DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

Twenty-Fourth Meeting

Volume I

Thursday, August 26, 2004

9:00 a.m.

Hyatt Regency Washington
400 New Jersey Avenue, N.W.
Washington, D.C. 20001

PARTICIPANTS

Mark Brecher, M.D., Chairman
Jerry Holmberg, Ph.D., Executive Secretary

VOTING MEMBERS

Larry Allen
Judy Angelbeck, Ph.D.
Celso Bianco, M.D.
Edward D. Gompert, M.D.
Paul Haas, Ph.D.
Christopher Healey, J.D.
William A. Heaton, M.D.
Jeanne Linden, M.D.
Karen Shoos Lipton, J.D.
Lola Lopes, Ph.D.
John Penner, M.D.
S. Gerald Sandler, M.D.
Merlyn Sayers, M.D., Ph.D.
Mark Skinner, J.D.
John Walsh
Wing-Yen Wong, M.D.

NON-VOTING MEMBERS

James S. Bowman, III, M.D.
Jay Epstein, M.D.
Harvey Klein, M.D.
Matthew Kuehnert, M.D.
CDR Michael Libby

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Conflict of Interest

DR. HOLMBERG: Good morning. It's a couple minutes after 9:00 and we really need to move forward. As you may have noticed by the agenda, we have a full day both today and tomorrow, a lot of issues to review.

I would imagine that today we will probably be here until 6:30. It is going to be a long day, so we will try to take the breaks appropriately and consolidate when we can.

I would like to open the 24th meeting of the Advisory Committee on Blood Safety and Availability. As far as the conflict of interest statements, we have discussed that with the committee members at previous meetings. The bottom line is that if there is any potential conflict or any perceived conflict, that you please state that before you talk.

I would also offer that same recommendation to the speakers, the public forum speakers, for you, when you come to the mike, that

you identify yourself and any affiliation that you may have.

At this time, I would like to take a roll call.

Dr. Brecher.

DR. BRECHER: Present.

DR. HOLMBERG: Larry Allen.

MR. ALLEN: Present.

DR. HOLMBERG: Dr. Angelbeck.

DR. ANGELBECK: Present.

DR. HOLMBERG: Dr. Bianco.

DR. BIANCO: Here.

DR. HOLMBERG: Gargi Pahuja.

[No response.]

DR. HOLMBERG: Dr. Penner.

DR. PENNER: Here.

DR. HOLMBERG: Dr. Sandler.

DR. SANDLER: Here.

DR. HOLMBERG: Dr. Gompert.

DR. GOMPERT: Here.

DR. HOLMBERG: Dr. Haas.

DR. HAAS: Here.

DR. HOLMBERG: Chris Healey.

MR. HEALEY: Here.

DR. HOLMBERG: Dr. Heaton.

DR. HEATON: Here.

DR. HOLMBERG: Dr. Linden.

DR. LINDEN: Here.

DR. HOLMBERG: Now, this next person, we just changed titles on, and if you will notice his name tag, he is now a lawyer. Dr. Sayers.

DR. SAYERS: Jerry, that was never a qualification that I aspired to, so I regard that insult as just an unintended slight.

DR. HOLMBERG: With that comment, I will see whether we have another lawyer present. Mark Skinner.

MR. SKINNER: Present.

DR. HOLMBERG: John Walsh.

MR. WALSH: Here.

DR. HOLMBERG: Dr. Wong.

DR. WONG: Here.

DR. HOLMBERG: Another lawyer, Karen Shoos Lipton.

MS. LIPTON: Present.

DR. HOLMBERG: Dr. Epstein.

DR. EPSTEIN: Here.

DR. HOLMBERG: Dr. Lopes.

DR. LOPES: Here.

DR. HOLMBERG: Dr. Klein.

DR. KLEIN: Here.

DR. HOLMBERG: Dr. Bowman.

DR. BOWMAN: Here.

DR. HOLMBERG: Dr. Kuehnert.

DR. KUEHNERT: Here.

DR. HOLMBERG: Commander Libby.

CDR LIBBY: Here.

DR. HOLMBERG: I just want to comment that since we met the last time, Colonel Sylvester has retired from the Air Force and Commander Mike Libby has replaced her as Director of the Armed Services Blood Program Office, and we are glad to see Mike joining us. Thank you.

Dr. Brecher.

Chairman's Comments

Mark Brecher, M.D.

DR. BRECHER: Thank you, Jerry.

I would also like to welcome all the committee members back for this meeting, particularly Celso, we are glad to see him back.

[Applause.]

DR. BRECHER: We have a packed agenda. We will stay on time, if not ahead of time, so I will keep a close eye on the clock.

I just wanted to mention one comment about the charter. We have a two-year charter that will expire in October of this year. The new charter is I understand already submitted and we are not anticipating any problems with getting that approved. That will be again for two years.

With those comments, I would like to give the mike back to Jerry for a review of the committee's recommendations.

Topics: Committee Activity and Follow-up of Recommendations

Review of Advisory Committee Recommendations

Jerry Holmberg, Ph.D.

DR. HOLMBERG: Before I move on to a

review of the recommendations, I do want to bring everyone's attention to the upcoming meetings in our Fiscal Year 2005. We will be having a meeting on December 8th and 9th, and then also May 25th and 26th, and September 7th and 8th of next year. We tried to avoid January because of the weather and the unpredictability of the weather. Of course, I just heard that Dr. Lopes got stuck in O'Hare and Dr. Busch, who is speaking to us tomorrow, also had some problems getting here. This is the summertime, but usually, that happens in the afternoon, difficulty with flights.

Just to tell you also that presenting these dates to you is really unofficial. The official notification will be in the Federal Register, and also, a draft agenda will be posted one week before the meeting. I hope people have seen the web page. We tried to identify and make it as clear as possible that we were changing venues this last time from the Metro Center location to this facility.

The last time I was in this room, I wasn't

real pleased with this room, but I hope that we have corrected some of the problems. I think the last time I was here, people were speaking to the gallery the way things were set up, so I know this is not the most ideal room, but if there are problems with that side of the room, seeing the screen, please feel free to move, so that you can see.

What I would like to do is go back and sort of do a self-reporting on ourselves. This is intended for the committee to look at some of the recommendations we have made over the years.

I initially tried to go back to 1997 and I thought that it would be just overwhelming, and I did not have enough time, besides many, many of the issues have resurfaced numerous times and we have tried to bring focus to the issues that need to be presented to the Secretary.

So, I will start with the last meeting, the first recommendation, and I have paraphrased these quite a bit, was to reiterate recommendations of the January 2004 meeting, and we will go back to

that in just a few minutes.

What I would like you to do as committee members, if you see issues that you think that we need to follow up on and more attention, please make those comments. We can either address them at the time or we can wait until after and discuss them later during the committee discussion period.

The second recommendation endorses the MMA Conference report statement that the Secretary is directed to compile and clarify procedures and policies for billing of blood and blood costs in the hospital inpatient and outpatient setting, as well as the operation of the collection of the blood deductibles, and then, of course, a timely response on the above.

I included in your package, in the notebook, a letter that was sent back to Dr. Brecher from Secretary Thompson, and I would draw your attention to the second paragraph. I don't have the letter in front of me right at the present time.

I know you all can read, but let me just

read this for clarification, because I think it really sets us in the right direction.

"The committee's comments on reimbursement at the meeting and at previous meetings indicate a continuing concern from the collector, provider, and user of blood and plasma products including the plasma clotting factor analogs. The three recommendations of the Advisory Committee for Blood Safety and Availability from April require more discussion. I am referring these recommendations to Dr. Christina Beato, Acting Assistant Secretary for Health, and Dr. Mark McClellan, Administrator for the Center of Medicare and Medicaid Services, for evaluation by their staff."

I think that that paragraph really sends a message and opens the door for much more discussion. We have already had discussion within the Department, talking to CMS, and we are now in the process of putting together agenda items for that meeting, so we are moving in the right direction.

Again, in April, we talked about the

Secretary to exclude blood clotting factors from competitive acquisition under the Exclusion Authority. The Secretary should use the authority contained in the MMA to exclude all blood products and transfusion medicine services from the establishment of quality standards and competitive acquisition provisions.

Again, these are topics of discussion that will be forthcoming between Dr. Beato and Dr. McClellan.

Also, in April, there were recommendations concerning the bacterial contamination of platelet products. The committee encourages dialog between HHS agencies, blood programs, and manufacturers to ensure strategies for prompt development of technologies, design and completion of feasible studies, satisfaction of licensing requirements to permit both the pre-storage pooling of whole blood derived platelets and extension of platelet dating.

The response here is that HHS agencies have joined AABB Task Force on Bacterial Contamination of Platelet Products to accomplish

additional guidance to the user community, design clinical studies, and clarification of regulatory requirements of platelet pooling and extension.

We are going to hear more about that tomorrow, and I think that we have made some great headway as far as not only additional clarification to the blood community, but also in the refinement of clinical studies, and those will be presented tomorrow.

I must thank the AABB for being the conduit for a lot of those discussions.

Going back to January 2004, the committee finds goals of supply, quality, accessibility and efficiency as stated in the 1974 National Blood Policy as applicable today, recommends development of a five- to seven-day inventory, recommends full funding of DHHS Blood Action Plan in the area of private and government supply monitoring, and increasing the blood supply, funding of a national blood reserve.

We will have discussion later today on some of the donor awareness projects that are going

on, again, with a cooperative effort between the AABB, ABC, and ARC. They will be presenting their Donor Awareness Program that will be rolling out soon.

As soon as some of you may have seen in numerous newsletters, Secretary Thompson, back on June 14th, announced the World Blood Donor Day and also an initiative for Federal Government employees called Donation Nation. The Department is working with the three blood communities to make sure that that gets kicked off. We are in a pilot phase right now. We will have more to report at the end of the year.

As always, funding remains an issue on supporting donor awareness, and also it remains an issue on the national blood reserve. We missed the presidential budget for 2004, but we are continuing to work in this area.

One of the things that we are working on within the Department is that we have worked very closely with the AABB Interorganizational Task Force. For the Democratic National Convention. We

did have blood set up in a reserve status at the Armed Services Whole Blood Processing Lab.

For the Republican National Convention, we are actually going to do a proof of concept, and Commander Libby will talk a little bit more about that later.

January 2004 reimbursement issues. The committee urges the Secretary to address funding needs at all levels of the blood system to support product safety, quality, availability, and access through targeting of, as Dr. Sandler said, additive resources and appropriate reform to the CMS reimbursement system for blood and blood products including plasma derived therapeutics and their recombinant analogs.

Again, I think with this most recent letter from Secretary Thompson, I think that that makes it clear that we have ways of speaking directly to Dr. McClellan with some of these issues.

In August of 2003, the Committee recommends that the Secretary direct CMS to examine

its framework for cost reimbursement in the product area and, in the interim, provide reimbursement based on actual costs of acquiring and providing blood, and Committee recommends that CMS utilize validated cost data available from product manufacturers and distributors.

Again, Secretary Thompson's letter sort of culminates a lot of our issues. We just have a mandate, that we have to follow through with that and make sure that we get the issues to the table.

The APC Panel recommended to CMS the use of community data. I believe this was in the February 2004 meeting, and in the August 2003 meeting, there was a recommendation to freeze the price of blood, and not to lower the price.

May 2003. Again, our recommendation for CMS to identify costs of blood products and services within the market basket. CMS to consolidate, simplify, and review reimbursement policies of all blood and blood derived products, and CMS to develop timely and adequate reimbursement mechanisms within and without the CMS

appropriation system to assure that improvements in blood safety can be concurrently implemented.

Again, some of the same responses that I have listed before. I think one of our frustrations even within the Department is the various silos within CMS and trying to go between those silos and talk to the right people and make sure that we get the right people to the table, so there is really a challenge there. But at the Department level, we certainly do hear what the Committee has said and we are moving forward with that.

Again, reimbursement, identify contingency funding for unanticipated blood safety initiatives that require immediate implementation. Again, that is trying to tag, if we have a new test that becomes mandatory, how do we get that into the reimbursement strategy.

CMS amends the definition of blood and blood products to include all plasma derived products for which there is a need to provide continuing access for therapies used to treat

chronic diseases and life-threatening conditions, specifically including IGIV.

I have to say that the MMA was corrected. We did have a report at the last meeting that I think it was the first part of April, went back and corrected some of the terminology issues in the MMA, and that was retrospective to January 1st, 2004.

Again, CMS establish parity of payment rates across different billing dosages.

So, you can see that reimbursement continues to be a major issue. I hope that by the next meeting, I can give you a real positive statement that we have moved forward on some of these things. I think that we have made progress, but we need to make more progress in this area.

January 2003. Recognized the current leading causes of transfusion related fatalities. I was not Executive Secretary at this time, but I have to say that I wish I would have been around for this meeting, because I think this was probably one of the most significant meetings that I have

been able to go back through and read in the archives, but I think what the Committee put forward really set the stage of where the safety issues are and what do we need to do.

Hopefully, you will see some of this being addressed in today's agenda and tomorrow's agenda.

The Secretary should take steps to encourage and facilitate implementation of available measures to reduce the risk of bacterial contamination, prevent errors, research that may improve safety and extend the shelf life of platelets, and research and technology practices that could reduce the incidence of TRALI.

The May 2004 recommendation got the Department involved. I wish the Department would have been engaged a lot more than it had been as the standard went forward from the AABB, but I think that we have made some great progress there for reducing the risk of bacterial contamination.

The other thing is the bar code ruling for common data identifiers for blood products. Just a point of clarification here is that the Secretary

did sign a ruling in April that required bar coding of drug products. It did not require bar coding of blood products.

The blood products were removed from that, but primarily, the intent of that was to foster electronic data identifiers, so that the blood community was not locked into the technology of bar coding, that if the blood community wanted to more forward with radio frequency or any other new technology, they could move forward with that, but the idea was that there would be common data identifiers that could try to reduce the risk of errors within, and that FDA ruling went into effect and must be in place by April 2006.

Let me just mention also because it is a subject dear to my heart, that I was for many years involved with the working group on the ISBT 128, and a lot of people have raised questions concerning the full implementation of ISBT-128.

The FDA has been silent on the technology or the symbology there, but the AABB clearly states in their standards as far as the moving forward

with the ISBT-128. The ISBT-128 hopefully will give more ability for data identifiers and also we need to continue to look, and maybe this is another discussion that we might have in upcoming meetings to talk about closing the loop between collection and transfusion, how do we reduce the risk of errors.

I don't know about you, but I see every day or I see at least--I shouldn't say every day--I see in the news, on a regular basis, problems taking place with misidentification of donors and the wrong either blood product or blood type being given.

The other thing is the research on platelets. I think we are addressing that with the task force, and we will hear more about that tomorrow.

Also, the research and technology and practices that could reduce the incidence of TRALI. We do have in the room here, a representative from NHLBI. We also have committee members from the working group that NHLBI put together, and Dr. Mark

Popovsky will be talking about TRALI tomorrow, as well as Dr. Kleinman, on this issue.

The reason I put this on the agenda was once again to go back, so that we didn't lose sight of it, and so that we could move forward with more of an awareness, keep it on the radar screen.

This is one that no action has been taken, and I bring this to the committee because I think that if it is the desire of the committee to move forward with this, then, I think that some action should be taken on it.

But the committee tasked itself to develop a process to identify and evaluate residual known and unknown risks affecting blood safety and secondarily availability, both in relation to etiological agents and the processes used in transfusion medicine, is tasked to use the process as one tool combined with other relevant data to propose prioritization of efforts by government, industry, and the health care system to address these risks for further consideration by the committee.

Somebody that has been on the committee for a while, can you tell me what all those words mean? What was the intent of the committee at the time?

While you are trying to think, if you historically go back to January 2003, let me tell you that we do have the capability within the Federal Advisory Committee Act to have subcommittees. The only thing is that the subcommittee cannot make recommendations by itself, it can report those comments to the full committee, and it is an full, open meeting that those recommendations are discussed by the full committee.

Dr. Brecher, do you want to address that?

DR. BRECHER: Jerry, this was initially recommended by Mike Fitzpatrick when he was on the committee, and the thought was, my recollection, that we would form a subcommittee to monitor this and report back to the main committee. However, you are correct, no action was taken until now, so we will have to reconsider this.

DR. HOLMBERG: Do we want to discuss this now or do we want to hold this for later discussion?

DR. BRECHER: I would say hold this for later.

DR. HOLMBERG: Okay. It's down on my list.

Another issue that has had no action, and maybe we can address this when we have a meeting with CMS, is in regards to recombinant clotting factors, and further recommends, the Committee reaffirms its previous recommendations regarding recombinant clotting factors, and further recommends that the Secretary direct CMS to promptly revise the Carrier Manual provisions regarding reimbursement for hemophilia clotting factor to remove all insurance barriers to recombinant technology.

I guess what I will do it take that on as an action, as a point when we do have our discussion with CMS.

Any other comments on that?

Okay. September 2002, again reimbursement. The Secretary direct CMS to establish 2003 Medicare HOPPS rates for blood, blood components, transfusion services, and transfusion laboratory procedures based on current year acquisition and actual total costs of providing such products and services rather than hospital outpatient claims from previous years.

Again, this may be a difficult one. It is part of the way CMS does business. Jim, any clarification on this? We can discuss this when we do sit down with the CMS people and bring this to Dr. McClellan's attention, but I think that the issue is that it is very difficult to have a rapid response in the actual pricing of products. Historically, you go back to previous years.

DR. BOWMAN: Right. There is some logistical and operational difficulties with getting real-time, you know, current year acquisition costs, but I will leave it at that for now.

DR. HOLMBERG: Okay. For guidance to me,

does the Committee still feel that this is a valid point, that we can't wait 12 months to change the cost? Dr. Sandler?

