patient populations that we are concerned about.

I mean it is not directly important, but in the grand scheme of availability and safety, it is important.

MR. HAAS: I am not quite sure of the right way to ask this. Maybe it is because I am too far away from some of the issues, but would it be possible to either tell us areas where you have no discretion around the issues that

have been discussed this afternoon and/or tell us the areas where there is discretion, so that then we can start engaging in productive dialogue?

DR. BOWMAN: Sure. I think with the issues that have been addressed today, I think it is pretty obvious that the agency has no discretion with the 20 percent Part B co-pay.

Within the exact framework of the payment systems, to the extent that there is a differential payment between the physician's office, ASP plus 6 percent, for example, and the outpatient prospective payment system, as Dr. Bazell alluded to, which is a payment methodology that is fixed in statute and changes from year to year obviously, there will be discrepancies even though maybe we would like to see a site of service neutral sort of payment system.

That is just not the way it is. To the extent that that results in some documentable access to care issues, there may or may not be discretion within the Secretary's discretion to make some allowances to counteract that.

Those would have to be looked at on an issue-by-issue basis, I think. Just to put things in context, the

MMA made some, as all of you I think are aware, some humongous drastic cutbacks in what physicians will see in their office payment or reimbursement for drug infusions.

Now, the oncology community approached Congress and CMS, and was able to get some partial reimbursement for their services, their services in the office related to infusions, but it was related primarily to biological response modifiers and chemotherapy drugs.

That is an issue that is going to certainly impact the rest of the physicians or those physicians who previously had larger margins when they infused the non-chemo drugs, and I think that is some of what we heard today.

Those are issues that there is not a whole lot of discretion available. The question of like product-specific NDC codes or HCPCS codes certain is I think still under review and on the table. FDA has certain ways they look at those products, and there probably is some discretion within the CMS agency to look at it in different ways.

But I think each individual issue is probably going to have to be addressed with the most appropriate

people within the agency to get those types of issues addressed.

Just as you have already seen, the agency has been able to respond to when external stakeholders bring about conflicting information or contradictory information that CMS just was not aware of, did not have, as we saw earlier, and we are able to make adjustments that are appropriate adjustments in their payment.

DR. BRECHER: Mark.

MR. SKINNER: I think one of the challenges that we face and, you know, having lived with one of these disorders for over 40 years, you know, you could write a short novel if you followed my insurance chase over the years to maintain my coverage.

I like to think I am a reasonably intelligent person, and it is daunting for me, the amount of time that I have to take. I think the challenge for any of us is articulating why we need the products that we need.

I mean medicine is not an exact science, so to know exactly why we need one product or another product, it is very difficult in the absence of a lot of scientific evidence to actually say why we need the full spectrum. We

have tried to do our best to articulate the need and the importance to having access to the full range of products, but short of a long-term clinical study, we aren't going to be able to answer that, and we may not even be able to answer that then.

I mean we are just a rare patient population, and the information isn't going to available. So, the important thing is for the ability of our anecdotal information to be persuasive.

To what extent is CMS willing to accept the patient information in terms of their clinical outcomes as a reliable indication for the importance of having access to all products, or physician information in the absence of any kind of aggregated database or clinical study, because it is just not going to be available, and if wait on that, you know, people's lives are in jeopardy?

DR. BAZELL: I would say we welcome information, recognizing that that information may have its limitations because of the frequency of a condition or a treatment, or the treatment hasn't been around long enough, and we realize those limitations.

But specific information is helpful even if it is maybe anecdotal or it may be an individual physician reporting on certain experiences. Certainly, our coverage brethren who are making national coverage decisions, you know, have a specific set of criteria for making those that they lay out.

We are not talking in much of what we are discussing here necessarily about evidence that rises to that level. We all prefer to receive data and studies that are rigorous and that really may show specific effects, but realize that that is limited in many cases.

So, we would encourage you, either yourselves or the committee or the groups that you are associated with, to bring forth the specific information to us that you have.

DR. BRECHER: Jerry.

DR. HOLMBERG: I guess I will ask the same question that Celso asked earlier, because I really don't have a clear-cut answer on this.

What has been exempted under the competitive bid, has only IGIV, or has all clotting factors and also all blood products?

DR. BAZELL: Blood products are not subject to competitive bidding nor IVIG in statute. The agency has not come out specifically, there is discretion there about exemptions. The agency has not, and it was mentioned, Dr. Bowman mentioned that there will be a phased rollout of that program over several years likely.

So, the agency, as it moves forward, will be doing notice and comment and rulemaking, where it will be proposing what it proposes to do at a given point in time, and accepting comment on that.

The specifics of that haven't been put out publicly.

DR. HOLMBERG: Okay. But as far as what I have just described, the only one of the categories that we do not have exempted, are the clotting factors for the bleeding disorders, is that correct?

MR. HEALEY: A1PI also is not exempt. So, as I understand it, the only one that is exempt by statute under the MMA is IVIG although the Secretary has discretion to exempt others, and I think that is what you are referring to when you say there will be some notice and comment.

DR. BAZELL: Yes, and again it will be a phased, it won't be, as of January 1st, 2006, it will necessarily happen for all drugs. The Secretary even might intend competitive bidding to happen for, so again, there will be a series of notice and comment and rulemaking about how the agency is proposing to proceed.

DR. BRECHER: Two more questions or comments, and then I think we are going to move on in the interest of time.

Jerry and then Andy.

DR. SANDLER: Dr. Bowman, I wonder if you could define for me the medical and scientific resources that are available to you for decisionmaking on issues.

You mentioned one issue that is on the table, and that is whether there would be individual J codes for the different types of IVIG. We heard an explanation today that broke down maybe five technical differences.

I give IVIG frequently, and I do have to pick between the products, because they really are different. The IgA content is very important as was explained. Certain people really shouldn't get sucrose in their product, other people should get different ones.

It takes an awful lot of medical and technical experience to make decisions like that. When I visited FDA, I was very impressed with the in-house resources. They have laboratories, they have scientists right there, so when decisions are made at FDA, from my first-hand experience, I know that they really have depth in scientific resources there.

Could you define what your agency has at your disposal for analogous decisionmaking?

DR. BOWMAN: I will let Dr. Bazell also make comments if she would like to, but I think we are fortunate that we do consider ourselves one big family, and the FDA and NIH and HRSA and AHRQ, to use some acronyms, are available to us, and are used not infrequently.

The specific individuals within those agencies are also available, and obviously, we are, of course, open to unsolicited comments and suggestions from external sources, but not only that, we also seek out additional information as is needed from external nongovernmental sources.