DR. SANDLER: I am on the committee to represent the American Hospital Association, and our member hospitals all pay their bills on time, and I think that it is appropriate that everyone in the chain does the same thing.

I would like to see this continue to be there and that we should work in this direction.

DR. HOLMBERG: Chris?

MR. HEALEY: At least with respect to the plasma therapies, the methodology has changed, so that now they are not using the claims-based system, and instead the GAO has been mandated under the MMA to do a hospital acquisition cost survey, the results of which are due, I believe, sometime in 2005, will be used to set rates for 2006.

So, as written, I believe this would be an obsolete recommendation with regard to the plasma therapies.

DR. HOLMBERG: Any other comments? What I

will do is I will take this for action and this will be a discussion point. We will clarify what Chris has said and also reiterate the concern from the hospitals.

DR. BRECHER: So, that sounds like there was some action taken on that and that they are now considering acquisition costs.

DR. HOLMBERG: It does, and I think that we can add this to our report card.

Any other comments?

Again, CMS, direct CMS that payment for plasma derived therapies and their recombinant analogs be based on current year acquisition and actual total costs of providing such products and services both within hospitals and in non-inpatient settings, including physician offices, to ensure patient access to care.

Is this in the same light, Chris? Okay.

September 2002 was public awareness. Secretary should promote public awareness of the ongoing need for routine blood donations by healthy persons via: PSAs and visible blood donations by

top officials and paid advertising campaigns; funding of demonstration projects, support specific initiatives to encourage routine donations by young persons and minorities, play a lead role in increasing participation of the federal employee.

We did have a campaign, Give Life, Give Twice campaign, that Secretary Thompson pushed, and one of the things that we recognized from that campaign was the problem with campaigns, is that there is usually an endpoint and what happens after the campaign is over with.

So, this is one reason why we have really looked to the AABB, the ARC, and the ABC to help us try to motivate the federal employee with the donation--I don't want to call it campaign--but I want to say our donation program, and hopefully, this will continue on, and we have already learned many lessons from the Give Life, Give Twice campaign, and Secretary Thompson has already provided donations and also press releases.

We are pleased that the various blood communities have already put together with the Ad

Council the ads. We will see some more of that this afternoon. Again, funding is always an issue, and we will have some discussion about that this afternoon.

I would encourage all of us to continue to look at that third bullet under there, as far as encouraging routine donations of our young people and also the minorities. I think the good point with what we will hear this afternoon is where the Ad Council ads are directing their attention.

Also, I just want to encourage the committee to really look at the minorities. I think that within our country, with the growing minority of the hispanic population and the frequency of group O's, I think that we really need to be much more aware of our growing minority groups in this country.

September 2002, also, we talked about monitoring. The Secretary should fund and support blood supply monitoring to address: long-term trends in blood collection and use, data on daily nationally distributed blood inventories,

indications of blood shortages and excesses, predictive models to identify trigger points for coordinated national campaigns, and coordination of governmental and non-governmental initiatives.

In 2002 and 2003, my office, with Captain McMurtry, did a lot of analysis, worked with an outside organization to really look at ways that we could improve the monitoring system and to make it more statistically significant.

When I am finished, and when I am trying to make sure that we stay on track, we will have a presentation from the Secretary's Command Center with a short demonstration of where we are with our monitoring system.

Inventory management. The Secretary should support initiatives to improve management of blood inventories including: defining the roles of liquid and frozen reserves, to moderate fluctuations in supply, and to improve disaster response preparedness.

Integration of supply forecasting into intervention strategies directed to correct

imbalances in supply and needs, and strategies to facilitate movement of blood from areas of surplus to areas of shortages.

Again, we must work with private sector, the AABB, the ARC, and the ABC, and BCA, as far as moving blood products and identification of excesses and shortfalls, and let them handle the majority of that.

We are looking at some of the principles of the National Blood Reserve. Dr. Beato, when she reviewed these with me, really had a question concerning the recommendation of frozen reserves, not only from this meeting, September 2002, but also with the August 2003 meeting.

In going back into the records and the transcripts, really trying to find a clear reasoning behind the lack of frozen blood and the lack of support for frozen blood. I think it just was really not substantiated well within the transcripts.

So, she has expressed a desire to readdress the frozen reserves along with the

National Blood Reserve issue, and if the Committee does not think that frozen blood is a viable resource to complement the National Blood Reserve, she would really like to hear some of the Committee's rationale on the recommendation not to include frozen blood.

So, I just put that out there as maybe a topic for future meetings. I know we have addressed that issue numerous times.

Any other comments on that? This was one area that she really wanted to have more discussion.

MS. LIPTON: I would just suggest that I think that maybe not in the transcripts, but certainly within the deliberation of the task force that has done this, there has been a lot of discussion, and if you would like, we could prepare a paper on the specific reasoning on why the task force did not recommend that.

DR. HOLMBERG: I would appreciate that, too, especially as we put together documentation for the National Blood Reserve.

DR. BRECHER: Jerry, I believe much of the discussion actually was in the January 2004 meeting that Celso chaired, and it came down to frozen inventories were not rapidly available and that you have to keep turning over the inventory as new tests and new questions come along, so that it is very expensive to maintain a frozen inventory.

MS. LIPTON: I also recall that we did say that it might be appropriate in specific regions that could handle it, but that, as a national reserve, that that did not make sense, but we can put all these into a review paper or white paper.

DR. HOLMBERG: Very good. Thank you.

January 2002. Response to disasters. Again, just to remind people this was the first meeting after 9/11. The Secretary should act to promote and coordinate a single, consistent public message on blood issues.

ESF-8 of the Federal Response Plan should be reviewed to incorporate the recommendations and organizational members of the AABB Task Force, and I have simplified the correct title for the AABB

Interorganizational Task Force on Domestic Disasters and Acts of Terrorism to just the AABB Task Force.

Also, the AABB Task Force should coordinate the national response of the blood community, and the Secretary should fund the evaluation and potential development of the National Blood Reserve.

Again, I think that this meeting was very good in the sense that from the outfall of this meeting was the Assistant Secretary for Health, who is the Blood Safety Director, took more of the responsibility for being the blood czar, and in the time of disaster, a coordinated message will be prepared by the ASH's office.

Also, Captain McMurtry will be reporting to you later today on ESF-8, which has been rewritten, and we have worked very closely with the blood organizations to make sure that the wording is amenable to all the parties involved, and as we mentioned also, the evaluation of the National Blood Reserve is currently underway, and Commander

Libby will talk a little bit more about that.

Donor awareness, 2002. The Secretary should recognize and incorporate the FDA's Office of Blood Research and Review strategic plan into the DHHS response plan for counterterrorism and disaster preparedness, and this has been done.

April 2001, more on the global blood safety issues. The Secretary should foster research, training, and standard setting activities in international blood safety, including development and transfer of appropriate technologies for the developing world.

Support the establishment of a mechanism to identify priorities and coordinate the exchange of information and activities among government and non-government agencies in the U.S. and international communities.

I have to say that on the committee here, we do have the Chairman of the Global Collaboration for Blood Safety. Dr. Epstein is the current chair for that group. Through his invitation and prompting, I have been involved with that, so we

continue to work with the groups, the Global Collaboration on Blood Safety, other professional organizations, such as AABB, PPTA, and the World Hemophilic Foundation, we work with, and we are reaching out to the global impact on that.

Again, April 2001. Blood monitoring data collection, the Secretary should establish an office that has responsibility to facilitate the gathering and dissemination of national blood collection, distribution and utilization data, and the development of analytical models to predict shortages. Federal dollars should be provided to support collection, analysis and distribution of these critical public health data. Support programs for public health and physician education.

We are moving ahead with the blood monitoring, and Dean Ross will give that presentation in just a few minutes.

The national blood data collection, that still is a weak link. I am constantly looking for extra money to be able to support more of a national data survey, so that we know where we are

within the country as far as blood supply, transfusions, utilization, and what the future trends are, but once again, this may be an issue that the committee may want to address a little bit more.

Sad to say, I think education programs for the public and physician education, I really can't say that we have done too much on that and again raise that to your awareness level.

January 2001, the topic of universal leukocyte reduction. The Secretary should strive to minimize the impact on supply, assure adequate funding for universal leukocyte reduction.

Issue a regulation to implement universal leukoreduction that addresses these concerns.

Support research to investigate unresolved scientific issues in the area of universal leukoreduction.

The Secretary should appoint non-voting member from CMS. The Secretary definitely has not had a formal discussion or a formal decision on universal leukoreduction. NHLBI is continuing to

fund research, and we were successful in getting a CMS representative, Dr. Bowman, to the table.

So, I think at some point we may want to come back to the issue of universal leukoreduction, leukocyte reduction, but I will bring this to your attention again.

That brings me right on time.

Chris.

MR. HEALEY: Jerry, just a comment. I noticed early on in your presentation some of the early recommendations, particularly the ones pertaining to reimbursement, said that the Secretary directed the ASH to discuss the topic with CMS or with some other party, and I guess my concern as a committee member is that these recommendations might be taken by the ASH and to the relevant agency without the benefit of the input of committee members who were perhaps proponents of the recommendation or who could provide the necessary context, so that the ASH and CMS and some other government officials would have a full appreciation for the rationale for the

recommendation and what is behind it.

So, a long-winded way of saying is there a way that we, as a committee, could creates some subcommittees, as you have mentioned, are permissible, to work with you and the ASH and/or participate in some of that dialogue that the Secretary has recommended, so that again, these recommendations just don't kind of go into the black box and come out with a response without having committee members and invested parties involved.

DR. HOLMBERG: I think that is a very good point. In my discussions with a lot of the various groups, I have tried to maintain an open dialogue, and I have asked for input, but I think it is your committee's decision whether you want to form a subgroup. I would definitely be willing and I would encourage getting input from the committee.

So, Dr. Brecher, I will throw that back to you.

DR. BRECHER: I think when we have our discussion later today, we will address the

formation of subcommittees and membership, so we will save that for the end of the day.

MS. LIPTON: I just had a quick question as you are winding up, Jerry. I noticed in here a memorandum dated April 22nd, 2004, from a Carrie Dallas, health promotion student, and it has some of our names on it as being addressed to, but I don't think we have ever seen it.

My only concern is, is there a mechanism for responding to someone who writes in like this?

DR. HOLMBERG: Other than me directly responding back, no, there isn't a mechanism.

How would the committee like to handle that? She makes some valid points and some concerns.

DR. BRECHER: Jerry, was there a response?

DR. HOLMBERG: No, there was not. I think there was just an e-mail response back to her that I had mentioned just briefly what the committee was doing, but nothing substantial.

DR. EPSTEIN: Jerry, I just wondered if I could comment further on your remark about bar

coding.

FDA's bar coding rule created a requirement for machine-readable code for blood components. That was done instead of imposing a more standardized bar code system that is now required for pharmaceuticals, recognizing that the blood system already has codification schemes.

That said, we have also published a proposed rule, that when finalized, will remove all barriers to the implementation of ISBT-128. The reason we have not required that system is that it is not under U.S. control, is developed abroad by an entity which is not regulated.

So, therefore, we would have no ability to deal with changes made in that system, but we do expect that by removing the barriers and by requiring machine-readable code, the industry itself will move to a more standardized system, but hospitals may still need to retain two systems unless there is some ultimate migration to what a common codification scheme for all pharmaceuticals and for blood, but I have been told repeatedly that

that is not a serious technology issue, that there are readily available readers that can read more than one code.

DR. HOLMBERG: Thank you for that clarification. I think it brings a good point and maybe Commander Libby will address that with our proof of concept, some of the things that we are observing as we go through with the proof of concept. One of the issues is exactly this with the hospitals and the ISBT issue.

DR. BRECHER: We are already behind schedule, so let's move forward with the HHS Blood monitoring. Mr. Dean Ross will speak first.

DHHS Blood Monitoring

Mr. Dean Ross

MR. ROSS: Thank you. I will go ahead and get started, but before I do, I would like to make just a couple notes or comments.

First of all, I would be remiss without coming in this group and really bring forth a great deal of thanks for the recent participation by the blood community working with us on preparedness and

response efforts.

We have been working very closely with the ASH's office and, of course, with the AABB Task Force, and we have had extremely tremendous success in preparing for some of the initiatives that we have had to overcome with the Republican Convention, Democratic Convention, and all the other components.

I think the blood communities probably, as far as the Secretary looks, is one of the governmental-nongovernmental relationships that is really absolutely a stellar example of what we have been able to accomplish working across that border.

The second quick comment is, as of two days ago, we actually changed our name from the Secretary's Command Center to the Secretary's Operation Center to be more in line with a more collaborative concept and mission that we have at the current time.

DR. HOLMBERG: So, now you are a SOC?

MR. ROSS: We are a SOC, yes, unfortunately, we are a SOC, and no longer an SCC.

I talk a little bit about basis and some of the objectives. When we started out looking at the objectives, they were not just the Secretary's Operation Center objectives, it is the objectives that we looked at from their user groups, as well, of what they wanted to look at.

We wanted to be integrated into a public health emergency management system. I will show you a slide secondary to this that will tell you a little bit about what that system does. We want to develop a web-based system. We didn't want to develop a system that required you to have to load a thin client on a machine or trade any special requirements on your computer, so it's a web-based system.

Currently, our web-based systems gather about 268,000 entries every 12 months on public health information, so this will just add to that particular requirement.

Scalable access to user and manager were given, and an organization had five collection points and you wanted to have a manager over those

five points that could review the data from five single points of entry, all of that is scalable, so it continues to grow or diminish based on permission levels.

Easily create new data fields for reporting. I will show you a demonstration of this and why it is important, intuitive to the user. One of the things that we have done in all the systems we rolled out is not create systems that require training, training, training, training.

We try to develop systems that are relatively intuitive, that are easy for a new user to understand, and therefore, our recurrency for training is much less.

Geospatial integration, the use of GIS or geographic information systems to geospatially look at the data, and to compare data against other datasets in affected communities is an important function of how we operate in the Secretary's Operation Center.

Again, web-based reporting tools is again the focus of this.

The Public Health Emergency Management System is currently an existing web-based application that it out there. We design it to look at a couple of different components out there.

One was HARTS. There is the Hospital Asset Reporting and Tracking System. This is a system that allows 6,533 hospitals nationally the ability to respond to 10 to 12 different categories of information that we may need during an emergency.

They do not, however, report on a day-to-day basis. They only report as defined by us during a particular emergency basis, which is one of the other than we are talking about today, MMS, the Medical Materials and Supplies, a similar organization to blood out there, and future modules for managing resources, as well, out there.

One is a personnel asset to look at governmental and nongovernmental assets for response, all integrated into that system.

Why do you really want to have a system like that? Well, we have the capability when we

look at preparedness and response issues to model out perhaps what we think is the threat by looking at what could be classified and/or unclassified data over a geographic data.

We can determine casualty or the insult to the public health community, and from that, we always like to go back and look at what the available resources are currently and what deficits need to be corrected to appropriately prepare for those.

So, that is what the Public Health Emergency Management System is all about. It is 95 percent voluntary to the aspect that these are not government entities that are reporting, these are nongovernment entities that are reporting to this.

I am just going to have a couple of slides, and take you through some of the screen shots. This system is actually up and operating. We are kind of doing some debugging right now, but it is called, it is a BASIS system. The looks are contemporary, so if you happen to be a hospital administrator or a hospital that was inputting data

and you were inputting data on medical materials and supplies in two or three other categories, the screen fields are identical, so they would only have to train on just blood, they can understand the entire process.

It is a web-based application. It is part of the HHS Secretary's Operation Center secure domain, it is not publicly accessible. It is data, it is not housed by vendor.

We have facilities set up. Actually, it has triple redundancy across the United States. It has clustered service systems. All of our data is stored at the final process in a secure facility about 600 miles away from the Washington, D.C. area, so it is very secure.

We haven't lost any data, and we have currently, as to date, about terabytes of data, so as you develop these systems, having ability to store data, it is just as critical as it is to actually have a system to collect it. So, that system right now sits at 20 terabytes, so lots of room for additional input.

So SOPA [ph] application to load, no thin clients to load, no special applications. An Internet Explorer or Netscape Navigator environment is perfectly acceptable to input that data, intuitive application to eliminate recurring training, I alluded to that just recently.

There is two ways that BASIS can actually work. BASIS can work gathering routine data from reporting entities. It also can be event-driven data. So, if we want to create an event, such as Hurricane Charlie, and have an event where we add a particular category or two to the blood reporting, is your facility operational, what damage do you have to your facility, are you on generators, things that traditionally are not routine reported within that event environment, we can get that data and information, and that helps us work through our partners, such as FEMA, for different funding issues, and also work along on several other components, so again routine or event-driven data.

The hospital sector is event-only drive data.

Just quickly to reiterate what I brought forth, user and manager access, I have alluded to this earlier. If you want to be a single point of entry, you can be a single point of entry.

If you want to be a multiple point of entry, such as you represented five collection centers in a particular system, and only want to have one person input data for five, they can do that. The same one person that inputs data for five can view the data for those five, so it is completely scalable by permission and access.

The Asset Reporting Management, for lack of a better word, what do you report about and to. We have all the different categories that were provided by Jerry and his group, and by working through some of the issues with the blood group in here to determine what are necessary, but the ability to add new reporting categories on the fly is inherent in all our systems. It is very dynamic.

If we need to add, for instance, are you on generators, some of the things I talked about

earlier, or have you seen this is any blood, or do you have any indication that this is happening, we can add Yes or No answers. We can add comment fields.

We can add quantity fields immediately to the system. It takes about three seconds to add a new field, everybody sees it globally, and you get a notification the next time you log on that says we have added a new field for you to report to. So, it can be a very valuable tool to utilize that.

Sample data field, user input for availability, you know, very tabular input field that we have on here. That field could be expanded or contracted based on those new specific questions that we have out there.

One of the things about gathering data, and I will tell you just a little bit about it in the future, about geospatial data, this is relational data, and I will explain what that means to us in our preparedness environment very shortly.

The common terminology, I think one of the things that we have asked to come back to, is to

look at some data dictionary components, so that everybody is talking about exactly the same thing and what the definition for that input is.

User input, asset info. This is part of your same user screen. So, if you need to update who that person is to reporting, you have a telephone number change, you have any of those components, that is a very quick, easy screen to go out and fill out that information.

What happened in our other systems where people begin to put accurate information, they also discover that there is a value in that, and not that we inundate individuals with information in e-mails, but when we do see an item of issue that could be geographically specifically, we are able through out system to project on out a message to those e-mail addresses and say we think that, you know, perhaps even some of the messages we sent out during Hurricane Charlie to ask people to prepare or do different things, we can push that information back out through the system, so basically, we can go back into those e-mail

addresses and telephone numbers, and put those within the notification systems that we have, so you also get a return for your input, as well.

How we use our information is very interesting. I told you a minute ago there is about 268,000 entries a year. The majority of our analysis is done by using geospatial tools or GIS, so we as we look into a particular community across the United States, not only can we look at those pieces of critical infrastructure that are out there and what their availability are, it could be blood, it could be hospitals, it could be medical materials and supplies, but we can also focus those over a geographic area, looking at different census diversity - age, sex, race, who owns, who buys, you know, all that information over that affected area to determine what our population that is going to be affected within that area is.

This often is an extremely valuable tool when we are looking at the distribution of medical countermeasures because we can determine what our geriatric populations are in those specific areas

and/or populations of, say, five and under, which might require an oral suspension or a slightly different approach, so it is not a one paintbrush paints everything, we are rather detailed on our information.

The little data screen that has popped up here in the middle of that image actually represents how hospital data comes into our system, and it comes up, it tells not only what their certified level of beds are, but what their availability is in particular categories, such as emergency department beds, staffed ventilators, a wide variety of different components, and it pops up.

So, visually, you can do the same thing where you get to a predetermined percentage and the icon will flash to let you know that there is an issue there, whether value is too high or too low, and so it allows us a visual tool to do this. This is probably, for preparedness of planners, is becoming the best tool to analyze so many different forms of data in the environment.

So, geospatial tools, part of the geospatial tools that comes out, we put out what we also a feature set capability, so as this data goes into a relational database and you are a manager out there, and you say, okay, I want to see all the data I put into that system from X date to Y date, you can query within your own dataset and have it produce a report of that data that you put into that system.

It can be put into a format where even you can import it into your own individual geospatial programs.

Reporting. We currently use a reporting system that is an enterprise or web-based reporting system to help individuals work through that their own reporting needs are. It could be tabular, it could be any kind of graph format, anything that really falls out, and it can all be on the same page. You can set up a predetermined report, and it would be focused to your particular needs or the needs of that particular event or incident.

So, very enterprise solution, feature

service for extracting the data. We found that has been valuable for hospitals. They want to look at data over a particular time frame, and they can extract that data, so they can use it in their own graphs, tables, and charts along that component.

That is how BASIS is set up and functional to operate. Again, it is contemporary with HARTS and the Medical Materials and Supplies, which are both operating systems at this time.

I will take any questions from anyone if they have some. Yes, sir.

Committee Discussion/Recommendations

DR. KLEIN: Two questions. The first is, have you had any opportunity to use this in any disaster yet?

MR. ROSS: We have been using HARTS, which is the Hospital Asset Reporting System.

DR. KLEIN: I am talking about BASIS.

MR. ROSS: No, BASIS, we are going through the debugging component of it now. We have inputted only notional data at this time. Our intent is to go ahead and throw it out here and

begin to utilize it here within the next month to begin to develop sample datasets.

From that, we would generally go out to the users that use the systems and also get input from them to determine how we can make it function better within that particular environment.

DR. KLEIN: What is the central mechanism for analysis and subsequently publication, so that you will have lessons learned as you apply this to various disasters?

MR. ROSS: After each individual disaster, event, or occurrence that we have done, and I will go back to HARTS because we have been doing that now for over a year, we look at after-action reviews. We gather data and input from the individual users.

We also take that particular data and look and see how our--as HHS's plans, States, and local government plans, if the data we are producing meets their individual needs and also how they use that need, or how they use that data to respond to their individual needs.

So, there is a rather good evaluation component in there, however, it is only currently shared with the users that participate, so we are not publishing it in an open format.

I will tell you one thing about the systems. When you begin to look at informational systems like BASIS and HARTS, and those components out there, individually, those have some level of sensitivity, and that sensitive data is kept within a rather cloistered environment of those that either participate or within the command center.

One of the issues that you have to look at from our standpoint is if we collectively publish data for two or three or four more sectors, that begins to let--from the terrorism standpoint--begins to let the more sinister individuals out there in the world begin to determine how our business function operates.

So, typically, we don't publish anything externally that would not be driven out by the ASH's office or approved by a particular entity.

DR. HOLMBERG: Just to clarify a few

comments from Dr. Klein, and what Dean has already said, what we are trying to do during this next month of working out the bugs, actually, utilizing it during the Republican National Convention with the information that we have, but also we do currently have 26 sentinel hospitals that we utilize, we are concurrently going to be using that data in addition to the way we already collect it, so we will be manually putting that data in and tracking that, and massaging that to try to identify any bugs in the system before we go full tilt.

DR. KLEIN: I was more concerned as to whether there might be lessons learned from these things, that either the general public or some of the non-users at the time might derive from the data that are being collected, and, in fact, since this is voluntary, it might actually stimulate more entities to become users.

DR. HOLMBERG: That is a very good point and what i think Dean was referring to as far as the reports, what we have tried to do is be very

careful of not only information that may be leaked for terrorists' benefit, but also proprietary information and new information, that we very carefully protect that, but we have had blood centers that say what they would like to do is they would like to be able to roll up their entire area, to be able to take the hospitals that are reporting in, and the centers, the hospitals that report back or that get the blood from them, to be able to roll that up to look at maybe utilization information and some of the benefits of how further can we use this information, and for the hospital to be able to look at it as far as the blood utilization committees.

But I think that there will be ample opportunity, not only for publications, but also for definitely a hot wash after any event to be able to identify lessons learned.

DR. EPSTEIN: Mr. Ross, could I get you to comment on how TransNet has been integrated into this system, and then if you could also comment, the system seems to be designed for response, but

does it contain any elements of ongoing surveillance?

MR. ROSS: Well, let me go back to the TransNet. Currently, the Secretary's Operation Center TransNet is not an application that we are using within the Command Center. We will roll forward from hereon, looking at using a BASIS or this web-based type tool.

The second part of your question, it is not all about response, it is very much about preparedness. I think if we go forward and look at some of the things we have been doing with the task force, we are looking at issues six, two, three, four months in advance, that we know are known issues, of course, we are always going to have those issues that are immediate issues that are unpredictable, but we are using it to look at blood supply prior to the event.

As a matter of fact, I think we have been working on the Republican National Convention now for over 90 days to look at that, so it's a scaled-up approach. So, it is quite a bit about

preparedness issues.

We don't have enough data at this time. One thing that is interesting about hospitals, we have been able to collect enough data during emergencies to determine where weaknesses are and how they need to build their infrastructure and look at their planning, and we hope that the blood community would actually use the same tool in the same way, so that you use it as a preparedness component, as well.

That is part of my business function at the Secretary's Operation Center. There are other applications through the ASH's office, how they want to analyze or look at that data statistically, but from our standpoint, we look at preparedness and response. I would say, well, we actually run a program called Predictive Services, so the majority of our business is predictive in nature. It's about preparedness, and not necessarily just about response.

DR. BRECHER: Celso.

DR. BIANCO: This seems to be a very nice

system, but the sense I had as you presented it is you get a lot of things in, but I think that we don't know yet what is going to come out and how useful this can be to the community in terms of planning, in terms of understanding what we do.

I know you are coordinating these with the task force very much, and that is very, very important, but my concern is that maybe this is the time, as you are starting with it, to have these very well planned on how actions can be based on all the information that you are going to get.

I am following very much on the question of Dr. Klein and maybe you can tell us a little bit more about that.

MR. ROSS: Correct. I will address this. As we develop data, for instance, hospital data, that we have had for a long time, or data in a specific resource, once you gather a large enough aggregate amount of data, we begin to develop decisionmaking tools of where the spikes, cutoffs, and other components are.

For instance, we look at poison control

data now for well over nine years, we have a very long data train in there, and we can see individual spikes or different occurrences. We know their seasonalities, we know a lot of information about those environments.

To date, in the blood community, we don't--from the Secretary's Operation Center--we don't have a sufficient enough dataset to make decisions on that, but we do have the output within this system, within all our systems, so that whether it was an individual blood gathering entity or a regional entity, such as a state health officer or someone who has permission to look at the data, could look at the data to make their informed decision based on local knowledge.

By no means do we think that in all the systems where we gather all these data, we still always have a human influence in the decisionmaking process. It is not always a decisionmaking tool that's rather automatic, if it hits a spike of 52 percent do we turn something on. We look at several other causal factors generally against

that.

DR. BRECHER: Just two more comment. Jerry and then Merlyn.

DR. HOLMBERG: I just wanted to follow up on, Jay, your comment on the TransNet. We are, as Dean mentioned, this is the guts of it, but as far as the TransNet portion of that, that will be up on the front page, so that a lot of those issues can be reported, and take many of the attributes of the TransNet, frontload it.

The other thing is that in your comment about response, that it appears to be primarily response, what we will have is that you have two systems here, basically, one system that is doing two things.

You have a system that is daily monitoring what is happening at all of the facilities that are reporting, so you have a constant background report. Those facilities are contributing with this. If there is an event, what would happen is that we would hone into a geographic location and at that point, we are looking at not only what the

baseline was, but also the response.

So, once that happens, it becomes very focused into that geographic location and it becomes a response. Now, at the same time, what we envision, and what Dean may not have mentioned, is that that TransNet aspect of it will be up on the front portion.

Those people that are in that geographic location will be given user ID's to be able to hone into that geographic area and be able to put their information in, but other locations across the nation, that may be experiencing shortages and concerns that TransNet has, can be able to report that upfront without going to the detail levels of that.

I guess what I hear from Celso's comment is that--and I hear this loud and clear--that we definitely need to work more with the Interorganizational Task Force and especially in the reporting aspect of this, so I take that comment, if that is what I hear you saying.

DR. BRECHER: Dr. Sandler and then Dr.

Sayers.

DR. SANDLER: A little more than four years ago, Steve Nightingale, with support from members of the committee, established a network of the sentinel hospitals reporting in with the idea that the information has to get to the Assistant Secretary of Health when there is an inadequate preparedness, an inadequate supply.

I can tell you that yesterday, in the nation's capital, there wasn't one unit of platelet available, not one. Patients were bleeding, and we had no platelets available in Baltimore or Washington. That is about the lowest level of preparedness you can have.

My question is, did the Assistant Secretary of Health, four years after we put a system in, have a clue of the relative lack of preparedness we had in the blood community in the nation's capital yesterday and probably as I speak to you today?

And we have got to get going, we don't need megabytes, we just need phones. We don't need

terabytes, and we don't need global analysis. I mean I can just make a phone call using a dial phone to get this information, but that is the person that has got to get the information, and four years later we are still up in cyberspace somewhere.

DR. HOLMBERG: To answer your question, no, we were not aware of it. There are limitations to the current sentinel system, and we monitor only a few hospitals in the Washington/Baltimore area, and to be honest with you, I don't think the current sentinel system is sensitive enough to be able to predict that.

Like you say, if there is areas of shortages, then, that needs to be communicated.

DR. BRECHER: Merlyn.

DR. SAYERS: That last illustration, I might have missed this, but what did Enterprise solution refer to?

MR. ROSS: The Enterprise solution, when we look at an Enterprise solution for reporting or different things, we are looking at an application

that is carried over particular internet where you don't have to load a particular application, such as a reporting application to your desktop, so you can analyze the data. It is inherent within the program itself to generate the report as necessary, so you are not looking at an additional application or anything you have to load on a computer or a PC.

DR. BRECHER: I have one final comment or question. Right now data is being collected on about 10 percent of the blood supply with the sentinel sites. What percent would we need to be able to predict shortages, that we would have good feel for the country, do we need 70 percent, 80 percent of all units being reported? Does anyone have a clue as to what we would need? I think we need to define that.

MS. LIPTON: I think the problem is that even if it's 99 percent, and you are in the 1 percent that has got the shortage, we have a problem. I mean I think you could design a system that is statistically valid, but it doesn't help you in Jerry's situation if he happens to be in the

hospital or the region.

So, I don't think there is an absolute answer. I think the more people we can get to participate in this, and the way you do that, I think is by, as Celso said, making sure that they get something out of the system, so that they feel that it's useful.

If they think they are going to get something useful out of the system, they will use it. I think that is what everyone is trying to work towards, and I think the system design right now looks like it could be very helpful. We have to make sure it gets useful information out to the hospitals.

DR. BRECHER: Jay.

DR. EPSTEIN: This is why I asked my question about surveillance, because the concept that was put forward, developed by Allen Williams and the contractor of TransNet, was that it would be a web-based system where all centers voluntarily could report their current status of shortage of surplus, and that that would then create a daily

geospatial model of the blood system.

A system of that sort would not fail to capture a finding of zero platelets in a region. What I heard you say is that the graphical interface incorporates TransNet, but this system is not live yet.

So, I think the answer is that we don't presently have a system which is web based, which is simple, which has a minimal technology requirement, and which, albeit voluntary, has the capability to capture information from all sites.

The incentive is that these sites would then be able to benchmark where they are relative to their region or other regions. It would also facilitate their ability to perhaps make arrangements to offset their circumstances by being able to immediately see where the resources are.

So, I guess I hear us migrating in that direction, but I somewhat share Dr. Sandler's frustration that we are not where we need to be yet.

DR. BRECHER: Jerry, it's too bad that you

didn't let us know. We would have each brought you one or two platelets.

DR. KLEIN: Mark, that is actually a good point because what we don't know is whether, in fact, there was a national shortage, and the sentinel system that was designed, and I was never a fan of that, as you know, was designed as a macro system, and in theory, would tell us whether there were national shortages, and if there weren't, then, it's a distribution issue, and, in fact, it's your local supplier who has dropped the ball if, in fact, there were platelets available in some other area that could have been sent here.

We don't have any way of knowing that right now as far as I understand, which either means that the sentinel system isn't working the way it was supposed to, or that there wasn't a national shortage and it was as distribution issue.

DR. BRECHER: I think you are correct, Harvey, I think the sentinel set at 10 percent cannot make any significant predictions. It was set up to pave the road for a larger system, and

that we just never have gotten there yet.

Were you short on platelets at the NIH yesterday?

DR. KLEIN: No, we weren't.

DR. SANDLER: I think a point of clarification is needed. Dr. Klein and I have had a long discussion about this. His distribution of platelets is for research, and if he becomes a supplier in the Washington community, then, he loses the status that those platelets were funded for by the government. He can't become a replacement for the community supply.

Dr. Klein has made it very clear if there is a patient whose life can be saved, he will give us platelets, and I will ask for them.

DR. HOLMBERG: I hear what you are saying, Jay, and Dr. Sandler also. As we move forward with this, this is just the prototype for the actual BASIS itself as far as the member organizations. We will have 100--I believe it's 135 hospitals and 35, I believe it's 35 blood centers, that will participate with this.

The greater number we have, yes, it will be a better indicator of the overall picture, and we can see whether we have a national problem or a local problem, but it is still our intent, Jay, and I really want to emphasize this point, is that there will be a front page to this, that anyone can report shortages.

We are taking the TransNet very seriously. We want to combine the best of both worlds together. So, we will be able to monitor what is going with the TransNet, but we will also be able to look at those facilities, if you will, the 135 facilities, whether they are trauma centers or what level of care they are, and then the blood centers that feed into those.

We need to have that base, so that we can do a statistical analysis on it. So, we will put weights to the various things, and when we do the reporting, that is what we are working on right now is the final reporting.

What we want to be able to do is those people who are participating, make it added value

to them, so that they can do it, but I don't want to give the impression that we have given up on the TransNet. We have not given up on the TransNet. We want to be able to capture information from any facility nationwide that wants to report a shortage.

DR. KUEHNERT: As a comment as far as the output, the concern over output is concerned, I would encourage you to look at the National Health Care Safety Network at CDC, which looks at health care associated infections, and started with the National Nosocomial Infection Surveillance System, which started over 30 years ago, and has the advantage of having aggregate and anonymized data confidentially from over 300 hospitals and is used for benchmarking.

One could use a similar model where data is shared as an aggregate, but also fed back to the individual facility to help categorize and summarize the data that they sent to the system. It gets sent back to them in a way that they could use it effectively.

The NHSN is actually working on a component that allows for both detail participation and also a so-called later or more minimal participation level that is possible, so sort of looking at that as a model, allowing for different levels of participation, aggregate data to be used for the public, as well as detailed data to be used by each individual facility for the data they contribute might make this more effective.

MR. ALLEN: Getting back to Dr. Sandler's discussion with Harvey, other hospitals in the urban areas, are they aware that if they have the same issue you had yesterday, that they can call Harvey or call the NIH?

DR. SANDLER: I can't speak to the knowledge available to leadership in other hospitals.

DR. BRECHER: Lola.

DR. LOPES: I wanted to ask Dr. Sandler, was this zero level in your hospital caused by a burst of events that drew down your personal supplies or was this more broadly your distributor

providing sort of a sub-safe level of these products over some period of time?

DR. SANDLER: We use 10 to 15 or 20 pheresis platelet concentrates a day. We needed about 20 on that day. We called every hospital that we knew of in the area. I personally called the CEO of the Regional Blood Center and told him I wanted him to know the patient level consequences of this, and asked if regional supply could help.