I didn't mention the VA also. I should mention the VA. That becomes very important in issues of prosthetics, orthotics, and durable medical equipment, which

is not related, of course, to this committee, but is another important agency that we have available to us.

DR. BAZELL: I would agree with Dr. Bowman that regularly, we both have people with in-house expertise. There are few to none, no bench researchers in CMS, but regularly interact with people in the various agencies, and I think especially in areas of emerging technology, that CMS is very proactive under our current administrator about developing very specific and explicit collaborative relationships with other agencies to facilitate understanding of technology, evaluation of those, so that we can all do the various things that are with our agency's specific mission, whether that be approve, set payment rates or what have you.

DR. HEATON: I wanted to ask some questions relative to whole blood and whole blood products. Today, we have been talking about the plasma sector, and relative to the number of patients who receive specialized plasma products, there is obviously a very much larger market receiving whole blood products and components, both in outpatients and as inpatients.

We have talked a lot about mechanisms that CMS could use to adjust the AWP for blood and blood components, and it is heavily dependent on the BLS, the Bureau of Labor Statistics and its cost basis.

What activities is CMS undertaking to work with BLS to allow new technologies to get incorporated into the BLS reported price rather than factored out, as they now are, and therefore treated as an extra expense, when a patient receives a blood product either as an outpatient under OPPS, or as an inpatient under DRG?

DR. BAZELL: I think that was your question maybe that was forwarded yesterday to me, and I sent a couple notes and haven't heard back as of this morning. I believe it is the Office of the Actuary that deals with the PPI issues that we use on our inpatient prospective payment system. That is maybe what you are referring to.

DR. HEATON: Exactly.

DR. BAZELL: I will be happy to get back to you when I have a little bit more information about what might be occurring in that arena.

I would say on the outpatient side for 2005, we changed our specific methodology, and in the end, have

increased payments for most of the cellular products on average about 25 percent between 2004 to 2005.

As was mentioned before, we make separate specific payments on the outpatient hospital side for each blood product that is administered, but I understand the PPI is particularly relevant to the inpatient prospective payment system, unless you know anything--

DR. BOWMAN: Let me just mention that Dr. Holmberg has been a little proactive on this, and he did set up a meeting with several external stakeholders of the blood community and the Office of the Actuary, as a matter of fact, the chief actuarial officer at CMS, about I am guessing three or four months ago to bring this.

It was a fact-finding, a mutual exchange, sharing, and presenting of some issues directly related to what you are referring to, and trying to pursue that further with the Bureau of Labor Statistics and their specific component that is charged with gathering the raw data for this.

So, that is still in process and Jerry has been working on this, and I think we don't have any definite answers yet.

DR. HEATON: It would be very helpful if we could include the follow-up review of this at later meetings, because when you look at the dollar value and the number of patients impacted, this is probably an order of magnitude different to the plasma products that we are discussing today.

DR. HOLMBERG: I think that one of the other things that we forwarded in the package to the committee was also a package that the AABB, PPTA, ABC, ARC put together to CMS basically asking for or suggesting some things, such as improving the documents, the guidance documents for reporting, some of the issues, and the PPI was part of that in the entire letter that went forward to Mr. Koon at the CMS.

I know that Mark wants to move on here, but the other thing, too, that I would strongly encourage, whether it be the subcommittee or different special interest groups, we can take some of these things off line and we can meet with CMS. They are very open to hearing more from the community.

Yesterday, I was on the phone with them. Also, they expressed very clearly that they need to hear. Now,

granted, there are many things that are limited by statutory requirements and that we are not the mechanism for that, but clearly, there are some mechanisms that we have, as you, as a person that puts forth recommendations to the Secretary, you have the ability to make those recommendations to the Secretary on things that the Secretary can change.

DR. BRECHER: Jay, last comment.

DR. EPSTEIN: Well, it is a question for Jim triggered by your remark, things the Secretary can change.

In the statute, are there any exemption or waiver provisions that are options for the Secretary to exercise, in other words, can the Secretary make any summary decisionmaking that would otherwise affect the reimbursement structure? Can the Secretary make an exception, for example?

DR. BOWMAN: The competitive bidding is the first thing that comes to mind, just because that was on the presentation earlier, within the entire statutes and certainly within MMA, there probably are other areas.

DR. BAZELL: To some extent it might depend upon the specifics of the payment system. I think what is hopefully clear to you all here, is the payment systems to

some extent operate under different provisions, and there may not be an overarching, like the Secretary sort of can do anything they want and any payment system they want, but within a given payment system, there may be some discretion for the Secretary, and it may have different terms that are used in different payment systems.

So, we would be willing again to talk about the specific area of interest and the specific payment system, and we could look and see.

DR. BRECHER: Thank you.

We are going to move into the public comment period. I will ask that the people who come to the microphone identify themselves, what organization they represent, if they are from a specific organization, and to keep comments to no longer than five minutes. I will cut people off after five minutes.

MS. HAMILTON: Good afternoon. My name is Jan Hamilton. I am Advocacy Director for Hemophilia Federation of America.

First of all, I would like to thank the committee for addressing these very important matters on reimbursement this afternoon. They are very heavy, looming over our

heads, and all the users as the community, and something that we have been working towards for a long, long time, and it is good to see some of these things coming to the forefront.

I also want to say that one of the things that came up this afternoon in several arenas, but I would like to just report to the committee and to those in the audience that on October 26th, members of Hemophilia Federation of America met with Dr. Mark McClellon on several issues of concern, but in particular, also brought up standards of care and discussed this with him.

He is very interested in working on standards of care, which if we can get that going and get it out to the states, I think it would eliminate a whole, whole bunch of problems that we are seeing in the single source provider and the preferred drug list, and these sorts of things.

So, I would just encourage all of you who have the ear to echo what we have already started a discussion with him, and let's get this one brought to a head.

Thank you again.

DR. BRECHER: Thank you.

MR. DUBIN: Good afternoon, ladies and gentlemen. Corey Dubin with the Committee of Ten Thousand.

Some of the members of the panel will remember me. Some don't know me, but I think you know the agency. I think it is important as we look at this to remember we are talking about human beings, and I will give you an example.

We are aware of a client, who a factor 8 order was made on his behalf, couldn't be delivered because the carrier notified the provider that they needed a $6,000, not just a check, but a money order upfront. These are the kind of things that are happening.

It is very good to see CMS here. In the nineties, we wondered if you guys were just a big computer that only certain people had the codes to, because we didn't really see you guys when you were HCFA.