He told me he had tried everything deliverable in the region. To answer the question in a broader way, platelets, as a consequence of current logistics, are coming to us with a two-day dating, and when platelets come with a two-day dating, that contributes to a difficulty in maintaining the supply.

I think that is where the real root of the problem is, but everyone in the community was short yesterday.

DR. KLEIN: As Dr. Sandler pointed out, we are not a regional supplier, we are a small institution that is virtually 100 percent

self-sufficient. We do give platelets to other federal facilities when there is a patient care issue and to non-federal facilities in that order, when there is a patient care issue involved.

We are in no position to become a regional supplier. I would add, though, that regardless of whether this was a national supply issue or a regional distribution issue, I think the fact of the matter is that for the Washington, D.C. area yesterday, the system failed and patient care was at risk, and frankly, preparedness was at risk because our federal/nonfederal system failed, and perhaps we need to think about how we are going to deal with that.

Probably the way to deal with it is not to get a larger supply at the National Institutes of Health.

DR. KUEHNERT: I was just going to ask Dr. Sandler, I think you mentioned the two-day supply issue, and I seem to be referring to bacterial screening as having an impact. I just wondered if you can estimate what kind of impact you think

bacterial screening had on this particular shortage.

DR. SANDLER: I think there are two components. Prior to the March 1 change, we had a three-day dating in hospitals in this region. The additional testing release and other issues have changed that to two days, and we have documented that although the Red Cross has not, but I can tell you that it is two days, and it was two days as of before I left the hospital this morning.

The second element is that without a licensed method for testing pooled platelets, suppliers are reluctant to get into the position of continuing supplying pooled platelets because they can't test them for bacterial testing, and there has been a decreased availability, in other words, there were just a gazillion donors giving whole blood in double packs when they could have been triple packs.

The solution to the problem tomorrow could be if the collector would collect enough random donor or whole blood derived platelets, but there

is a resistance because of the way the policy at the national level has evolved, there is risk to a blood center that does that.

DR. BRECHER: Mike Fitzpatrick, America's Blood Centers.

DR. FITZPATRICK: Mike Fitzpatrick, America's Blood Centers. Just if I could remind the committee of a few meetings back where they received a number of presentations on different ways nations approach their blood supply, and in reference to Dr. Sandler's problem, our nation has a multiple method of supplying blood through private non-profit organizations, and while a local area might have a severe shortage, as is described in Washington, D.C., there are three national mechanisms that I know of to address that shortage, but they are dependent on the supplier applying the mechanism. That is the National Blood Exchange to the AABB, that is a broadcast message through America's Blood Centers--actually, there is four methods--Blood Centers of America has a method of finding blood, and the American Red Cross can,

throughout its entire system, find blood and platelets when necessary.

So, there is four systems available to help address Dr. Sandler's problem, but it is dependent upon the hospital and the supplier applying those systems, and it points out a problem with the sentinel monitoring system that we have discussed over the past four years, which is identifying a shortage at the hospital level is several days too late.

I am sure that the Chesapeake Baltimore region knew that they were in a situation where they were short of platelets, that this was not a surprise to them, so internally, within the Red Cross, they knew they had a supply problem in this region, just as our members know when they are short of platelets and have a supply issue.

So, it is the supplier at the front end of the chain whose shortages can be addressed to meet Dr. Sandler's needs in advance of him getting to that point. When we get to the point that Dr. Sandler doesn't have any platelets, and NIH has to

be relief upon to help level the inventory in the D.C. region, we are beyond that point of intervention, and that is the second point that this committee has discussed several times, gathering the data and doing the trend analysis is valuable and has predictive value.

Using that data for immediate intervention to solve an immediate issue, one is next to impossible because the agency gathering the information has no authority, has no inventory of its own to address the issue, and there are already four separate systems that would allow someone to post over supply and post shortages, and exchange products, so that is being covered.

So, gathering the data, as is pointed out by CDC, to do trend analysis and review data, and so those sorts of things is one issue, gather the data to expect that government can step in and intervene and solve Dr. Sandler's problem is an entirely separate issue, and really is not one that the system can be designed to do or the agency owning the system has the authority to solve.

I just wanted to point those things out.

DR. BRECHER: Thank you, Mike.

Would the committee like to discuss the two suggestions from earlier in the morning on setting up committees, one on emerging transfusion-transmitted diseases and one on reimbursement? Would the committee like to hold this until the end of the day? Does the committee want to have subcommittees?

DR. HEATON: Yes. From the perspective of the manufacturing organizations, we would like to see a subcommittee that would allow review of potential infectious disease threats to the blood supply and to place some priority around those to allow for a very long and a very expensive development cycle.

So, for us, we would like to see a subcommittee reviewing these issues and providing some general strategic guidance because the lead times are so long and the costs are simply so great.

DR. BRECHER: Merlyn.

DR. SAYERS: I am afraid that any comment is going to ensure instant appointment to a subcommittee, so with that concern aside, I would like to see a Reimbursement Subcommittee.

You know, at a time when there really needs to be collaborative relationships between hospitals and blood programs, the collaboration quite often is replaced with really an abrasive relationship, and inevitably, a lot of that abrasiveness reflects back to reimbursement issues.

I would like to see a committee addressing that.

DR. BRECHER: Jerry.

DR. SANDLER: Dr. Sandler volunteers for Dr. Sayers' committee on reimbursement.

[Laughter.]

MS. LIPTON: I just wanted to say that with respect to putting together another group that we talked about, it isn't really just transfusion-transmitted diseases, and if we do something, I think we should focus on the original committee recommendation, which really was broader.

It was risks of transfusion, which I think would be far more appropriate than just focusing on the emerging transmissible diseases.

DR. BRECHER: It seems like the committee would like to do these committees.

MR. WALSH: From a plasma users' perspective, we think it is very valuable and important to have consumer participation on the Reimbursement Committee.

DR. BRECHER: I think there should be consumer, industry, academia, all on each of these committees.

I would like the committees not to be too large, perhaps a membership of five on each subcommittee maximum. Let's talk about the Emerging Threats Subcommittee first. I think there certainly should be a role for the CDC in that, so thank you for volunteering, Matt.

DR. KUEHNERT: My pleasure. Actually, I wanted to make a comment. I think it is really important to understand the objective of this committee, though.

We have a number of emerging infectious diseases, you know, committees within HHS and routine discussions on teleconference calls, and so I think we just need to work out exactly what the unique objectives of this particular subcommittee are.

Karen's comments, I think are important in understanding the breadth of what the charge will be.

DR. BRECHER: Celso.

DR. BIANCO: I think that this is very clear in the summary and in the transcripts of the discussion we had, because we are confronted with 100 priorities - can we rank them, can we see where our efforts. That is your job, Matt.

DR. BRECHER: Yes, so I see this subcommittee as reporting back to the original committee, reporting to the Chair and to the Executive Secretary to help prioritize agenda items for upcoming meetings.

Who else would like to serve on this subcommittee? Karen, Mark Skinner, Jay, and Dr.

Heaton. I think that is five, maybe Mr. Ross. That will be six. Oh, Jeanne. We have a subcommittee of seven.

Let's talk about the Reimbursement Committee. We have got John Walsh, Judy Angelbeck. I think Chris Healey wanted to be on there, Jerry Sandler, John Penner, not Dr. Sayers unless you want to be. You do? Okay, Dr. Sayers.

So, we would charge these committees with overseeing these topics, reporting back to the committee as a whole at each meeting that we have. If there are important action items that need to be addressed ahead of time, please contact Jerry or myself to make sure we get these on the agenda for the upcoming meetings.

MR. WALSH: We would like to request Jim Bowman to be on our committee, Reimbursement.

DR. BRECHER: Good point. Dr. Bowman is happy to volunteer to serve on the Reimbursement Committee. Thank you.

Jay.

DR. EPSTEIN: Your last remark, Mark, that

the chief goal for this blood risks committee's prioritization of issues to bring to the Advisory Committee, I think raises a more general question whether what you are really looking for is a subcommittee to think through candidate agenda items for the committee, which may not be restricted just to those two domains, although those two domains have been recurrent issue areas, but they are certainly not the only domains. You know, blood reserve is another domain.

DR. BRECHER: Right. In the past, we have had an Agenda Subcommittee that has met sporadically, and I would imagine that that subcommittee will continue, so actually, there will be three subcommittees.

DR. EPSTEIN: But I am really asking whether this is overlapping work.

DR. BRECHER: I think we could take the recommendations from these two subcommittees to the Agenda Committee and then prioritize, so I think it's okay.

Is the committee in favor of the

subcommittee structure?

All in favor, raise your hands.

[Show of hands.]

DR. BRECHER: All opposed?

[No response.]

DR. BRECHER: This carries. Mr. Healey is returning to the table, and thank you for volunteering for the Reimbursement Committee.

We are going to take a break. We will be back at 11 o'clock.

[Break.]

DR. BRECHER: Will everyone please take their seats. We are going to start again.

Dr. Angelbeck, what committee did you volunteer for?

DR. ANGELBECK: Reimbursement.

DR. BRECHER: We are going to start with the National Response Plan. Captain McMurtry is going to be talking about the National Response Plan.

National Response Plan

National Response Plan and Executive

Support Function #8

Captain McMurtry

CAPT McMURTRY: I am here to talk about the Emergency Support Function No. 8. You will recall that after the 9/11 terrorist attack, there was difficulty coordinating a message from the blood community to the public regarding the need to donate blood, and because we weren't able to get a coordinated message through the Secretary's Office, the blood industry saw that this was something that needed to be done and they took charge themselves and organized an Interorganizational Task Force, the AABB organized an Interorganizational Task Force.

Once this was organized, it prompted a letter from AABB to FEMA outlining the task force function, to which FEMA did not respond. This was in April of 2002 when that letter went to FEMA. In July of 2003, Roger Dodd, who was then President of the AABB, sent a letter to the Secretary outlining the function of the Interorganizational Task Force.

There was also a recommendation from the

Advisory Committee along about that same time recommending that the Interorganizational Task Force take over the blood function listed in ESF-8.

Since that time, there has been quite a bit of work done on ESF-8. Roger Dodd's letter was not ignored, but it was also not acted upon.

What we have come up with--and when I say "we," I don't mean the Advisory Committee, but I mean the Federal Government in general--is that we have up with a new Emergency Response Plan, not just a federal response plan, but an overall Emergency Response Plan.

This didn't turn out very well. I mean it didn't scan it well, but this is a schematic of what the thing, how it is constructed. There is a base plan. There are emergency support function annexes to the base plan. There are support annexes, incident annexes, and then there is any number of appendices.

The important part for our purposes, the blood community's purposes, is the Emergency Support Function No. 8, which is up here in the

beginning of this. In this, there is a federal function to ESF-8, but there is also a civil function or a civilian function for the thing.

The final draft of the National Response Plan came out in June of 2004. The document itself is about 120 pages long, so there is a long of detail in there, and it describes the structure and processes that make up a national approach to domestic incident management.

It includes planning assumptions, roles and responsibilities. It has preparedness guideline and planned maintenance instruction.

Then, as I said, it has the 15 annexes. Once again, the public health and medical services is covered under ESF-8. The primary agency for ESF-8 is the Department of Health and Human Services, but it does list the support agencies, and I hope that I didn't use too much alphabet soup up here, but I think you recognize all of them, perhaps maybe not the Agency for International Development, and then, of course, our new federal acronym, the Department of Homeland Security.

You will notice that the American Red Cross is listed down here, and I am going to talk about the Red Cross and its place in ESF-8 here in just a minute, but let me talk more about ESF-8's effect on the blood community.

Section C discusses the notification of the Department of Health and Human Services. The actual document itself talks about the way, the methods through which the Department may be notified.

It talks about law enforcement, intelligence sources, monitoring programs. It leaves out NPR and CNN, but those are also real valid ways that the Department finds out that something is up.

The information, when it is received, goes to--I had to change my notes this morning--it is the Secretary's Operational Center, the SOC, and then the SOC follows its own internal policies. Once again, that is specified in the actual annex ESF-8.

Once notification occurs, once again, as

far as the blood community is concerned, Section D(1)(8) is the important part in here, and it states--I don't like to read slides that are on the screen, but I am going to here--Health and Human Services monitors blood activity and maintains contact with the American Association of Blood Banks Interorganizational Task Force on Domestic Disasters and Acts of Terrorism, and, as necessary, as individuals to determine (a) the need for blood, blood products, and the supplies used in their manufacture, testing, and storage, the ability of existing supply chain resources to meet these needs, and any emergency measures needed to augment or replenish existing supplies.

While it doesn't say so exactly, the bottom line is two slides before this which says that Health and Human Services, the Secretary's Operational Command Center is the one that is notified, the Department is the one that makes decisions regarding blood supply.

We want to and will work very closely with the AABB Task Force, but the whole thing, all the

high-level policy decisions are made by the--the term somebody used this morning--the drug czar, the Assistant Secretary for Health.

Let me talk about the Red Cross here for just a minute. I said I would come back to that. There was some nervousness, well, maybe no nervousness, there was some dis-ease among the blood community about having the Red Cross listed in ESF-8, not only is it in ESF-8, it is also in ESF-6, but its functions under ESF-8 specify that it provides basic first-aid, it assists community health workers, it provides supportive counseling, it provides assistance in temporary clinics and hospitals, and such as that.

It does health resource education referrals for folks who have been affected by the disaster, victims of the disaster. It provides information about coordination of the various types of emergency response, and here is the important part. It provides blood products and services through regional blood centers in coordination with the American Association of Blood Banks

Interorganizational Task Force on Domestic Disasters and Acts of Terrorism at the request of HHS. That is a quote out of ESF-8.

So, ESF-8 has been reworked, if you will, and the role of the Interorganizational Task Force has been emphasized and underscored several times throughout ESF-8.

One of the things that we are doing, and somebody, I think it was Jerry that touched on it earlier, is the proof of concept for the national blood reserve as a way to test the functions of ESF-8 and Interorganizational Task Force.

We had, if you will, a tabletop exercise for the Democratic Convention in Boston, but we have the GOP Convention coming up starting this weekend in New York City, and we are going to actually do a real exercise. We are going to move 60 units of blood, two, 30-unit increments to two different sites on two different day, at two different times of the day during the convention just to make sure that the whole thing works.

Commander Libby is going to discuss this a

little bit more in his talk, but I guess the bottom line is that we are trying to actually make ESF-8 work, and this will be an opportunity for us to try that out. So, that is all I have to say about that.

DR. BIANCO: I think that one problem with ESF-8, the old one, was not the problem that the Red Cross was there, but the problem was that the Red Cross covers about half of the country, and the other half is covered by the community-based independent centers, and as they tried to coordinate with FEMA and other emergency organizations in their states and cities, they were never recognized as the blood providers in the region.

I don't think that this wording and the way things are written now solves the problem, so what you may find is that at the highest level at HHS, at the highest levels there seems to be good coordination, you are testing it, but when it comes to the state level, the city level, as they have to interact with lower layers of the organization, I

wish you could try to address that problem, too.

DR. BRECHER: Dr. Sayers.

DR. SAYERS: Mark, thanks.

Mac, would you go to that previous illustration. This is just to reinforce with emphasis what Celso had to say. What you have underlined in italics there does imply that the only source for blood products and services through regional centers is the Red Cross, and that really is a misstatement of what the national blood supply elements are made up of.

DR. BRECHER: Jerry.

DR. HOLMBERG: Just a point of clarification. I think this is sort of taken out of context, and you are not seeing the full picture.

This section specifically deals with the Red Cross and some of the responsibilities of the Red Cross. The requirement for the management of the blood inventory is the Assistant Secretary for Health and Human Services working with the AABB Interorganizational Task Force.

So, we are not pulling the Red Cross out separately. It is just that they are designated as one of the agencies, so this is one of their responsibilities to facilitate with this, but it is not to imply that they are the only sources.

Now, let me just also tell you, because I know that Dr. Davey has asked for some time to talk about the New York situation. One of the things that we have really emphasized, both in the Democratic and in the Republican Convention, some preparing for those, is the responsibility of the local blood bank.

In that case, for instance, in the New York area, we realized that the New York Blood Center provides 60 percent of the blood supply in that area. The New York Blood Center is recognized as the primary blood center in that location, and we will deal with them directly.

DR. BIANCO: Oh, I am not concerned. I think that the Red Cross has done a very good job in the regions they serve except for Washington, D.C., but the concern it that when those centers

walk into a FEMA office of discuss with them their emergency plans and all that, the doors are shut, because they say you are not the organization we have to talk to, what it says here in the plan, in the older one, is we have to talk with the American Red Cross.

Now it says you have to talk with the American Red Cross and the task force, but the local community blood center, they still have to go through you to get there.

CAPT McMURTRY: Let me back up and talk about this a minute and where this is in the ESF-8. I know that Jerry said that it is taken out of context, and I guess I didn't really explain that well enough.

But each of the agencies that are on this other slide, the responsibility of each of these agencies is discussed in detail in ESF-8. I wanted to point out what the Red Cross was. I think that it is important to know that this last line here, which I took out as a quote, sort of eliminates Red Cross's primacy for the blood supply and gives it

to AABB.

If the folks at FEMA will actually read the thing, which remains to be seen, that should help everybody.

DR. BRECHER: Jay.

DR. EPSTEIN: I haven't read the final draft that you have spoke about, but in the former iteration, one of the issues was that the emergency plan identified the Red Cross's functioning as a federal agency under the direction of the Secretary in times of a declared national emergency.

That was certainly a special role for the Red Cross, and I think that is why the document has to deal with the role and responsibilities of the Red Cross.

So, my question is whether the current version of the document retains that special role, in other words, is it still the expectation that Red Cross will function as a federal agency under the direction of the Secretary.