It is really good to see you here, and for us, we need rational reimbursement, standards and criteria, that meet the needs. Recently, we have seen consistent attempts at sole source provider contracts that scared all of us with the kind of things about reducing expenses by changing use patterns, changing types of factor used, and I want to remind the committee, when you are talking about treatment,

you are also talking, for instance, for those of us that are HIV and HCV coinfected, choice of factor can have a real impact on your immune stability.

Intermediate purity factor can cause instability in your immune system. There was a Swedish study in the mid-1990s that did a good job of demonstrating that.

So, we are really talking about not just a choice, not just somebody deciding whether they like Baxter or Bayer, but real issues, and it seems to me that this reimbursement landscape has been a mess for a long time.

We would be glad, as I hear the other organizations in the community saying, to work with whoever we have got to work to sort this out, but what it really cries for is some leadership.

It seems to me the leadership could come from a joint effort, the same type of joint effort that birthed this committee, that birthed the IOM report, and that got us kind of out of the quagmire of the AIDS disaster and moving again towards cleaning things up.

It seems to me this is an area we really have to address because as we don't, it creates a vacuum, and the natural tendency in the marketplace at this end is if you

can't get more clients and you can't push more units, well, then, maybe you sole source your contracts, and that way increase your market share.

It really cries for some leadership. I think the issues are not as complex as they have been made out to be. If you take a good look at who the clients are and who the community is, I think again hemophilia is a metaphor for the other user communities, and the things that we learn with hemophilia can be carried elsewhere as they have been before, but I think at the bottom line, there really is a leadership vacuum that needs to be filled at the level of HHS, at the level of working in the community, working with all of us, which we are glad to do, because the situation is getting out of hand on the ground.

It is absolutely getting scary for those of us who present multiple diseases with hemophilia. I think I am about to turn 50, and this is about the scariest I have seen it in a long, long time, certainly since the AIDS epidemic, to confront completely changing treatment, to confront those issues is difficult, and I don't think we need to.

I think we understand very clearly that we live in a period of declining resources and the need for self-

management and discussions inside the community about how these things go down, but I don't think the issues are so daunting that we can't get together and provide some leadership and solve it, preserve choice, preserve the marketplace that everybody believed was the best way for the hemophilia world to work.

We still have faith in that marketplace as long as everybody does what they do best, if not more. The treatment centers treat, the manufacturers manufacture, home delivery, home delivery, and that is the system that we should work to really strengthen and improve, and provide reimbursement that works, because that system has served us well and continues to serve us well.

So, I would hope that coming out of this, we have a continued dialogue with CMS, we keep seeing you guys, and can provide some assistance, and if the committee provides the leadership that we think it can and that it has before in earlier times.

Thank you.

DR. BRECHER: Thank you.

MS. MODELL: Good afternoon. Mary Modell, Alpha One Foundation. Our president, John Walsh, again sends his

regrets that he was not able to be here today at the Advisory Committee due to illness, and I really just wanted to go on the record.

As you are aware, Alpha-1 antitrypsin deficiency is a pediatric and adult liver disease, but the primary effect is adult onset emphysema, and the treatment for that is to receive a blood product infusion on a weekly basis.

We have three products available in the market, and our patients are concerned about many of the things that you heard here today, being a chronic disease population.

We are very concerned about exemption from the competitive bidding process. We are very concerned about the ASP and the fluctuation on a quarterly basis. We are very concerned that we only have two sites of service to select from for a very high percentage of our population who are Medicare dependent, and that is the physician's office and the hospital outpatient setting, and we do not have a home infusion benefit.

So, all of the things that you heard here today also apply to alpha-1 patients, and we appreciate the consideration that this committee has given us in the past,

of these short-term issues that were mentioned came up yesterday, too.

DR. BRECHER: My impression over the years is that our recommendations have gone down fast when we state the facts first, and then go on and make a recommendation based on those stated facts.

We can further discussion or we could break until tomorrow. What is the committee's pleasure?

One potential problem we have is that given the turnover in members, there are 18 voting members. There are currently 10 voting members present right now. If we lose one voting member, we no longer will have a quorum, so there is an advantage to pushing forward and trying to get as much done today, so we don't run out of time tomorrow.

Maybe what we could do is take a 5- or 10-minute break. Let's try to get Jay's proposal up on the screen, and then we could wordsmith it.

Let's take a 10-minute break.

[Recess.]

DR. BRECHER: Go ahead.

MS. LIPTON: While everybody is sitting down, I just wanted to comment about the role of the AABB in the

Bacterial Contamination Task Force, and after discussing this with a number of people, I mean I think the committee will still be in a position of monitoring and making sure that these issues are moving along.

We don't intend to just fall apart, but I think that our role in terms of actively participating in filing anything with the agency is not the direction we will be going, but we would be happy to keep the group intact and to make sure that all of these issues are moving along and that there is one group that is receiving all the information and reporting back to this committee.

DR. HOLMBERG: Karen, do you want to make a quick comment on the collection of data? There have been some references to how do we know what the current state of affairs are in the United States.

MS. LIPTON: Yes. I am sorry, I should have also stated that the AABB is now under contract with HHS to continue the collection of collection and transfusion data, to continue the work that was undertaken by the National Blood Data Resource Center.

We have a sole source contract for one year to collect data for the year 2003, I believe, is that right?

DR. HOLMBERG: Yes.

MS. LIPTON: Over a 12-month period, and it will be based on the questionnaire or the survey that we had done previously. As I said, it is a one-year contract and after that it will be competitively bid, but I just want to thank the Department for recognizing the importance of those data we were collecting and making sure that we have continuous data.

So, we are embarking on that as we speak, and hopefully, this will be part of the data collection activities. It is not intended to be everything, but it is really one way of looking at the supply issues in this country, and then there are other mechanisms that HHS had in place that are more immediate, or give more immediate data.

MR. SKINNER: I think we are ready. So, we are going to return to the issue of bacterial contamination, and Dr. Heaton has scribed for us a draft resolution, which is coming up on the screen.

Dr. Heaton, do you want to explain for us, please.

DR. HEATON: Yes. I have broken the resolution really into three parts. The first part acknowledges that the FDA has proposed an innovative regulatory pathway to

allow the collection of post-approval information to support approval of the bacterial detection system.

I mean I really think this has been a significant step forward and a response to our concerns.

The second paragraph identifies the fact that whereas this approval process will require the capture of much information about the extent of bacterial contamination and the efficacy of the new test system, the requirement for post-approval monitoring may not continue beyond the final approval.

The third block, which is the committee recommendation, is that the Secretary of HHS propose or request the appropriate agencies to work together to do three things: monitor residual bacterial contamination and generate a report, provide resources for the surveillance of transfusion-associated sepsis, and then make such additional recommendations as may be needed to maintain recipient safety.