My recollection is that one of the issues that surrounded part of the confusion of September

11th was the scope of that provision, in other words, did that apply to providing blood products or was it only under the umbrella of certain more general functions, like disaster relief.

DR. BRECHER: Jerry.

DR. HOLMBERG: Yes, the new document does address the activation of the American Red Cross by the Secretary. What it does is it clarifies the roles and responsibilities. In other words, I think that there was a misperception in the past that the American Red Cross was more than providing basic first-aid and first responder type of aid.

So, what we have tried to do is, by adding this last quotation here, is to clarify that they are not out there on their own, that they are part of the task force, and they are working with the task force under the direction of the Assistant Secretary for Health.

DR. BRECHER: Karen.

MS. LIPTON: I think it's clear this wasn't the language that we asked for, and, indeed, this issue has come up at the local level with some

of the independent centers, because in our manual that we prepared for the centers, we tell them don't wait until a disaster to go talk to your local emergency, the FEMA people, or even your other local officials.

Many of the independent centers have done that, and then they have asked us to make sure that we step in as the AABB Interorganizational Task Force to clarify their role. So, hopefully, if everyone does their job, we get these things resolved now. To the extent that people aren't making those contacts or haven't, it could be an issue if an emergency comes up, but we are trying to make sure that that doesn't happen by telling them to be prepared and make the contacts, and we have been helping them.

DR. HOLMBERG: Let me also just say that if you hear of people having problems with FEMA, let me know, I will run interference.

DR. BRECHER: We are going to move on. Thank you, Mac.

We are now going to hear from Commander

Libby--I am sorry, I am out of order. Jamie Blietz is going to talk about the AABB Interorganizational Task Force.

Activities of the AABB International Task Force

Jamie Blietz

MR. BLIETZ: Good morning. My name is Jamie Blietz. I am the Director of AABB's National Blood Exchange. The NBE handles a lot of the logistical type functions for the Disaster Task Force, so I have been asked to provide an update to the committee on some of the activities that have happened in 2004.

The update is going to include what we have termed the national special security event planning activities. These are for like the Republican National Convention, the Democratic National Convention, those types of things, the integration of the task force in the National Response Plan, which Captain McMurtry already alluded to, a little update on the National Blood Reserve, and then how the task force is cataloging the major learning points from real and simulated

events.

We will start out with what we call the NSSE events. These are events that have taken place over the past year, which the task force has been involved in pre-planning for. I think it is important to note that the Department of Homeland Security and kind of the concept of homeland security is still in a state of evolution.

A lot of the agencies, I don't know, maybe they are in the adolescent stage at this point and continuing to grow and learn, the threats are changing, the intelligence is changing, the ability to respond is changing.

So, the task force has been evolving with that, and this year there has been more emphasis placed on single events and looking at the kind of national assistance that might be needed in these locations, and really trying to pre-position that assistance ahead of time.

I think it is important to note, too, that the role of the task force, really, the planning for these types of events has taken place for

months by the local entities, and the goal of the task force is not to come in and interfere with that planning.

It is really there to come in and hopefully complement the planning at a national level, to look at what is already in place, and if assistance is needed, to pre-position that assistance with really the goal of trying to reduce any kind of time lag during an actual event.

One of the things that we have created has been an NSSE procedure, and we worked on that this summer. We actually have an SOP, and in this SOP, for each of the events, we run through a few things. I thought I would share this with you, so you can see the kind of information that is exchanged in these planning sessions.

Typically, we do about three conference calls, two before the event and one after-action report. We look at threat profile, and this typically comes from the SOC, and Dean Ross will typically feed this kind of information. Some of it comes through Dr. Holmberg's office.

In this case, we look at again the area of the event, how many people are going to be there, for instance, next week's RNC, we know there are going to be a certain amount of protesters in the area, the Mets are in town, the Yankees are in town, the U.S. Tennis Open is in town. Don't go to New York next week if you can avoid it.

There is a lot of other ancillary type of events, and we can look at those areas and create what we call a threat profile. In fact, one of the events that we planned for this year, it was determined that the most likely type of event would a truck bomb considering the population, the location, those types of things.

This triggers, based on the number of people, types of injuries, potential casualties, those types of things, and we can use that as somewhat of a baseline. Again, these are really based on probabilities, but it does help out in that planning.

So, we get a threat profile. We look at the major suppliers in the area, and those

suppliers are typically always in these planning sessions. We identify the major trauma hospitals, specifically, those are going to be that victims would be evacuated to in the event area.

We look at the current and projected blood supplies, and these are updated, of course, as we get closer and closer to the event, any transportation issues, immediate issues. One of the major things is to exchange all the emergency point of contact information ahead of time, so that all the participants know exactly who to call and how to reach them.

Then, we conduct an after-action review. We also, we just started this with the RNC, of really creating a standard report that goes out, and it is revised up until the event, and it is sent out to all the participants just prior. Again, this has all this type of information, and then we conduct an after-action review.

The next thing is the National Response Plan. I don't want to spend too much time on this as Captain McMurtry already did. This was the same

reference that he alluded to.

Again, Homeland Security is the one that is driving the response plan, with the goal of getting all of the federal agencies and anyone who has anything to do with preparing and responding to an event, to get them together and to create the response plan.

Obviously, the thing has been to include the task force in this, and it really defines our role in working kind of in coordination with the task force. It was actually very difficult to get this language into the document. I think this is probably one of the only association types of entities that has gotten in.

Typically, it is all the federal agencies, and that was one of the challenges in getting this through. I will say, too, that one of the groups that really did help a lot in this was the American Red Cross in getting this language into the document.

They were super helpful in terms of passing on information as this plan was being

developed to the task force and very open to helping us draft the different pieces that were in there.

The final version, by the way, is due out in about the next two months, so all that you have been looking at, there is no anticipation that any of this language would change, though, in the final.

A couple of quick comments on the blood reserve. The task force continues to advocate for the federal funding for the national blood reserve. In particular, a few of the task force members, AABB, America's Blood Centers, and the Red Cross have sought support from influential members of Congress, as well as HHS and Homeland Security, and appreciate, too, the support of Dr. Holmberg and his staff on his initiative in working with this concept.

There is concern, however, that the highest leadership in HHS still hasn't expressed clear support for the full scope of the blood reserve that the Advisory Committee endorsed last

January, and specifically, we would like Secretary Thompson to publicly state the Department's support for the creation of the 10,000 unit reserve and also funding the public awareness campaign that is needed.

It is very important in order to create this, the public information campaign has got to be in place and be federally funded, so we are asking that the Advisory Committee continue to kind of pressure Secretary Thompson to show full support for the blood reserve.

The last thing here is learning points. We have had several events over the past few years, simulated and real. We had the Topoff 2, which was the largest federal exercise in history, and this was conducted in Seattle and in Chicago. The task force participate in that, got some wonderful learning points in the after-action reports.

We had the Northeast power outages last year in Hurricane Isobel, now Charlie, and even we have already gotten some learning points in from some of the facilities in the Florida area.

Even though they are veterans at dealing with hurricanes, the local authorities pulled a little bit of a switch this year and shut the power down ahead of the hurricane, which didn't seem to affect anybody directly, but you certainly would want to know that ahead of time, so there was some good learning from that.

There have also been many state and regional drills, and the task force has participated alongside other state blood bank associations and individual members to participate in these drills.

It has been decided that the best way to catalog all of this learning is to implement this back into the Disaster Operations Handbook, and this was released nationwide back in March 03, and it is available on the AABB web site. You can just download the PDF file.

It has been discussed and determined that we will take all these learning points that we have been gathering and over the fall we are going to revise the Operations Handbook and re-release it in

early 05. We will put that in there.

It was always envisioned this way, that this Disaster Operations Handbook would be a bit of a living document with these types of lessons learned integrated in.

To end, I think a few challenges that still remain over the next year and years to come is the flexibility issue. As I mentioned, you know, this whole concept is homeland security and defense continues to evolve. The task force, it is important for us to not ever get static in our planning, but make sure that we are moving along and growing at the same rate, and secondly, staying ready.

I know, for myself, I was a long-time California native and got the fortune of living through earthquakes and wildfires, and all those types of things. I was an earthquake preparedness instructor for a while, and it struck how quickly after an event that individuals specifically would fall back into kind of a relaxed state of awareness.

I think that is just a natural thing that happens, the farther you get away from a major event like a 9/11, and there is nothing happened, it is easy to get comfortable and not necessarily stay at the same level. It is difficult to stay at a high level of readiness as we have seen around the country with all the homeland security initiatives.

But it is my hope that this committee, in helping us stay out there, will continue to make disaster planning and preparedness response a top priority for the committee in future meetings.

I did want to end out with a bit of an inspiring story. I just saw this a few days ago. This is a disaster that occurred in Roanoke, Illinois. I am going to show you a picture. This is a manufacturing plant, Parsons Manufacturing, Roanoke, Illinois.

On July 13th, I believe it was, was hit by an F4 tornado. Now, there were about 150 people in and around the campus at the time the tornado hit. This story, by the way, just so you know, this is a

great reminder of how thorough disaster planning pays off.

The employees were in and around, it was 3:30 on a Tuesday afternoon, so everyone was at work. The F4 tornado came through and here is what it looked like after the event, just completely gone. It was I think 246 mile an hour winds, a few other things, I mean just destroyed.

Miraculously, not even one person suffered injury, not even a scratch. You know, you wonder how in the world was that possible. The owner of the plant was interviewed afterwards, and he pointed to the fact that he had just spent a tremendous amount of time, energy, and money really in the planning phase to make sure that his employees were safe.

A few of the things he did were, you know, put in concrete shelters, got linked into the severe weather announcements. He tried to do everything he could possibly do to make sure that if something happened, that they would be ready, and these types of storms hadn't come through this

area in a long time, and his planning obviously paid off.

I think one of the things, his attitude at the end of the day, and this is a thought I want to leave us with here, is that, you know, even though he had spent all this time and energy preparing and planning, you know, he was asked was it worth it.

I wonder, you know, for us here, obviously, those members of the task force, since 9/11 and since the task force has come together, we have spent a lot of time and energy on these types of issues, and specifically, certain organizations and members have really done an outstanding job.

I also want to say Don Dodderidge, our chair, has gone above and beyond the call of duty on several occasions, so folks have really put in a lot of time, energy, a lot of money has been spent, and was it worth it.

I like what Mr. Parsons said when he was interviewed. He said, you know, that on that day, you know, all of the investment that he had put into this was paid back in full with dividends, and

I think the same will be true at the next event that we have, that all of our time and energy will be paid back in full with dividends.

With that, I will end.

DR. BRECHER: Thank you.

One comment, Jeanne, and then we are going to move on.

DR. LINDEN: Just sort of question and suggestion. Is there a reason that you don't coordinate with the state and local officials, because it seems like there is a lot of duplicated effort, and it might be helpful if you did that?

MR. BLIETZ: I think, to answer your question is to kind of explain emergency management, and emergency management, traditionally, the state and local entities are completely autonomous. It is really disasters are to be dealt with at the local level.

If the local resources are overwhelmed, then, they bump it up to the state. If the state resources are overwhelmed, then, the governor calls the President, and there is a nationally declared

disaster, and then federal assets can come in at that point.

The task force really exists at the federal level, the national level, and comes in when those local resources are overwhelmed, if that makes sense.

DR. LINDEN: Yes, but my point is that I direct the State Blood Resources Program, and I collected most of the same information that you did, and I know the City Health Department also was involved in doing the same thing, and my job would have been easier if you had shared your information with me.

MR. BLIETZ: For a specific event that occurred?

DR. LINDEN: Because of the RNC next week. So, it is like there were multiple parties all doing the same thing, and if we had worked together, we wouldn't have all, you know, duplicated the same efforts. Just as a suggestion.

MR. BLIETZ: Okay.

DR. BRECHER: Thank you.

DR. HOLMBERG: I just wanted to make a comment to what Dr. Linden said. What you have to understand is that the area that is in charge is the local community. Once the local community needs additional help, it does go up to the state level, and we are very fortunate to have Dr. Linden in New York and with the planning that has gone on with the blood.

But that is one thing that we have to be extremely cognizant of is constantly involving the state health officials in these decisions. The federal agencies do not get involved until after the state has invited them or asked for help.

So, we have to remember that we have the various levels of responsibility there. One of the things that New York does have is what they call the HERD system, and a lot of the data that Dr. Linden has referred to is a data collection system that is rolled up there, a very, very comprehensive amount of information on that, so just to give you an overview of what has taken place there and the levels of activation.

The other thing that I just wanted to make a point of is that there was another additional lesson learned after the Democratic National Convention, and that was that there were several hospitals that also collect blood in the Fleet Center area, and during the week of the Democratic National Convention, they could not collect blood.

So, what the AABB Interorganizational Task Force had to do was to actually bring in blood to sustain them in addition to adding blood in case of an event.

What we realized about halfway through was recovery, and one of the things that it does describe in ESF-8--and, by the way, Jamie is correct that the National Blood Response Plan does or is the responsibility of the Homeland Security, but as far as ESF-8, that is the responsibility of HHS, is the primary agency for that.

So, in that ESF-8, it clearly states that the Secretary is responsible for even the recovery period after an event. What we realized was that a lesson learned after the Democratic National

Convention was that we couldn't immediately pull out all the resources out of the New England area, that we had to maintain resources and have a backup plan until those hospitals and the American Red Cross got themselves back up and running after the convention.

So, I think that in any disaster planning, you also have to think of the recovery period.

DR. KUEHNERT: I just had one comment onto Dr. Linden's comment, which was that perhaps one thing that could be considered is a representative from the Council of State and Territorial Epidemiologists to be a liaison to the AABB Task Force. That might be helpful as far as enhancing communication.

DR. BRECHER: Commander.

National Blood Reserve, Proof of Concept Using the Armed Services Whole Blood Processing Laboratory

CDR Michael Libby

CDR LIBBY: Thank you.

I will be going over two things. One, I

will be going over the proof of concept, to provide blood products from DoD facilities to New York City for next week, and another thing I will be going over is some of the capabilities of our Armed Services Whole Blood Processing Laboratories, or as we know it, as ASWBPLs.

Proof of Concept, this is an HHS exercise that DoD is participating in, and will be using the ASWBPLs to provide coordinated blood shipments to the New York City area.

While the products that it will be shipping, actually, the number of products will be 30 units--I updated the slide yesterday--but will be two shipments of 30 units of red cell into the New York area.

We do this as daily part of business. We ship blood products between DoD and civilian sources almost every week, every day. The difference is that this shipment will be, as Dr. Holmberg states, will look at the roles and responsibilities of various elements of our government and civilian sectors.

It also will challenge some of our policy issues that we currently have. Communications is very complicated. I didn't realize it was so complicated in how communications work, but as far as the exercise goes in DoD, we will be receiving information from HHS to ASBPO, the blood program office, and we will have our ASWBPL make the shipments into New York.

Ordinarily, what would happen on a real life basis is that HHS would request assistance from NORTHCOM, NORTHCOM being part of the homeland defense system, and they would go through the Secretary of Defense to get approval for the DoD to provide blood support to the disaster to support HHS in this case.

Now, the request would come in through an RSA and Secretary of Defense Rumsfeld was very clear that he wants visibility in any DoD participation in any sort of civilian disaster or any participation in the exercises. That is why the financial reimbursement of DoD is really important in this.

I believe it is a matter of policy that Dr. Rumsfeld, it is between the DoD and civilian sector, whatever it is, there is a law or constitutional requirements that DoD did have appropriate approval before we participate in any kind of exercises, I guess, that requires finances.

Proof of concept brings visibility of DoD activities or ASWBPLs to support blood product needs in a domestic disaster, and hopefully, this proof of concept will eventually lead into us being able to write policy for domestic interagency relationships that haven't been drafted as of this point.

This also tests logistics between DoD and civilians. This includes the transportation issues during the New York events next week. We anticipate some high-end security issues and also, as Dr. Holmberg mentioned, our DoD blood products are almost entirely using ISBT 128 labeling.

The New York Blood Center, I think has an issue about receiving the products that are labeled with ISBT 128 labeling. That is another issue we

need to work on, standardize.

The capabilities of our ASWBPLs, in DoD, we have two of them. We have one on the West Coast, and that is at Travis Air Force Base in California, and one on the East Coast. That is at McGuire Air Force Base. These are DoD facilities, and they support our large unified commands overseas. These are secure facilities. I know on a list the requirements, so we are looking at security.

They are located on Air Force bases, and we have personnel that man these sites 24/7. The capabilities are that they are a central receiving point for all DoD blood centers that receive blood prior to shipment to overseas.

They store blood shipments. I have the amounts listed, ASWBPL East. They have the capability of storing 12,000 units of liquid red cells, 31,000 units of FFP or cryofrozen red cells. ASWBPL West is slightly smaller, they have a capability to store 8,000 units of red cells, 7,000 units of frozen products.

To address Dr. Sandler's concern, none of these facilities have the capability to store or trans-ship platelets. They are designed to have a lot of re-icing capability. They are designed to ship 7,200 units of red cells overseas daily.

One of the functions of the ASWBPLs, as they receive blood products in from our DoD donor centers, is that they will repeat the AB-Rh type on each product and do a label verification. The reason for this is some of these products, when they go overseas, they go to remote areas where AB-Rh typing is not available, and they would have to transfuse the O products on cross-match. So, each product that comes to these ASWBPLs, as you would see them in MPFs, get a repeat verification of the AB-Rh types.

This is just a section showing the blood refrigeration system and also the large pallets are on the lower left. Those that are pallets of 3,600 units of red cells. Each one of these pallets weighs 4,000 pounds.

This is a picture of our crew re-icing

some of the products on a loading dock, also doing temperature checks.

Logistics. Like I said, these facilities are located Air Force air heads. They have tremendous logistics ability to move blood products around.

That is the end of my presentation. Are there any questions?