So, those are the three blocks, the acknowledgment of the steps to be made forward, the statement of the problem that there may not be continued monitoring, and then the recommendation that we set up a monitoring mechanism

both with the obligation to produce a report and to suggest continuous improvements.

MR. SKINNER: Are there any questions of Dr. Heaton or comments on the draft resolution? Dr. Epstein.

DR. EPSTEIN: These are very minor points. I certainly agree with the thrust here. I think in the last paragraph, "The committee recommends that the Secretary request the appropriate agencies," I don't think you should spell out which ones they are, because it may not fall in those bins.

For example, maybe CMS, through hospital monitoring, so just the appropriate agencies work together."

Then, we typically say blood organizations rather than blood agencies, because we typically call the federal agencies "the agencies." So, I would change the word "agencies" to "organizations," and I would strike the words "including but not limited to the CDC, FDA, and PHS."

DR. HEATON: And I agree, I accept that.

MR. SKINNER: Any other comments? Dr. Kuehnert.

DR. KUEHNERT: Yes, this looks good. I just wonder if concerning to work together with the blood agencies, if there should be any language about the task

force, since it has led a lot of the activities to date that would sort of lead to these possible interventions. I just put that for a suggestion.

MR. SKINNER: Just for the screen, do we need to go back and review what the edits were that we have agreed to? I am sorry. So, there is the parentheses in the final recommendation, delete the parentheses and what is in it, and also delete the wording--

DR. HEATON: CDC and PHS.

MR. SKINNER: Through PHS, and then I think we need to delete the word "including." Delete that and then the word "including" before that.

Then, in the next section, there is blood organizations where you have blood agencies, and the next part of that same section. Change that to "organizations." Change "requests" to make requests plural, "HHS requests the appropriate agencies."

Back on the question of the task force, was there a suggestion?

DR. KUEHNERT: I am not really suggesting any language although I could. I just wanted to make sure the committee was on-board with the concept, but the way it

reads now, "work with the blood organizations," but it doesn't say how. There is no mechanism. I am just wondering is it implied that it is the task force, or is something new.

If it is not something new, then, it might be better to specify through the task force.

DR. HEATON: One of the issues we need to deal with, we have added in "surveillance of transfusion-associated sepsis," which will pick up representatives more of the hospital community and probably less of the blood manufacturing community, so the task force members probably would wish to be on this, but you would want it more biased towards public health service and hospitals.

MS. LIPTON: I am sorry, I couldn't hear everything you said, but if it needs to be more inclusive, we can certainly do that. Was that the issue?

DR. HEATON: Well, Matt was suggesting that instead of saying "blood organizations," it would refer specifically to the task force, but the task force at the moment is biased towards the regulators and those who manufacture the blood, whereas, this would involve

surveillance of transfusion recipients and would therefore be more hospital oriented.

MS. LIPTON: I agree, but I mean I think if we are trying to get to the hospital, a good way is to go through the AABB if we are going to do something like that. We have had the Bacon study before, which we did through AABB, which is a bacterial contamination study through the CDC.

I mean I think it could be constructed. I think what we are just trying to figure out, is this intending to, or what Matt was asking, does this mean they are working individually with each of these organizations, or should there be sort of a focal point at which all the blood organizations come together.

DR. HEATON: I believe there should be a focal point at which all the blood organizations come together, and that appropriately, CDC should be the nidus of that, but I also believe that we shouldn't specify the particular agency, the Secretary of HHS.

MR. SKINNER: Jay, did you have a comment?

DR. EPSTEIN: Yes, I have a few technical comments. In the first paragraph, the post-approval information is on the quality control tests, so it is,

"Allow collection of post-approval information on quality control tests to support applications for the approval of as release tests of that bacterial detection assays."

It wasn't clear to me whether your intent was to further comment on post-approval information on the release tests, because that is a piece of it, too. These are two different things here.

DR. HEATON: It was. I mean this is a significant step forward and I felt that the ACPSA should acknowledge that, so I did want this to be technically accurate.

DR. EPSTEIN: So, it should say, "to collect post-approval information on quality control tests to support applications for approval of bacterial detection assays," and right after the word "assays," add the word "as release tests."

Then, you wanted then to say, you know, "Additionally, the committee supports collection of post-approval data on release tests to confirm their sensitivity and the residual risk of bacterial contamination."

DR. HEATON: Yes.

DR. EPSTEIN: Because these are two different things.

DR. BRECHER: Also, isn't it that it is not just to reduce the risk of bacterial contamination, but also to alleviate problems or availability?

DR. EPSTEIN: Well, it gets into the whole question of extension of dating, right? I mean we can add, "to reduce the risk of bacterial contamination of platelet concentrates and to facilitate the availability of 7-day platelets," something like that.

DR. HEATON: Yes.

DR. KUEHNERT: Just the availability of platelets.

DR. EPSTEIN: Fine.

Then, again, it's a technical point, but the Phase IV protocols don't actually include monitoring for clinical safety. It is unfortunate that they don't, but no one really thinks we can incorporate monitoring of clinical sepsis into that protocol.

The protocol consists of doing the culture on day 7/8, which is short. We are, of course, encouraging the reporting of adverse clinical events, but again, that is not the core of the protocol, because we have no way to ensure that reporting. The only thing we can ensure is the culture will be done. That is on the outdating unit.

DR. HEATON: Yes. We should delete "monitoring of the clinical safety." It is really monitoring of the product safety and efficacy is the point you are making.

DR. EPSTEIN: Well, what we should say instead is say "in parallel with monitoring of the clinical safety, efficacy of screening concentrates."

DR. HEATON: Okay.

DR. EPSTEIN: Of course, we encourage complete reporting of any breakthrough episodes, but we have no way to ensure that in the protocol. The protocol consists in performing the culture and reporting the culture.

MR. SKINNER: Dr. Holmberg.

DR. HOLMBERG: Going back to the first paragraph, I think it would read smoother if it said, "to reduce the risk of bacterial contamination and to facilitate the availability of plate concentrates."

DR. HEATON: I don't know. I like the idea of keeping the 7-day platelets. This is innovative in that we are both improving safety and improving availability. It is not often that you get both outcomes in one approach.

MR. SKINNER: Dr. Kuehnert.

DR. KUEHNERT: I am still thinking about the third paragraph, about this work together with the blood organizations. Looking at that second bullet about surveillance of transfusion-associated sepsis, it is not really the organizations that primarily are going to detect these, so I think I would recommend you think about expanding that group, you know, blood organizations, health care facilities, clinicians. I mean it is clinicians that are actually going to pull the trigger on that second bullet for surveillance.

DR. HEATON: Maybe we could say blood manufacturing and transfusion organizations.

DR. EPSTEIN: Our term of art is "blood establishments."

MS. LIPTON: I don't think most transfusion services think of themselves as blood establishments.

DR. EPSTEIN: Legally, they are.

MS. LIPTON: Right, but I mean it is not going to resonate with them. I think getting into this idea, half of this is going to be clinicians recognizing what they are looking at.

DR. KUEHNERT: I think establishments, organizations, all that, but it really is clinicians.

DR. BIANCO: How can you revive the Bacon study? That is essentially what you are trying to say.

DR. KUEHNERT: I wouldn't want to revive it. I think that it did what it could, and I think we need to think differently this time, not to discourage hearing the word again, but I think we need to think differently.

DR. BIANCO: Thinking differently, I don't think we can do here in the committee. I think that will depend very much on the way FDA includes that statement about Phase IV studies and what they require from the manufacturers. That is going to drive the effort to get both the culture data and also the clinical data.

DR. KUEHNERT: I agree with you that that will enable it, but you still need to reach the clinicians. I mean in a survey that we did recently of clinicians, 20 percent said that they were aware that there was any effort to culture platelets.

MR. SKINNER: Be mindful of time. Is there a specific language that we want to propose?

DR. BIANCO: I think we should leave it vague and let the system work it through. I still believe, and Jay can change our minds, but that this is going to come, that is, the power of enforcement. The only organization that has the power is FDA, and the blood banking organizations are going to divulge the message and try to convince everybody that this is the right thing to do, because FDA told us that that is the right thing to do.

CDC can beg, but FDA can mandate.

DR. HEATON: Celso, the point Matt is making is that the FDA regulates blood manufacture, but not the practice of medicine, so what we need to do is to add in the blood manufacturing and transfusing organizations.

DR. BIANCO: But FDA was able to do that in the old times of HCFA, to add lookback to the regulations. There are mechanisms, I am sure, creative mechanisms by which the--

DR. HEATON: Lookback wasn't regulated on the transfusing physician. It was incumbent upon the blood bank to tell the hospital that it wasn't--the practicing doctor didn't have to notify his patient.

MR. SKINNER: Dr. Holmberg.

DR. HOLMBERG: Could we say "blood organizations and transfusion services?"

MR. SKINNER: Is there any objection?

MS. LIPTON: Yes, you could just say "blood collection and transfusion facilities," and in that way you have blood collection organizations and transfusion facilities, and you have got the whole group in there without--

MR. SKINNER: "Blood organizations and transfusion facilities." Okay.

Any comments on any other parts of the recommendation? Dr. Holmberg, do we need to read it for the record or can we vote on it as it is on the screen?

DR. HOLMBERG: Let's read it.

MR. SKINNER: You are sitting closer and your eyes are better than mine, if you could read it, please.

DR. HOLMBERG: "The Advisory Committee of the Blood Safety and Availability acknowledges the innovative regulatory pathway proposed by the United States Food and Drug Administration allowing collection of post-approval information on quality control tests to support application for the approval of bacterial detection assays as release

tests to reduce the risk of bacterial contamination of platelet concentrates and to facilitate the availability of 7-day platelets.

"Whereas, the approval process as proposed will require the capture of accurate information describing the extent of bacterial contamination of platelet concentrates, the capacity of diagnostic tests to detect this in parallel with monitoring of the clinical safety, efficacy of screening concentrates, the requirement for post-approval monitoring of bacterial contamination events may not persist beyond final approval.

"The committee recommends that the Secretary, HHS, requests the appropriate agencies to work together with the blood organizations and transfusion facilities to establish an ongoing program to monitor residual bacterial contamination risk and generate summary reports and provide resources for surveillance of transfusion-associated sepsis and make such additional recommendations as may be needed to maintain recipient safety."

MR. SKINNER: You have heard the resolution. Any other discussion?

All in favor, raise your hand.

Opposed?

The motion is adopted unanimously.

DR. EPSTEIN: Mark, can I just mention that there are a few points here where the grammar and punctuation do need correction?

MR. SKINNER: Yes. The record should note that the Department has the authority to correct and clean up any grammar and language that is necessary.

DR. BIANCO: And kindly mail to us the final version.

DR. BRECHER: Yes, we will e-mail around the final resolution before we forward them to the Secretary for everyone to see.

Maybe we could put the resolution that Jay drafted on the screen.

DR. EPSTEIN: The proposal reads as follows: The committee finds that current reimbursement schedules for plasma-derived products and their recombinant analogs are not adequate to support optimal patient care.

The committee therefore recommends that the Secretary should take steps to augment reimbursement of plasma-derived products and recombinant analogs. The

committee endorses the following principles to guide such efforts.

Plasma-derived products and their recombinant analogs should be reimbursed at rates consistent with their true costs including costs of distribution and administration. Individual products within product classes should be recognized as unique.

Equivalent reimbursement should be provided in different care settings, and co-payments should be kept affordable.

MR. SKINNER: I guess I have a question about the last sentence, "co-payments should be kept affordable." I mean that is kind of an abstract number, when the presentation that we heard is that there should in essence be no co-payment, so I am wondering if this is consistent with the information that we received or if we should have a whereas or something, that the current co-payment structure is unaffordable, so that at least there is some context for that last bullet.

DR. BRECHER: I guess we could have an e.g., for example, that completely eliminated stopgap or something in between.

DR. EPSTEIN: We could say, "co-payments should be eliminated or rendered affordable," because I don't think the principle is no co-payment. I mean, you know, if it were a dollar a dose, there wouldn't be a big furor.

MR. SKINNER: I think that takes into account what I was saying.

DR. EPSTEIN: The proposal is to revise it to say, "Co-payments should be eliminated or rendered affordable."

DR. HEATON: I don't know that that is consistent with practice anywhere else. I am not aware of any other health care service that does not have a co-payment.

DR. BRECHER: Besides chronic renal failure.

DR. HEATON: Besides chronic renal failure, and I don't believe that we should take such an aggressive position. I believe that co-payments should be affordable, but for us to go on record that they should be eliminated, I very much doubt the Federal Government would create another renal program, and I don't know that we should be on record as seeking to create a second one.

MR. HAAS: I think the renal program is a very good example to be concerned about. I would think--and this is something that I know the bleeding disorders community

has to do a little more work on--but it would be my guess that making the factor, say no co-payment, you are not going to see an increase in usage, because it is not something like diseases that progress.

There is a technicality here, and I think the issue becomes one of what gets into the principles language. In some cases, zero co-payment might make sense, and in other cases, it might not.