DR. BRECHER: If not, thank you, Commander.

Dr. Davey from the New York Blood Center had requested to speak for a few minutes.

Rick.

Dr. Richard Davey

DR. DAVEY: Thank you, Mark. I am Richard Davey, Chief Medical Officer of the New York Blood Center. I just wanted to bring the committee up to date with a couple other additional items and information about preparations for the RNC in New York City.

First, I do want to say that from my perspective, this has been a remarkable

collaboration between federal, state, and local officials and organizations.

Actually, I think Jeanne's point, it has almost been a little too much, there has been so much activity and interest, which is great, that it has been a challenge to almost sort out the different groups and activities and interests in making sure that we are prepared, not only for next week, but down the road, both in New York City and elsewhere.

So, I want to thank Jerry in DHHS and Jeanne in New York State, Commander Libby and the government, also, actually, the Red Cross in the Northeast was very helpful for us, also, Dr. Benjamin, Dr. O'Neill have shared information from the New England region of the Red Cross on how they managed the blood supply in Boston, and that has been again very helpful in our preparations, and, of course, the AABB Interorganizational Task Force and Don Dodderidge have been very helpful.

We have been in touch with all of these organizations in our preparations.

In terms of the City of New York, the Greater New York Hospital Association has been very active. Jerry has been there at their meetings with us, so that the hospitals in New York are now coordinated, not only with emergency planning, but with how we are going to handle emergency shipments and supplies of blood in the area.

We appreciate the acknowledgment of the New York Blood Center as the focal point in New York. I think that is appropriate.

The New York Police Department has been very helpful. We are very closely in contact with them, and they have assured us that they will escort any blood deliveries in areas that are secure or areas where there are emergencies, so that there will be no delays in getting through security barriers, we hope.

We have also worked with the Office of Emergency Management in New York City. They have a 800-megahertz radio system which we are now a part of. We have those radios on 24 hours a day, and we participate in the New York City roll call, Fire

Department, Police Department, New York Blood Center twice a day on these emergency radio frequencies, and we will monitor them again 24/7.

In terms of the blood center itself, we have been fortunate with some good planning to have a very good inventory moving into the RNC, so we are not anticipating a shortage. Of course, we can't anticipate what might occur, but we are in pretty good shape in terms of the inventory.

We have decided to move blood out of Manhattan actually into our other regional blood centers in Westchester County, Long Island, and Northern New Jersey, most of our blood in Manhattan, but we want to have a higher percentage of our inventory in our satellite regions. We feel that might be a little better way to manage where the blood is.

Just an aside. Actually, we are holding a blood drive in the Times Squire Marriott for the Republican delegates. That is well and good, but the security people have told us that we cannot announce the time and the place of the blood drive.

So, if I tell you, as they say, I will have to kill you. So, this negates a little bit of the goal there, but we are going to hold it anyway.

Yesterday, actually, we had a drill, a practice drill in the blood center where we called an emergency situation to see if our communications worked, and they did work pretty well. We have command centers in all of our regions. We have redundant communications with lan lines, AOL, Nextel telephones, and then the 800-megahertz system with OEM.

While the drill pointed out a few little glitches, a couple telephone numbers that didn't work, we feel it went pretty well. So, I think with the help of our friends in other organizations, that we are in pretty good shape, not only for the short term for the Republican Convention, but for the long term for other emergencies that might occur.

Of course, we can't tell what might occur, but I think we are as prepared as we can be.

Thank you.

DR. BRECHER: Jay.

DR. EPSTEIN: Rick, could I ask you to comment on Commander Libby's remark about incompatible bar coding?

DR. DAVEY: Jay, as far as I understand it, we do not use ISBT 128, so we are going to have to find additional ways of the exchange of that information. We are working through the logistics of this exercise with Commander Libby, and I think that issues, such as bar coding, actually, paperwork, billing, shipment locations and receiving locations still have to be worked out.

So, we are happy to go through the exercise, see how it works, so that the next time we will have some of these things ironed out.

DR. SAYERS: Rick, I think all of us would be interested to know the donor deferral rates of that Marriott blood drive.

[Laughter.]

DR. DAVEY: Yes.

DR. SAYERS: Particularly as they might compare with the City's averages.

DR. DAVEY: Right.

DR. SAYERS: That aside, when you said that you were redistributing blood, does that include components, you are redistributing platelets, as well?

DR. DAVEY: Yes, we will. We are going to be moving both red cells and platelets, not totally, but a relative redistribution to New Jersey, Long Island, and Northern New Jersey. In terms of the Republican donations, at least we may not have to get the chiller right up there. The blood may be a little on the cold side when we draw it.

[Laughter.]

DR. SAYERS: Others of us are confronted with considerations about redistribution of inventory, so we would be keen to hear what that redistribution did to outdates after this event, we would be keen to hear if you did do this at the expense of--

DR. DAVEY: We can certainly get that information. We don't anticipate that. We have

blood in these areas all the time, so that we don't anticipate that a modest redistribution will affect our outdates in any way.

DR. BRECHER: Rick, I am sure Dr. Sandler would be happy to store some of your platelets.

DR. DAVEY: It is interesting. To Jerry's point, just an aside. One of the issues obviously that has come up to this committee in terms of platelet outdating is the increasing importance of collecting platelets on weekends, Saturdays and Sundays. You have got to collect on Sundays or you are going to run out in the middle of the week.

These are issues that I think are important as we look forward to 7-day platelets or pooling random platelets at the end of storage.

DR. BRECHER: Thank you.

In the interest of time, I think we are going to hold off our committee discussion until right before lunch.

We are going to move ahead to the report for Centers for Medicare and Medicaid. Dr. Hambrick will be talking on the proposed 200 rule

for outpatient prospective payment.

Report for Centers for Medicare and Medicaid Services

Proposed 2005 Rule for Hospital Outpatient Prospective Payment System and Medicare Part B

Edith Hambrick, M.D.

DR. HAMBRICK: Good morning. I have been asked to brief the committee on selective portions of the Medicare Physician Fee Schedule and the Hospital Outpatient Prospective Payment System Rules.

I would just like to preface my remarks by noting that CMS is within the comment period for these rules, therefore, I will be limiting my comments to a discussion of the language found in these rules.

I plan to speak about the proposed payment for blood in the hospital outpatient and non-hospital outpatient settings, payment for drugs and biologicals in the hospital outpatient and physician office setting, and the payment for clotting factors and intravenous immune globulin,

discussion of physician payment rule.

First, I am going to talk about blood. The Notice of Proposed Rulemaking for the Hospital Outpatient Prospective System, or OPPS as we call it, for Calendar Year 2005 went on display on August 9, 2004, and was published in the Federal Register on August 16, 2004.

If you wish to comment, comments must be submitted by 5:00 p.m. on October 8, 2004. I think Jim Bowman might have done me a favor and copied the specific web sites of CMS where you can find the data, so we will distribute that.

The Centers for Medicare and Medicaid Services believes the critical role blood and blood products play in being a life-saving therapy warrant special consideration and treatment.

Since the OPPS was first implemented in August 2000, separate payment has been made for blood and blood products in ambulatory payment classifications, or APCs, rather than packaging them into payment for the procedures with which they were administered.

The APCs for these products were intended to make payment for the costs of the products. For 2005, CMS is proposing to continue making separate payment for blood and blood products under APCs. We also are proposing to establish new APCs to allow each blood product to be in its own APC since a few of the previous APCs containing blood products lack clinical and/or cost homogeneity.

While preparing the 2005 NPRM, we conducted a thorough analysis of our claims data, and by using revised methodology, we were able to rely on claims that hospitals actually billed for blood products.

As a result of using this revised methodology, there was an overall increase of 25 percent in median costs for blood and blood products. For low volume blood products, for example, pooled frozen plasma, we saw an overall decline of 14 percent for 2005.

As I noted earlier, we are proposing to assign each blood product health care common procedure coding system, or HCFC code, to its own

APC in order to improve our claims data for 2005.

Some of the facts that were considered when devising our revised methodology included the information that 81 percent of hospitals billed at least one blood and blood product in 2003. Forty-seven percent of hospitals reported separate costs and changes in the two blood specific cost centers on their most recent cost reports.

Using this information, we matched the two blood specific cost centers to the appropriate revenue codes and found a significant difference in the cost-to-charge ratios for hospitals reporting charges in the blood specific cost center and those without the blood specific cost centers.

Next, for each hospital reporting costs and charges for the blood cost centers on its cost report, we calculated the ratio of the cost-to-charge ratios in the blood specific cost centers to the overall cost-to-charge ratio, followed by a calculation of the geometric mean of this ratio.

For each hospital not reporting costs and

charges for the blood cost centers on its cost report, we applied this mean ratio to its overall cost-to-charge ratio.

We then adjusted charges to costs for all hospitals and calculated the median cost of all blood products. For low volume HCFC codes, we employed the following methodology to determine the payment.

In order to increase our sample size for determining a payment rate for these low volume blood HCFC codes, we combined claims from 2002 and 2003, and updated the claims from 2002 to the base year 2003 using the producer price index.

After combining the two years, we were able to raise the volume of blood units billed for five or about half of these products to over 1,000.

Next, I will talk about blood products administered to non-hospital outpatients. For blood products administered to outpatients who are not hospital outpatients, payment is made under a reasonable charge basis.

In accordance with regulations, the

reasonable charge may not exceed the lowest of the actual charge or the customary or prevailing charge for the previous 12-month period ending June 30th, updated by the inflation indexed update.

The inflation indexed update is calculated using the change in the applicable consumer price index for the 12-month period ending June 30 of each year.

Manual instructions for determining the reasonable charge payment can be found in the Medicare Claims Processing Manual. If there is insufficient charge data for a code, the instructions permit considering charges for other similar services and price lists.

Also, for certain codes, for example, the codes for whole blood and leukocyte reduced red cells should be applied to the blood deductible. Payment may not be made for the first three pints of whole blood or equivalent units of packed red cells received under Medicare Part A and Part B combined in a calendar year.

Next, I am going to move on to talk about

the 2005 payment proposals for drugs and biologicals.

As some of you may remember, the packaging threshold was $50 for 2004, and will also be $50 for 2005. The same threshold was used in 2004, as I mentioned, is mandated by the Medicare Prescription Drug Improvement and Modernization Act of 2003, or MMA.

Hospitals will receive separate payment for products that have median cost for administration that are greater than $50. Some of the biologicals, for example, gamma globulin, will receive separate payments.

Drugs and biologicals that have pass-through status as of December 31, 2002, will continue to be paid as specified covered outpatient drugs in accordance with the payment limits established by the Medicare Modernization Act.

In 2005, as some of you recall who have read it, there are three categories of drugs. The first is sole source drugs, which will be paid between 83 percent and 95 percent of the reference

average wholesale price or AWP. Factor VIII falls into this category, for example.

The second category is innovator multiple-source drugs, which we have paid no more than 68 percent of the reference AWP.

The last category is non-innovator multiple-source drugs which will be paid no more than 46 percent of the reference AWP. The reference AWP is defined by the MMA as AWP for the product as of May 1, 2003.

Drugs and biologicals with, and new drugs and biologicals without pass-through status in Calendar Year 2005 will be paid at a rate that is equivalent to the payment that these items would receive in a physician office setting.

This payment rate will be established in accordance with the methodology described in the Medicare Physician Fee Schedule Rule, which I will be discussing shortly.

Payment for separately payable drugs and biologicals that never received pass-through status from the beginning of OPPS was based on the median

costs derived from the 2003 hospital claims data.

MMA requires that we pay drugs and biologicals for which there is no HCFC code at 95 percent of AWP. We proposed to implement this MMA provision by requiring hospitals to bill a not otherwise classified alphanumeric HCFC code and to show the NDC number for the item, the charge, and the amount administered in the Comment Section of the claim.

Fiscal intermediaries will manually price and pay these claims.

Now, on to the Physician Rule. The Notice of Proposed Rulemaking for the Medicare physician fee schedule went on display July 26, 2004, and was published in the Federal Register on August 5, 2004.

Again, if you care to comment, comments must be submitted by 5:00 p.m. on September 24th, so that you can see that the comment period for the Physician Rule closes a little bit earlier than the OPPS Rule.

I am going to talk about clotting factors,

drugs, and intravenous immune globulins administered at home.

First, the clotting factors. For clotting factors furnished on or after January 1, 2005, CMS proposed to establish a separate payment of 5 cents per unit to hemophilia treatment centers and home care companies for the items and services associated with the furnishing of blood clotting factor.

These items and services include the mixing and delivery of factors including special inventory management and storage requirements, as well as ancillary supplies and patient training necessary for the self-administration of these factors.

With regard to drugs, Medicare Part B covers a limited number of prescription drugs and biologicals, which generally fall into three categories: drugs furnished incident to a physician service, durable medical equipment or DME drugs, or drugs specifically covered by statute, for example, immunosuppressive drugs.

Section 303 of the MMA revises the payment methodology for Part B covered drugs that are not paid on a cost or prospective payment basis by establishing a new average sales price or the infamous ASP that you have all heard about, drug payment system beginning in 2005 for almost all such drugs.

The new ASP drug payment system is based upon data submitted to us quarterly by manufacturers, which are due to CMS not later than 30 days after the last day of each calendar quarter.

For multiple storage drug included within the same HCFC code, the Act requires that the Medicare payment allowance be equal to 106 percent of the ASP for the HCFC code.

For a single source drug HCFC code, the Act requires that the Medicare payment allowance be equal to the lesser of 106 percent of ASP for the HCFC code or 106 percent of the wholesale acquisition cost of the HCFC code.

The payment limits are subject to

applicable deductible and co-insurance and other limitations, such as those concerning widely available market prices and the average manufacturer prices in the Medicaid Drug Rebate Programs.

The calculation of ASP and limitation on the use of ASP data are described in the rule, and I urge you if you have an interest, to review it.

Lastly, we will talk about the coverage of intravenous immune globulin for treatment of primary immune deficiency diseases in the home beginning for the dates of service on or after January 1, 2004, the MMA provides coverage for intravenous immune globulin for the treatment of primary immune deficiency diseases in the home.

The Act defines intravenous immune globulin as, "An approved pooled plasma derivative for the treatment of primary immune deficiency disease." It is covered under this benefit when the patient has a diagnosed primary immune deficiency disease, it is administered in the home of a patient with such a diagnosis, and the

physician determines that administration of the derivative in the patient's home is medically appropriate.

The benefit does not include coverage for items or services related to the administration of the derivative. For coverage of IVIG under this benefit, it is not necessary for the derivative to be administered through a piece of durable medical equipment.

Contractors are instructed to pay for the drug and may pay any entity licensed in the state to furnish intravenous immune globulin. Payment will be furnished to the entity with the authority to furnish the drug. Beneficiaries are ineligible to receive payment for the drug.

Pharmacies and hospitals dispensing IVIG would bill the durable medical equipment regional carrier or DMERC. Home health agencies dispensing the immune globulin would bill the regional home health intermediary, and physicians furnishing IVIG for the refilling of an external pump for home infusion will bill the DMERC.

That concludes my presentation. If there are any questions that I can answer, I would be happy to.

DR. BRECHER: Dr. Sandler.

DR. SANDLER: I have a comment and a question.

Again speaking as a member hospital of the American Hospital Association, if I understand it, the proposed payment in 2005 for the most common blood product, which would be a leukocyte-reduced red cell, is $167. That would be an outpatient.

The American Red Cross in this community, their price list is $272. So, the proposal is in the right direction, there is a 40 percent increase, but for the record, my understanding is the payment will be 167, but most hospitals in this region are going to have to pay the Red Cross 272, so there is still a ways to go.

The specific question is do I understand that an outpatient who uses one, two, or three units of red blood cells, that payment is not going to be made, because most people coming to the

outpatient don't get more than that, you know, they get one, two, or three, what is the payment for outpatient red cell transfusions, the first three units?

DR. HAMBRICK: This is not specifically my area, and if you have a specific question about that, you could send me an e-mail and I will forward it on to the people who handle the blood policy.

Are you talking about hospital outpatients or non-hospital outpatients with respect to these first three units?

DR. SANDLER: I am referring to what you read.

DR. HAMBRICK: Which is talking about non-hospital outpatients.

DR. SANDLER: Okay, non-hospital outpatients. If there is a non-hospital outpatient who needs one, two, or three units of blood, what is the proposal for paying for those three units, which someone has got to pay for?

DR. HAMBRICK: As I said, this is not my

area of expertise. As I understand it, it is subject to the deductible and co-payment, so if indeed those units are included in that, then, I would imagine that the beneficiary would. However, as I said, please send me an e-mail, so I can get you a definitive answer to that question.

My e-mail address is ehambrick@CMS.HHS.gov.

DR. BRECHER: Jerry, I think that does tend to underscore things that the system has become so convoluted, nobody understands the system for payment.

Chris.

MR. HEALEY: Thank you. You can imagine that PPT and the industry, and I am sure a lot of the consumer organizations will be submitting comments on these proposed rules.

I would just like to note that under Part B, the physician fee schedule, the rule that has come out does indicate a 20 percent reduction for the recombinant clotting factor VIII, and that, of course, is a concern to us, that is, that reduction

is based on the new ASP reporting mechanism that was recently introduced, that the companies are reporting their ASPs average sales prices.

Given the fact that that is a new reporting system and a new methodology, we would like to make sure that the data that CMS are relying on are valid and accurate, that they have a sufficient database before they come out with a final schedule on that.

Again, the 20 percent reduction there is concerning.

Secondly, on the OPPS, we noted that the A1PI products, the alpha products have likewise seen a 29 percent reduction in payment under this proposed rule, again, very alarming, and we are concerned in that instance that maybe it doesn't adequately account for some of the innovation that has taken place in new products on the market.

So, two hits there that are very concerning, and you will imagine that CMS will be hearing from industry and others, as well.