MR. HEALEY: Just to comment on the second bullet, I guess, I like it. The only concern I have is that some of the therapies, for example, IVIG, are recognized as sole source therapies, but then they are bundled together under these J codes, so under the current structure, they are sort of both at the same time.

So, I am wondering if that could be revised to say, "Individual products with product classes should be recognized as unique for the purposes of reimbursement" or somehow link it back, so that that unique nature of them is tied to the reimbursement schedule, more directly rather than by reference to the superseding paragraph.

DR. BRECHER: Jerry.

DR. HOLMBERG: I think you want to convey the thought that each individual product is unique for that individual recipient. I mean that becomes very clear on the reimbursement aspect.

DR. BRECHER: Celso.

DR. BIANCO: Actually, I think that if you say "for reimbursement," you are taking away the medical character of what was presented to us today. It is just because of money we are going to divide them into different pieces.

We want to say that they are medically unique.

MR. HEALEY: I agree with you, but I think that is well recognized by the medical community, certainly by the patient communities, and I thought that the purpose of the resolution was to address the reimbursement needs where that recognition hasn't been fully acknowledged or fully realized.

DR. BIANCO: I just think that we have to say both. We have to say that they are medically unique.

DR. BRECHER: Well, you could say unique in terms of efficacy and reimbursement. State the facts. You don't like efficacy?

MR. HEALEY: It sounds like there are good products and bad products, some are more efficacious than others.

DR. BRECHER: For particular patients, that is probably true.

MR. HEALEY: The is why I was throwing that term, for individual patients.

DR. KLEIN: I would probably say "for therapy," because efficacy doesn't include safety, and there are certainly safety issues in the individual products.

DR. BRECHER: Take out "efficacy" and insert "therapy."

DR. BIANCO: That sounds good.

DR. BRECHER: Are there other comments or suggestions?

DR. BOWMAN: I wonder if it might be better to say something like, "The individual products within broad classes should be recognized as therapeutically unique for individual patients or each individual patient" to stress the clinical aspect that you are trying to drive at.

DR. BRECHER: That would put the emphasis at the end of the sentence back on reimbursement. I think we are trying to go off of that a bit.

Paul.

MR. HAAS: I think your beginning paragraph has the emphasis on reimbursement. I am not sure it is necessary in that bullet, and if we change the language around, as Jim was suggesting, then, it is getting to the point that we are trying to identify.

DR. HEATON: That was a good suggestion.

DR. BOWMAN: I just want to go on record that that is not necessarily my personal or professional or clinical opinion. It is just for the benefit of the committee.

DR. BRECHER: For the record.

So, why don't take "reimbursement" out, move the word "therapy" in front of "unique," therapeutically unique. Then, get rid of "in terms of therapy and reimbursement."

DR. BIANCO: But what about adding the words "for individual patients"?

DR. HEATON: That is what unique is.

DR. EPSTEIN: What troubles me here is a logical issue. If the products were not different, they couldn't

have different effects on different patients, so it is really part and parcel of the same thing, to say that you need to customize the product to the patient is to recognize that the products have intrinsic differences.

Whether it is important from a communication point of view to mention the individual patient, I think is fine, but it is not really a different issue.

DR. HEATON: Is it the goal of the committee to keep "should be eliminated" in? I continue to be opposed. I believe this would create a standard of practice that is quite different from that in the industry. I believe a co-payment should be kept affordable, but I believe "eliminated" would be extraordinary.

MR. SKINNER: I think we at least need to take note that we are dealing with an extraordinarily expensive condition, and I could be corrected, but I think that hemophilia is the single most expensive chronic disease for which there is a therapy.

So, it not that--I mean we are dealing with something extraordinary. I mean if I am going to pay $20,000 a year of a $100,000 bill or 30- or $40,000 a year, or as Dr. Metz indicated, 20 percent of 300,000, I mean

where does affordable come? The percentage really doesn't solve that problem, because the dollar amount goes up, so how you create a formula that is affordable for everybody, I think is extremely difficult.

I am not sure there is a solution other than eliminating it, which creates affordability for all.

MR. HEALEY: Is there a way to, rather than say "eliminate the co-payment," say "rendered affordable or funded through an alternative means that would eliminate the burden on the patient" or "on the user," or something like that, because what you are trying to get at is the user's responsibility, it is too expensive for the users to pay. Technically, whether you change the statute or whatever to eliminate the co-pay is really irrelevant. It is how you get it funded.

DR. HEATON: Well, we could say should be capped.

DR. BRECHER: That would be "eliminated, rendered affordable, or capped." Capped may be one way of rendering it affordable.

DR. HEATON: That is my perspective. I am concerned that we not end up making extraordinary recommendations.

DR. BRECHER: Maybe capped would be like an e.g., for rendering it affordable.

MR. SKINNER: How about "All options should be explored to render co-payments being affordable from capping to elimination," something.

DR. SANDLER: I think what we are missing in this very last item is the concept that this is a life-long financial burden. I think that that is how renal dialysis got their exemption. It is not that you go in for one shot and get titanium hips, and it is expensive, it is that it is a life-long burden, and I don't know how to word it.

MS. LIPTON: Mark, you could just say on the bottom, instead of eliminated, you could just say, " Co-payments should be rendered affordable for over the life of the patient or the recipient," so you do have that long-term view that it isn't just one time you are going in there, it is can a person in their lifetime afford these therapies, and that may mean, if you have to render it affordable, it may mean that it is a penny co-payment each time.

DR. BRECHER: It sounds like the sense of the committee is that we need to have life-long in there

somewhere. The question is does it go in the last bullet or do we put it in the introductory paragraph.

DR. HOLMBERG: I think what Mark was saying, I think it really belongs up at the top where you are setting the stage for it.

DR. BRECHER: So we could say "to support optimal patient care in these life-long conditions" or how would you--

DR. BIANCO: I really think that it is going to get lost up there. I think that it has to be connected with the cap. It's a life-long cap, a life-long payment or co-payment, and that is what you want to emphasize in a certain way.

DR. BRECHER: Solomon to my right here has suggested we put it in both places.

DR. GOMPERTS: I have another issue. One of the major challenges over the last few years, that the committee has actually dealt with, is supply. We have gone through phases whether it is IVIG or recombinant clotting factor concentrates or whatever during serious supply shortage issues.

Part of the reimbursement, not direct, but certainly from a long-term point of view and particularly in regards to a life-long disorder, is a continuity of supply, so somehow of other, perhaps with a second bullet point, we can put a life-long component in there together with the supply verbiage.

DR. BRECHER: I am not sure that the second bullet point would be the place for that.

DR. EPSTEIN: Back on the earlier point, not to lose Ed's point, but I think one suggested revision of the first sentence would be, "The committee finds that current reimbursement schedules for plasma-derived products and their recombinant analogs for treatment of chronic conditions are not adequate to support optimal"--and I am suggesting that we change it from "patient care" to "care of the individual patients," and that is back to Dr. Bowman's point that we really want to emphasize that this is a problem for individuals, because there are those who might argue that, you know, well, care on average is adequate, and that that sort of misses the whole point, which is that the reimbursement problem--

DR. BRECHER: We don't want to take of the average patient, we want to take care of the majority of patients.

DR. EPSTEIN: Right.

DR. BRECHER: Do we want to include another bullet point, then, about supply? Are you drafting something perchance?

Jim.

DR. BOWMAN: While he is drafting it, let me, if you don't mind, go back to that last bullet of "Co-payments should be eliminated" and back to what Dr. Heaton I believe said. I think he has got a good point that the problem isn't the concept of a copayment, it is the fact that it is a horrendously expensive co-payment over the course of a year or 10 years or lifetime.

Something that might convey the same intent and message, but less dogmatic in terms of just eliminating co-payment as the solution to everything, might be something like the "financial burden of onerous life-long co-payments should be addressed in an appropriate fashion" or blah-blah-blah, something to call attention to it, but not to tell the Secretary to eliminate co-payments, which he or she doesn't have the discretion to do anyway, to be honest with you.

DR. BRECHER: Repeat that slowly.

DR. BOWMAN: The financial burdens of onerous life-long co-payments should be minimized or alleviated, ameliorated. You have to get at the source or something, but--

DR. BIANCO: I had an alternative to yours, Jim, that was, "Co-payments should be adjusted taking into account the lifetime character of the disease."

DR. SANDLER: I have an alternative to yours, Celso. How about simply, "Costs to patients should be rendered affordable," not getting into the mechanisms, which is a bit out of our purview.

MR. SKINNER: How about one more option? The one I wrote down was, "The life-long cost of treatment to the end user must be considered in any pricing structure including the extraordinary impact of co-payments."

DR. BRECHER: Is everyone happy with that? Okay. Say it slowly, so they can type it in there.

MR. SKINNER: "The life-long cost of treatment to the end user must be considered in any pricing structure including the extraordinary impact of co-payments."

DR. BRECHER: Do you think we could substitute the word "individual patient" rather than "end user?"

MR. SKINNER: Sure. You can call me whatever you want.

[Laughter.]

DR. KLEIN: How about, "must be addressed." I would like to see more than considered.

DR. BRECHER: Take out the word "considered" and add the word "addressed."

MR. SKINNER: These are long-term principles that I think we are articulating, so I don't know that we want to tie it to something specific, because I understood we are setting principles for the future.

DR. BRECHER: Is "including the extraordinary impact," is that a parenthetical statement after "pricing structure" should be put in parentheses?

DR. BIANCO: It just needs a comma after the "pricing structure."

DR. HOLMBERG: I was going to go back to another one. Are you still working on this one?

DR. EPSTEIN: On this point if you could indulge me. I was going to suggest that "must" be changed to

"should," because these are recommendations. "Life-long cost to treat individual patients should be addressed."

DR. HOLMBERG: While he is typing that, let me go back to the "Equivalent reimbursement should be provided in different care settings." Could we say, "Equivalent reimbursement should be harmonized"?

MR. SKINNER: How about parity of reimbursement across treatment settings? I think that is the phrase that we used before.

DR. HOLMBERG: Okay.

DR. EPSTEIN: Mark, on the recently added last bullet, it strikes me that shortages in supply of the needed therapeutics has impacted the health care of these life-long disorders is a finding rather than a statement of principle, so that part of the point I think belongs in the opening paragraph somewhere, and then we need to sharpen what it is we want to say about it in that bullet, but the first part is a finding.

DR. BRECHER: Put that bullet up to the bottom of the intro paragraph and let's see how it fits there, before the last sentence.

DR. EPSTEIN: I would just make it the second sentence. Just say, "Additionally," the second sentence of the first paragraph.

DR. BRECHER: I don't know that we need to say, "consideration of reimbursement" at that point. We are going to be talking reimbursement later, so I would put a period after "life-long disorders" and drop that.

DR. EPSTEIN: I think what we are looking for in the added bullet is something along the lines that reimbursement policy should avoid untoward impacts on product supply.

DR. BIANCO: Actually, I thought we could say in a positive way, Jay something like reimbursements should be sufficient to ensure a steady supply of those therapies.

DR. BRECHER: Or adequate supply.

DR. BIANCO: Or adequate supply.

DR. BRECHER: Say it slowly.

DR. BIANCO: Reimbursement should be sufficient to ensure an adequate supply of these therapies.

DR. EPSTEIN: That should be the second bullet, because it is really logically the same thing as the first bullet. If you cover the real costs, you can ensure that

they will continue to be made. I think it is okay to have it as a stand-alone point, but i would make it the second bullet because it is related to the first.

DR. BRECHER: The scenario I can see is that you cover the costs of one product, but there is another manufacturer whose costs are much higher. You are going to drive them out of business.

DR. EPSTEIN: But that conflicts with recognizing them as unique. In other words, if you recognize them as unique, you reimburse each of them at their real cost. I am okay with the bullet, I am just suggesting we make it the second bullet.

DR. BRECHER: Are we happy? All those in favor of being happy, raise their hand.

DR. BRECHER: Rich is happy. Well, that is unanimous.

Let's look at the other one quickly, nine minutes or less. Is this the one you mean, Paul? It looks in some ways very similar.

MR. HAAS: I think what it does is take what we heard today and all the "whereas's," and when we get down to

the last statement, I am hoping there is nothing controversial in that, because that is what we were hearing.

Get down to the bottom. The "resolve" statement is simply encouraging the Secretary to be supportive of any legislative action that would relate to the very things we have been talking about. So, it doesn't ask the Secretary to do anything other than to be supportive.

DR. BRECHER: I am not sure that the intent is that different than what we have already just said, Paul.

MR. HAAS: I guess I would differ in the sense that those in the bleeding disorder community feel a real strong need to have the specific statement of their conditions in, take Mark's comments a little bit earlier in terms of the impact of this 20 percent on this population is incredibly high.

DR. BIANCO: Is there a way that we could blend that last statement into the previous resolution?

MR. SKINNER: Mark, if I can comment. I think the difference is the last one was a set of guiding principles that would stand the test of time in terms of how the committee thought reimbursement should be structure. So,

that is kind of a bedrock of what the committee wants to use going forward.