DR. HAMBRICK: As to your first point, as

you I am sure are aware, those data that were published as far as the Physician Rule represent the first quarter of data that we have, because obviously, I have not seen the data for I guess it would October-November, which hasn't been sent in yet, but those will be the ones upon which you will be paid in 2005.

So, hopefully, as you mentioned, the reporting mechanisms will get better. Obviously, we are relying on what the manufacturers report, so if the manufacturers report something that is less than that, you know, CMS can only rely on the data that they are given.

As to your second point, please, if you make comments to the rule, and you feel that there is data that has been left out or not considered in developing our payment rates for 2005, specific information that could be publicly available, remember that anything you submit for comment is publicly available, so please don't submit any proprietary information thinking that it will be held confidential, but submit it to the Rule with

specific information about where you think those costs might be being lost or our methodology.

Then, we can take a look at it and respond to them in the final rule.

DR. BRECHER: Judy.

DR. ANGELBECK: Do we have a copy, does the committee have a copy of your comments, Dr. Hambrick?

DR. HAMBRICK: No.

DR. ANGELBECK: Can we get a copy?

DR. HAMBRICK: It is what is in the rule. I have taken whatever I have read straight out of the rules from the Medicare Physician Fee Schedule and the Hospital Outpatient Rule.

DR. HOLMBERG: I have submitted in your notebook, both the Physician and the HOPPS ruling, and we will have the transcripts that will be available, so that you can go back.

DR. HAMBRICK: And if I have misspoken, what is in the rule is what is correct.

MR. ALLEN: I would like to ask that we ask Dr. Hambrick and whoever else she feels, as

necessary, to come back at a later date. I did not know that this issue would be brought up at this committee, and there is a lot of issues along this line that I would like to discuss with her and whoever else she feels could answer some of these additional questions, to help us not only deal with these issues and the barriers that they cause, but also find some solutions to these issues.

There is just too much to try and deal with right now.

DR. BRECHER: I agree that reimbursement is a major issue. We have had a meeting in the past that dealt with this, and I imagine we will address this in some depth in the future, as well.

Dr. Heaton.

DR. HEATON: In general, it seems that CMS has really attempted to improve APC rates, and I very much commend this effort, but an ongoing issue is the failure of the hospitals to provide cost reporting. In fact, only 47 percent provided specific cost reporting in the database that was used to calculate the AWP rates.

My specific question is, is what action CMS is undertaking to encourage the hospitals to improve their cost reporting, because in this case, you had to average out the costs using the CCR ratios between those that reported and those that didn't. Obviously, the key issue here is to improve the accuracy by getting the hospitals to complete proper cost reporting structures.

So, what actions are you taking to improve that?

DR. HAMBRICK: Every year, we ask that hospitals accurately report all their costs, so that they can be swept up in not just our payment system, but other payment systems where cost reports are important.

I am sure that hospitals feel overwhelmed by the numbers. There is CMS, there is Blue Cross/Blue Shield, there are a number of different data reporting mechanisms. I am sure that there are Medlearn and outreach efforts, not specifically about blood, I can't speak specifically to blood, but about reporting all their costs appropriately.

We have the same problem when we have expensive devices. When we have pass-through status for some expensive devices, even though the hospital could receive a separate payment for, say, the ICD lead, they didn't report them, so therefore our data, you know, does not contain those costs.

So, that is an ongoing dialog that we have with AHA hospitals and whenever we put out, I am sure the Inpatient Rule, as well.

DR. HEATON: Usually, nothing concentrates the mind as much as the prospect of not being paid for an expense that you know you are going to incur. I believe that there is much that CMS could do to raise the priority for the hospitals to complete this documentation in a more accurate fashion.

I guess the second observation I would like to make is that you have used the producer price index to make some adjustments for some of the less frequently used product lines.

The difficulty there is that the PPI, particularly in the case of plasma derivatives,

this is a classic boom and bust market, and therefore, while it may be true that there is a decline in the PPI index for some products for a short period of time, if you look over a significant period of time, that is a very inaccurate measure of the cost of certain products.

A question I would have for you is we have asked on a number of occasions that CMS pursue outside data to calculate or to generate an accurate estimate of the actual purchase price.

Is there any action in that area to look at actual outside costs?

DR. HAMBRICK: We have asked on--I have been with the agency about 18 months--and we have asked for specific data from some of the large, I won't say blood producers, they don't produce the blood, but suppliers, and what we need are specific invoices and data such as that.

I am not going to speak for them, they are here to speak for themselves. Some of that information has not come. We have had a good working relationship with some of them, and they

have provided us with some costs of things, but the invoices and the types of data and documentary proof we usually require for every other, like the device manufacturers, et cetera, sometimes has not come for each of the blood products.

DR. BRECHER: Chris.

MR. HEALEY: To your point there, PPTA went in and met with the General Accounting Office because, of course, they are doing this hospital acquisition cost survey, and that was exactly the point we raised, is that in a cyclical market, with the plasma derivatives, you can have highs and lows in the pricing, and whatever sampling method they use, they need to make sure that they are not capturing either the peak or the valley there, and they need to find a way to look on the longer horizon, so they get an accurate presentation.

DR. BOWMAN: Just a quick clarification for Dr. Sandler, the blood deductible I think is in statute, and it is the responsibility of the beneficiary, and I believe it's a calendar year deductible for three units, but I will follow up

and get a more thorough response for you on that.

DR. BRECHER: We have a comment. We might as well move into public comment.

Public Comment Period

MS. WIGMAN: Just briefly, this is Teresa Wigman from the American Association of Blood Banks, and I will be speaking to your advisory panel next week, so I won't go into too much detail.

In terms of background for this committee, AABB is pleased that CMS has paid more attention to blood this time around in its proposed rulemaking for outpatient payments in 2005, and with the direction that most payments are going for the larger volume products.

However, I think further analysis is needed in that area to make sure that all those payments are truly adequate.

I would note that we are particularly concerned about the payments that have been proposed for low-volume products, and, in fact, they have come up with a methodology that has

actually decreased the payments for these products. On average, I think it is a decline in payments of 40 percent for low-volume products, and some of these products, you say they are low volume, but they can hurt the hospital a lot because some of them are the more expensive blood components.

For instance, granulocytes collected by pheresis, they are proposing to pay this coming year $791 as opposed to $1,249 last year, so that is clearly problematic to our community. So, at a minimum, we would say that the agency should turn to using external data for those products that they have clearly come out totally off base in their proposed payments, and we would be willing to work with the agency on providing that data.

In response to Dr. Heaton's comments and concerns about hospitals still not providing adequate cost data, we continue to think that that is a concern, and as we have said repeatedly to your committee, we, within AABB and others in the blood banking community, are trying to work on that be educating hospitals, but we cannot do it alone.

We need improved and clarified guidance from the agency to try to help our hospital members get through this complex web of reimbursement guidance, which leads them not to submit accurate claims data, because it is so confusing to them.

Thank you.

DR. BRECHER: We are in the public comment period.

MS. VOGEL: Thank you. My name is Michelle Vogel from the Immune Deficiency Foundation, and I will be talking later about reimbursement issues and how it affects our community, but I just want to address one major issue that you spoke about, and that is the new benefit for home infusion for primary immune deficiency patients.

You discussed and there is language that CMS came out with that is affecting patients' ability to receive the new benefit, and it is the language that states, "For coverage of IVIG, it is not necessary for the derivative to be administered through a piece of durable medical equipment."

What that has done is if a patient receives IVIG through an infusion pump, which most patients receive it through an infusion pump, the claims are being denied because they say that the infusion pump is medically unnecessary, therefore, the drug is medically unnecessary.

This is going on in many different regions, and we are pulling claims data of the denials, and what is happening there is that some of the home care companies are trying to transfer the patients to the old-fashioned gravity drip vads, which takes twice as long to do the infusion, which typically last maybe three to five hours, maybe even up to eight hours, so double that, and especially if you are not covering the nursing services and the patients have to pay for that out of pocket, it gets very expensive.

I want to just point out one example just to show you where this gets very costly and what is happening. I have a patient in Boston, who is in a skilled nursing facility, who no longer can receive IVIG through the veins, who went to a port, can no

longer receive it through a port, so needs to go subcutaneous.

This person wants to go out of a skilled nursing facility into a community-based setting, okay. It is a developmentally disabled person, so is currently Medicaid and Medicare eligible.

If they leave the skilled nursing facility, Medicare becomes the primary, and if they do that, subcutaneous has to be administered through an infusion pump, Medicare will no longer cover the drug.

So, that patient is stuck in a skilled nursing facility, which is a lot more expensive.

DR. HAMBRICK: You mean the interpretation by the regional home health intermediary, the DMERC, because the statement, as I read it, and I can understand how that interpretation could be made, and I will take that back with me, but it just says it is not necessary for it to be--it doesn't say that it has to be, it doesn't have to be. It just says it is not necessary.

But--I am not arguing with you--

MS. VOGEL: Using that terminology, "not necessary," it is being determined that therefore we don't need to infuse through an infusion pump, and all the clinical trials on the products were used through infusion pumps, that is the technology.

So, if that language can be changed, the DMERCs will start covering, and the benefit can start being utilized, which is what the intent of Congress was.

DR. HAMBRICK: So, do you plan to write a letter or come and see us about it?

MS. VOGEL: Oh, I have been. I have had meetings and worked with the members of Congress, and will be submitting comments, but if you can take that back, that would be very helpful.

DR. HAMBRICK: Okay.

MS. VOGEL: Thank you.

MS. PEMBERTHY: To end on a positive note, when CMS does something correctly--and I will introduce myself, Shannon Pemberthy with the National Hemophilia Foundation--when CMS does

something correctly and does it well, we want to say thank you.

So, I wanted to say thank you very much. I had the opportunity, along with PPTA, to testify before your committee in February of this year regarding the Hospital Outpatient Rule and some misclassification of products.

Our interest was the misclassification of clotting factor products, some as single source, some as multi-source, and the speed at which the committee adopted our recommendations and then in which CMS implemented those, I think the committee meeting was in mid-February, and by the end of February, there was a program memorandum sent out to all the intermediaries noting the correction.

I just thought it was incredible. So, thank you very much for that. You could have made us wait until the Rule came out. Instead, they moved quicker to immediately solve what had happened and corrected it. Thank you.

DR. HAMBRICK: We try to follow the law, follow the regs, and be of service to the

beneficiaries and to the Medicare Program.

MS. SAVORY-TAYLOR: Hi. I am Mary Beth Savory-Taylor with the American Hospital Association. I wanted to respond briefly to the comment that was made about hospitals and coding particular types of services within an overall service. I just want to make a couple points.

Number one, we are paid based on diagnostic-related groups, DRGs, and because of that, we are paid a lump sum of money.

With that in mind, it hasn't historically been advantageous, if you will, for hospital to go through all the individual coding of every single component within a service, because, for instance, an x-ray or blood historically was a smaller sum of money, so therefore, because we are paid again with a lump sum of money, it didn't make any sense to really write it down.

We are starting to see blood costs going up and up and up. As a result, we are educating our members, I know others are doing, as well, we are educating our members about the importance of

coding blood and blood components.

Finally, though, I would end with that again because it's a zero-sum game, it's a budget-neutral system, we aren't paid our full costs for both inpatient, as well as especially on the outpatient side. I know Dr. Sandler has made the point many, many times that each new test that comes along, each new procedure, there needs to be new money into the system, so that it does really benefit the patient in the end.

But we appreciate your comment, we are trying to do a better job with coding, but recognize that it is, from an historical standpoint, that blood was a smaller sum of that overall amount of money, and it really didn't make sense for hospitals to expend those additional resources to get every single component of that particular service noted, and it is start to now, with the increased blood costs, make a difference, and we really are working with our members on that.

Thank you.

DR. HEATON: I have a specific question.

Is it not correct that blood is usually the single largest expense line item of support laboratory services in the average hospital, provided by a single vendor?

MS. SAVORY-TAYLOR: I would not be able to answer that question. I can certainly get back to you. What I can tell you is that as a percentage--now, recognize blood is only roughly 1 to 2 percent depending on the size of the hospital and that type of thing--the blood costs have gone up dramatically again within that small percentage of a hospital's overall budget.

But I don't know if blood, in and of itself, is a highest driver. I suspect it might be particular drugs, but I may be incorrect. And, Dr. Sandler, I don't know if you could comment on that.

DR. SANDLER: I can't comment on that.

MS. BOSTIC: My name is Elena Bostic. I am the Executive Director of the Hemophilia Association of New Jersey, so I am here to make a statement for the record from a consumer perspective.

The current situation in hemophilia reimbursement for Medicare recipients, our most vulnerable population, is that they are registered with a home care company, and the home care company writes the 20 percent co-payoff as bad debt with financial justification.

Treatments for hemophilia are expensive. The average cost is 100- to 150,000 a year. A Medicare recipient and many others cannot afford 20- to 30,000 a year every year.

My question is, with the new Medicare Rule, who will pay the co-pay? What will occur in hemophilia treatment is this: They will be forced back to the emergency room. Most emergency rooms do not stock clotting factor, so treatment will be delayed, they will have to be treated either in an emergency room or, in many cases, admitted, and we are setting hemophilia care back 20 years.

We will be back to show you the data then.

Thank you.

DR. HAMBRICK: I guess my response to that would be that whatever the normal practices are

when a beneficiary is not able to pay a co-pay and for the providers who provide that service would be in effect, whether that is off writing it off as bad debt, whether that is if they duly eligible, Medicaid picking up part of the co-pay, if they have third-party insurance, Medicare--I am blanking on the name--but if they have supplemental Medicare coverage, then, that, but whatever the normal processes that would pay for a co-pay when someone is unable to pay, those would be the processes that I am sure the providers will go through to get their money, or either write it off as bad debt, or to collect money from alternate sources.

MR. HANNON: I am Tim Hannon. I am an anesthesiologist from Indianapolis.

I have one general comment for the committee and then one sort of economic comment. The general comment for the committee is as an anesthesiologist that is involved in blood conservation and with blood banks at the local and state and national level, one thing that I think has been conspicuously absent from this committee

is any comments about better blood utilization as part of the picture to improve blood safety and availability in the United States.

There has been a number of people in the Transfusion Medicine Committee that have commented that in excess of 15 to 20 percent or more of transfusions in the United States are unnecessary, unwarranted, or sort of nonsensical. So, as emphasis as part of the drive to increase blood safety and availability for better blood utilization, I think is warranted from this committee.

The other comment from an economic standpoint, I am also an MBA, and I just finished a book chapter on economics of transfusions. Even if Medicare today would pay for the actual sales price, so to speak, of blood products, that sales price or procurement price probably only reflects about 25 percent of the total cost to deliver that blood product in a hospital setting, accounting for labor, supplies, managerial overhead, et cetera.

So, even if Medicare today provided that,

you would still have substantial shortfalls in terms of your actual costs. What that really should be at the local hospital level is again better blood utilization would also help with that, as well, because again, although the cost of blood, it is a resource-intensive process, that every time you transfuse a unit of blood, you also use nursing resources, laboratory resources.

There are some links between increased ventilator stay and infection rates, et cetera. Each unit that you reduce in your hospital through better blood utilization practices, also then reduces nursing time, laboratory time, and potentially hospital length of stay, as well.

Thank you.

DR. BRECHER: Harvey.

DR. KLEIN: I think the comment that we need to emphasize, better utilization of blood is sort of like mother and apple pie, and I think certainly we all endorse that. The urban legend, the 20 to 25 percent of transfusions in the United States are inappropriate, I think is just that. We

have tossed it around since before the AIDS epidemic.

It may well be so, but I don't think we have any data really to support that, or if there are such data, I would certainly like to see them.

MR. ROMANO: I am Jim Romano with the Hemophilia Federation. I know most of you know Jan Hamilton, unfortunately, she couldn't be here.

But I am echoing the concerns of the Hemophilia Federation when I say that we are very concerned with the rule. We are concerned that it is going to limit the access of our patients through home care, and we are also concerned with our lack of response from CMS to our concerns that the Hemophilia Federation has brought to their attention.

I am hoping you could take, Dr. Hambrick, that they need to start meeting with hemophilia patients and actually seeing firsthand how this rule is going to affect them. Like Elena said, the 20 percent co-pay is a major, major problem for our patients, and if our home care companies aren't

going to provide that treatment because they are going to not be able to write that 20 percent off, the patients are going to suffer.

I think CMS has to show a little concern for that.

Thank you.

DR. HAMBRICK: I think CMS is always concerned about access to care, however, there are regulatory or statutory, which the outpatient 20 percent co-pay--and I repeat that this particular part is not my area of expertise--but with all hospital outpatient services, there is a 20 percent co-pay, so that would be across the board, which is what Congress has mandated.

But we will be sensitive to that, and I also believe that within he statutory and regulatory guidelines, we will be willing to assist. Certainly, if you have met with people from the agency, if you would like to, give me a call or send me an e-mail, and then I will see that I can do about facilitating another meeting if you feel that those were not successful or

satisfactory.

MS. LEE: Hi. My name is Teresa Lee with the Advanced Medical Technology Association. Thank you, Dr. Hambrick, for your remarks on hospital outpatient PPS and on the Physician Fee Schedule.

I wanted to just clarify one thing, and that is that clearly, those two settings are very important for blood, however, the last statistics I saw was that approximately 80 percent of blood is still being used in the inpatient setting as opposed to the outpatient setting.

As Dr. Heaton mentioned, the PPI for blood and derivatives, which is the basis for payment in the inpatient setting, has been very unstable, and working in coalition with the blood groups in addition to AHA and trying to bring attention to the fact that we need some significant improvements in the inpatient setting, as well, in terms of capturing the costs of blood.

So, I wanted to just put that down as a marker for this committee to support the efforts of our coalition in terms of trying to improve payment

in the inpatient setting, as well.