So, that is the general. This is the specific as to how those principles relate to where we are today, so I tend to think that they should be separate, because the other one covers all of the plasma user communities, not just hemophilia. It was generic in terms of plasma users.

This one then translates that specifically.

DR. BIANCO: But we could that is in addition, the Advisory Committee urges the Secretary to support any proposed--and at the end of the thing, the principles are there, and then we are asking for support at the legislative level.

It is just that I think they are too independent. They dilute each other. It is my own gut feeling.

MR. HAAS: In the spirit of what we have done, I think I am going to be repeating Mark, is that you want the principles to stand alone, and then when we start dealing with specifics--or this is the short-term process--but specific issues, I think they should be standing alone, because you put them together, you are going to be confusing the general principles with specific actions.

MR. HEALEY: I would just like to support that. I think this is a stand-alone. I could even envision a separate resolution for each of those principles that was just articulated. There might be one of the unique nature of therapies, and I think it is important to give some specific recommendations to the Secretary that further elucidate those principles.

DR. BRECHER: What is the pleasure of the committee? Let's just break this down. Do we want to have a separate resolution or do we want to hybridize the two?

All those in favor of a separate resolution, raise their hands.

All those in favor of hybridizing?

Okay. So it is going to be a separate resolution. Do we want to wordsmith this?

DR. SANDLER: It is really quite benign in a sense where it is just urging--we have a recommendation and we are urging the Secretary to work with a task force to explore something. I mean it's a motherhood statement. It seems very easy to let it go through.

It is not terribly specific or demanding.

DR. BRECHER: Andy.

DR. HEATON: It seems funny for me, coming from a socialist country where health care is provided free, to raise concerns here, but the United States health care is always assumed to not be funded by an individual who is acquiring the services.

There are very few areas in the United States where health care is provided at 100 percent cost to the government. I understand the issue here, which is lifetime costs and extraordinary medical expense, but I think that we would be ill advised to deviate from the concept that there is always a partial patient responsibility.

So, I am concerned to see this 100 percent of Medicare coverage providing that--I mean it is not clear to me whether this motion includes the residual co-pay that a Medicare beneficiary would make anyway.

DR. BRECHER: Could you move that up and see the top a little bit again?

DR. KLEIN: You might be able to solve that problem by eliminating the 100 percent and simply going down to the point at the bottom where you work with the task force to alleviate the burden.

MR. SKINNER: This probably isn't the place to debate social policy through insurance, but I think there is a history of community rating and insurance where the nature of insurance is that we aren't insuring the individuals, we are insuring a class of individuals, and certainly that principle holds true as it related to Medicare and the federal insurance mechanisms.

So, to say that we insure the individual, that is not the way at least the federal system is, and our concern I think is that the way these federal policies can translate out to individual society in the third-party payer policies that are available commercially, and we don't like the trend for people particularly with chronic diseases where they are forced in a situation where they are insured individually, and it renders insurance unaffordable, and at least the concept of community rating as it relates to insurance should be preserved in the federal system, and therefore, hopefully, that will carry forward into the private system.

DR. BIANCO: Mark, I think we understand that, but let's be a little bit realistic with the current administration and Congress. I think that you say 100

percent, you are not going to get the next Secretary of HHS very excited. It is not going to be his first commitment.

MR. HAAS: I think we need to remember that two-step aspect of this. This is asking the Secretary to be receptive to something, and those who wish to try to achieve this have to fight that very burden that you are identifying.

Going back to Andrew's point, in a typically market-based type of system, the concern that Andrew is raising in my literature is called moral hazard, which means the lower you drop a price, the more people treat it as a free good, and overuse of it.

I made a quick reference to that point a little bit earlier. Although we don't right now have the hard data, it is our pretty high expectation that the use of clotting factor isn't going to jump dramatically because it's cheaper, because you take what is therapeutically necessary and move forward.

The protocol now is for prophylactic treatment. If this was back in the days when my sons were younger and were treating on a crisis basis, and we said this, it would

have made a huge difference in the use of factor, but that protocol has changed.

So, I think we need to keep in mind that the nature of this particular recommendation doesn't fall under the same rules of this moral hazard that is a big issue in typical product markets.

DR. BRECHER: It is now 6:30. This is the time this meeting is scheduled to adjourn. We can either vote on this or we can table it and take it up again tomorrow.

All in favor of coming to conclusion today, raise their hands. Six.

All who would like to table it and start again tomorrow? It is close.

I guess we are going to try to fix it today. Jim.

DR. BOWMAN: Just to echo what Celso said, you are specifically asking the Secretary to support a legislation that has a very specific thing to eliminate the 20 percent co-pay, which is what cover 100 percent really means.

If you say to support policy legislation that would ameliorate or reduce again the onerous financial burden of the existing 20 percent co-pay, it says the same thing, conveys the same message, but it is not like telling

the Secretary how to do his job is the only reason I say it like that.

MS. LIPTON: I agree with that. I mean my concern is that it makes us--you know, it will just fall on deaf ears. I think what we say is if someone wants to propose that, we have these principles behind there, that they could say, well, yes, these are the principles against which we analyze any piece of legislation, we are in favor of that.

I think we are so likely to get a not good response to this, and then we have kind of done ourselves in. I would rather see us, you know, again, work with the community to reduce it to affordable over the lifetime, which I think is what we are really talking about.

DR. BRECHER: Jay.

DR. EPSTEIN: I think if we condensed the first and second sentences of the resolution to say, "Urge the Secretary of Health and Human Services to support any proposed policy and/or legislation to reduce the extraordinary financial burden for said beneficiaries."

MS. LIPTON: I think "address" is better than "reduce," because you could reduce it by small amounts.

DR. EPSTEIN: To address. I would say, "to address the extraordinary financial burden for said beneficiaries," and then strike everything else.

DR. BOWMAN: Just one more thing, just very minor, but do you have to say "for said beneficiaries," or could you say "for these beneficiaries?" It sounds awful bureaucratic.

DR. EPSTEIN: Well, likewise, the "Be it resolved," we can just say, "The committee recommends" or "The committee urges the Secretary."

DR. BRECHER: We can always say "end users."

DR. EPSTEIN: Individual end users."

[Laughter.]

DR. BRECHER: Individual patients. I like getting the word "patients" in these things.

DR. EPSTEIN: I think we should just say, "In parallel structure, the committee urges the Secretary."

DR. BRECHER: Can we say "patients" rather than "beneficiaries" at the end?

All right. Is everybody happy? All in favor of being happy? All opposed?

It carries. See you tomorrow.

[Whereupon, at 6:37 p.m., the proceedings were recessed, to reconvene on Wednesday, January 26, 2005.]