Thank you.

DR. WONG: I don't mean to just focus on one group of patients, but I just want to find out where we stand on NOVO 7 reimbursement in inpatient setting, because we are $3 million in debt at our hospital this year just for treating this special group of patients who need the product. It was FDA indicated, medically indicated product. But is it grouped under Factor VIII?

DR. HAMBRICK: I am sorry, I didn't hear what class of drug or product you are talking about.

DR. WONG: NOVO 7 reimbursement, is it grouped the same as the rest of recombinant Factor VIII products?

DR. HAMBRICK: Are you speaking of inpatients, outpatients?

DR. WONG: Inpatients.

DR. HAMBRICK: I don't deal primarily with that. If you want to send me an e-mail, I can find out, because I don't know about the inpatient

reimbursement. As someone mentioned, it's a DRG payment, and you are paid according to that classification, a lump sum.

So, I can refer that to someone on the inpatient side if there is a specific question about that. We do have some new tech payments, and I don't know if the product that you are talking about would fall into that category where you can get additional payment under a bump you up, but, in general, you know, you are grouped according to all of your diagnoses, comorbidities, complications, and that determines the level of payment.

DR. WONG: That would be very helpful. Thank you.

DR. HAMBRICK: Okay.

DR. BRECHER: Celso.

DR. BIANCO: I want to ask for your help. We heard from several people, Mary Beth left the room, that one of the reasons why the hospitals don't work in providing you with the data in terms of breaking down the categories, is because it doesn't make any difference.

What difference would it make if everybody would be perfect and provided you all the cost data to the total, what difference would it make to the total reimbursement of a hospital? Would it change their lives, or will they still be simply interning--that is what they tell me--reallocating funds, dividing, crossing different lines of the same pie and being able to recover all the costs that they have?

DR. HAMBRICK: Certainly, Congress has limited certain pots, like OPPS is a relatively fixed pot except for pass-through drugs and certain things, which, of course, is Part B, and Part A, inpatient, has a relatively fixed pot. There are certain things we can pay extra for.

So, if you are thinking in the macro sense, perhaps it wouldn't, but for us to pay you appropriately for OPPS, the way the system has been set up, and the way Congress has asked us to do it, we have to have accurate cost data.

So, some would be a little perturbed if, let's say, something was getting more money,

relatively speaking, than another area which they were interested in. Yes, in some respects, it is a zero sum game, there is a limited amount of money, but perhaps that hospital in that region, that makes a big difference.

DR. BRECHER: Dr. Hambrick, thank you.

We have on the schedule a committee discussion, but it seems like we have been having committee discussion as we go along, so unless there is a burning issue from the committee, I would suggest we break for lunch.

We are going to come back and discuss reimbursement later in the meeting again.

We have an hour. We are going to re-meet at quarter of 2:00 to reconvene.

[Luncheon recess taken at 12:49 p.m.]

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

DR. BRECHER: Now that all the speakers are here, we will move to the topic of raising donor awareness and we are going to begin by an update on the Ad Council Initiatives. Mr. Scott Caswell, from the ABC will begin.

Update on Ad Council Initiatives

Scott Caswell, ABC

MR. CASWELL: Good afternoon. Mr. Chairman, ladies and gentlemen of the committee, my name is Scott Caswell and I represent America's Blood Centers, a non-profit association of community blood centers. I am here this afternoon with Mr. Ryland Dodge, of the American Red Cross and Mr. Marc Pearce, of AABB, to report to you on our joint national blood education and awareness campaign.

It was a year ago this month that representatives of the three organizations spoke about their strategies to increase blood donation and each of us mentioned this campaign so it is entirely appropriate that we bring you up to date

on our progress.

The campaign was kicked off in July of 2002 as the then AABB president and blood center executive, Dale Malloy, brought representatives from the three blood organizations together to discuss a joint campaign. We began meeting with the advertising council later that fall, and last summer we concluded an agreement with the Ad Council for this campaign. Our presentation today is divided into three parts. I will give you a little bit of background then we will talk a little bit about the emergence of the campaign and its current status.

As members of this committee, you are very familiar with the challenges blood centers face. The bottom line is we need to bring donors into our blood centers each and every day of the year on a regular basis. We need new donors and we need regular donors to donate one more time. We need to reestablish for some and instill in others a culture of giving blood among Americans.

Essentially, this is where we are today.

But we all recognize that the face of America is changing and we, the blood community, need to recognize and adapt to this reality. This campaign is taking aim at young adults, 17 to 24, to make blood donation real for them. Why this group? It is the sheer numbers, the largest demographic group since the baby-boom generation. We also know that this group, while in high school, is prolific in giving blood but we lose them after they graduate. It is no coincidence that the fall and the spring are the high water marks for blood centers' collection throughout the year and the increased activity can be linked to greater high school blood drive activity.

Joining up with the Ad Council was a significant milestone for our three organizations. The Ad Council is very selective about the issues and organizations it chooses to work with and they chose to work with us on this campaign. In return, we agreed that no national campaign targeting this particular group of donors would be undertaken at the same time. The Ad Council, in addition, was

also attracted to us because we represent a significant amount of grassroots support in communities throughout the United States and they can count on the support of our members, our chapters and our regions to promote this campaign.

This campaign has also presented us with an opportunity to collaborate with some new corporate partners, particularly in the media and the advertising world, as well as several government entities such as the Department of Health and Human Services. While we have excellent relations with the Department, the Ad Council is involved with various government agencies in a variety of campaigns and that relationship helps us to solidify our relations with the U.S. government. This campaign also provides us with an opportunity to consolidate our resources to create greater awareness of the need and the importance to give blood.

A little bit about the Ad Council--it was founded in 1942 as the war advertising council. It rallied both funds and moral support necessary for

America to win World War II. The Ad Council also gives us the opportunity to harness the power of public service advertising to change attitudes and behaviors of Americans. It is important to note that we are not paying for any of the advertising we receive for this campaign; it is all donated media.

The Ad Council, rather than disband following the war, chose to evolve to tackle pressing and relevant social problems of the day. The mission of the Ad Council is to identify a select number of significant public issues and stimulate action on those issues through communications programs that make a measurable difference in our society. The Ad Council today is recognized by the media and the public as the preeminent expert in public service advertising and for the highest quality creative work. The Ad Council is better poised to compete in today's media environment for donated media time and space on behalf of its clients.

With any advertising, education and

awareness effort, it can be very difficult to quantify the results to allow for further reflection and to assess success or failure. The Ad Council has a proven record of success and understands the need to prove its value time and again. How we intend to measure the success for this campaign will be discussed later.

Ryland Cross, ARC

MR. DODGE: Good afternoon. I am Ryland Dodge, and I would like to take you through the next section, which is actually developing the campaign.

To actually develop this project we got together with the Ad Council and selected EURO RSCG worldwide, which is actually known in the industry as the Messner Ad Agency, from New York. They are advertising and communications experts and they were responsible for developing the campaign strategy, the creative approach, as well as the production of materials. As Scott mentioned, this is a pro bono campaign. They donated their services to this campaign.

The campaign goals had to be developed, and that was through research, to come up with a comprehensive outreach plan for nationwide media support. It also entailed reaching our target audience, which is young adults, using non-traditional forms of media--Internet, web sites, partnerships with stores, universities, a network of co-branded messages, etc. The bottom line is we want to creatively explore the options that best reach the target audience.

Messner conducted research with our target population and some of their general findings are here. Currently their target audience only relates to the broad-level issues that directly impact them. They don't feel they can make a big difference on large social issues. They are a bit self-absorbed due to the life stage they are in and if it benefits them they may consider it. They also feel busy and pressed for time so they only get involved in issues that impact them or someone they know.

The exploratory research found some

interesting observations about the young adult target group. They care more about friends and direct family members than the community or the world at large. They are concerned about major events, like 9/11 terrorist incidents, but also car accidents that may impact friends or family, and this gives them a real reason to participate. These are the things that they respond to. But the process itself of blood donation is very mysterious to them. Unless there is a personal reality-based association for them on some level, they don't respond.

In general, they need to become more aware. We must position blood donation as a simple, effective way to make a difference. The issue is not "top of mind" for the target audience because they aren't aware it can directly impact them or their peer group. While they are more motivated by the idea of helping a loved one than a greater sense of duty, they can be motivated to consider helping others once they understand how and why their help is needed. They stated an

interest in more "in your face" type messages, like the anti-smoking truth campaign, versus celebrity spokespeople or more general promises.

The effectiveness of this campaign will be assessed in several ways--donated media dollar, and this will be calculated by measuring TV, radio, web and out-of-home materials provided on a quarterly basis, and a tracking study will gauge advertising and issues awareness on a weekly basis over a one-year period. Also, we will track the hits to the web site and monitor that for use and questions that come through there.

At this time I would like to turn the floor over to Mark Pearce, from AABB, who will describe the details of the campaign.

Marc Pearce, AABB

MR. PEARCE: Thank you, Ryland and Scott. I felt fortunate that they gave me the fun part, which is to present the material to you. You have heard a little bit about how the three organizations got together, and I think you have heard a little bit about how we, I believe, did our

homework with the use of Messner in looking at these gen wires, which are 74 million strong, to come up with these two campaigns that I am about to present to you now.

One of the big questions we had was how do we reach this group who, as of right now, don't know and don't believe that blood donation is an issue for them. What we did was we came up with two different campaigns. One is a traditional campaign and one is a more non-traditional campaign. The traditional campaign we refer to as "save the world." It is a powerful truth and we look to take issues that are important to this group--world hunger, industrial pollution, global warming--and take that and say, yes, you know, those are important issues. You can't necessarily save the world but you can save a life by donating blood, and that is really where this first campaign is looking to attract the donors.

The second one, and that is one where I am hesitating, is called a grabber. We spent a lot of time developing this one and it refers to the

gentleman as Al Blood. I can't tell you a lot about Al Blood because it is non-traditional. I can tell you that Al is a puppet, and Al is a puppet that oozes blood and is looking to inform you and educate you about blood donation and the fact that you have an extra pint to give. But, as I said, it is non-traditional and we, right now, have Al in a development stage as a puppet and you will hear more about him later.

As I said, "the save the world" campaign is traditional. We are going to be looking to traditional mass media to get the message out. Radio and television will be the primary media of communication for this campaign. We have radio and TV spots that I am going to be showing to you in just a minute and I hope that you will find them enjoyable. Once again, I want to mention that this is for the demographic group 18 to 24 years old. Al Blood will be disseminated differently. It will be a web-based approach in distribution. This might be something that you will get in your in-box. I know that recently I have been betting

political web clips in my in-box and, hopefully, in the future you will be seeing Al Blood in your in-box.

So, the site kits that we have developed with the "save the world" campaign include this material, and these site kits are going to be distributed through the Ad Council to over 20,000 media outlets, both radio and TV. That is the Ad Council's responsibility. Our responsibility as the blood community is to distribute this to our members and to our regions, and that is our job. I think Scott spoke briefly about this, that this is not only a top-down from the Ad Council's perspective but we, as the blood community, have a bottom-up responsibility. So, we are looking to target media outlets, and in particular media outlets that focus on this demographic age group, the WB network, MTV, Viacom TV outlets, as well as radio stations that target this demographic group.

With that, I have a couple of PSAs for you to see.

[Video presentation]

["When I found my jeans were make in child labor and sweat shops I wrote a letter to the company saying reconsider your labor practices. A few months later I get a letter back saying thanks for being a loyal customer, and they included a coupon for a 25 percent discount on their jeans. So, I got smart; wrote letters every day to all the stores that carried the brand, asking them to stop supporting the companies using child labor and sweat shops, and I just kept getting letters back thanking me for my concern and more coupons for more discounts on more jeans.

So, I'm telling my friend about it and she flips out, saying between all the letters and coupons some paper company cut down a small forest, driving off two indigenous tribes, hundreds of endangered animals and killing thousands of plant species, some of which may contain vaccines for HIV, cancer and syphilis. Meanwhile, the guy is cutting down the trees for 13 year-old kids who work night and day for months just to save up enough money to buy a pair of jeans made by child

labor in sweat shops."

"I heard about this company dumping toxins in local rivers and I called their executives to say stop, but they were too busy counting profits while the rivers were being destroyed and birds and fish are dying and the local kids are getting cancer. So, I organized a huge protest and I actually got the company shut down, and now half the town is unemployed and the kids are twice as sick since they can't get healthcare since their parents lost the insurance they had when they worked for the company who dumped all the toxins in the first place."]

MR. PEARCE: So, those are the three pieces of material that I have to present to you today. The goal of this campaign is to drive the traffic to the web site. This is a web site that is actually operational right now and I would recommend that everybody in the room go and visit it. It is www.bloodsaves.com. It is completely operational. On there, you really can learn--well, hopefully you already know, but you would learn

more about blood if you didn't and, certainly if you are in this age demographic group you wouldn't know about blood or we assume you wouldn't and that is one of the reasons to go, visit it.

On this site is primary education and that is really the goal of the campaign. It is not necessarily one time to increase donations as much as it is to increase education about the need to donate blood as ongoing. We did realize, of course, that people would visit this site and one of the first questions they would want to ask is, well, where can I go to donate? So, yes, it does have a search engine that has been designed by the Red Cross, ABC and AABB that includes all the sites where you can donate blood in certain geographic regions, done by zip code. It also includes other features, one of which is that you can actually e-mail this link to a friend and that is one of the ways we were looking to spread this information.

This is the web site that will be up that we are going to use. A lot of the success of this project is people visiting this web site and

passing it onto their friend, and if they don't see it through the "save the world" campaign, hopefully, Al Blood will be coming to your in-box very soon.

These are the three of us presenting here today, Scott, Ryland and myself. There have been many individuals involved in this project and it has been a learning experience for all of us. Vicky, who is here, and Sharon and Jennifer have helped us make the team. This group of people also has been helping Jerry with the "Donation Nation" campaign that HHS has been working with.

So, I think what it has afforded us, at least with this campaign--one of the take-aways from this campaign is that the relationships that AABB, ABC and ARC have built, which is why we call it Operation AAA in case you haven't figured that out by now, has helped us work as a good team on other projects. So, when projects like Donation Nation come along it is very easy for Jerry to know who to get in touch with, where he can use the resources and we can all work together. Thank you

very much. If you have any questions let me know.

MS. LIPTON: Actually, you said something or I think it might have been Scott who said something that surprised me and I didn't recognize. The studies were based on focus groups, right, of kids this age, 17 to 24, and you said the celebrity role models are not particularly compelling. We talked about this on this committee about why don't we get celebrities involved in this. Is that what you actually did say?

MR. PEARCE: That is correct, yes, that it wasn't as effective as we originally thought and that was certainly one of our assumptions going into it that was disproved.

DR. PENNER: It is certainly a respite from our political ads and I would be very happy to have you use these in our State of Michigan and get rid of some of those others. On the other hand, we have always in the past been very successful because the automotive plants were willing to donate time for their workers to come down and we had large numbers of donations as a result of that.

Since they have withdrawn that access, I think that has had an impact at least in our area. I don't know if that is true elsewhere.

The last note is that it still comes down to the fact that I think local community, person-to-person operation is the most effective way of getting blood donors out when your neighbor asks if you are going down to donate, you do. Whereas, if you see an ad you don't necessarily get the gumption to get out of your chair and march down.

MR. PEARCE: And I think the three organizations completely agree with you. That is why when we started looking at this campaign and saying do we want to do blood donations, you know, do we want to bring out new blood donors, the answer to that was no because it can be done better at the local level. I think we felt, as the three organizations together, that we can do public education better at a national level but not blood donation at a national level. So, we really tried to focus on the education. We look at this

campaign as a way to, if you want, soften the market so that when a donor recruiter at a local level goes in they reach a more informed consumer.

But it is the component of the campaign that I am very excited about and, certainly, we will be getting this information out at the AABB annual meeting in Baltimore, in October. We will also be getting it to all members of the three organizations before that, that is, the recruiters on the local level can take these kids into their TV and radio stations and get them placed and then they can be prepared for the response that they get if they need to.

DR. KUEHNERT: It seems like the key is getting them onto the web site. So, I was just wondering if you have some ability to have it pop up on search engines. You know, if they hear the commercial but don't quite catch the web site name, that it will come up in a search.

MR. PEARCE: Yes, we have worked with the Ad Council to put in certain key words in order that it does pop up when they search. As well, the

three organizations have separate words that they would like to keep the pop up for them.

DR. SANDER: Somewhere along the line the catch-phrase that one donation can save three lives has gotten into everything and it is now in three of the ads that you showed. I think if that were tested against evidence-based medicine it wouldn't stand and, since you want to really be credible, I think you want to go back not to this group here but to some other folks and just ask them if they think that one donation, that is to say, an FFP, a platelet and the red cell, each of those saves a life. Dr. Penner says it could in pediatrics and I would agree with that.

DR. BRECHER: It probably doesn't hurt the lives.

DR. SANDLER: No, but the point is one FFP is not going to save a life. One sixth of a dose of platelets isn't going to save a life. And, if someone asked me real hard did I save three lives when I gave blood I am going to have a hard time saying, yes, you saved three lives.

DR. BRECHER: Particularly when they didn't make the random platelet.

DR. EPSTEIN: One donation can help save three lives.

DR. SANDLER: Is that what you read? It is not what I read.

DR. EPSTEIN: No, no, no, I am just saying that it is more correct--

DR. SANDLER: You are getting my message. Thank you.

MR. PEARCE: But my question is did you like the videos?

[Laughter]

DR. SAYERS: Marc, the focus groups--one of the bullets made the point that individuals in these groups only relate to broad-level issues that directly impact them. You know, homelessness is something that this group feels removed from. Yet, those rapid-fire TV ads really sounded as if they were addressing issues which the focus groups suggest the targets are not interested in.

MR. PEARCE: I think they want to know

that they can make a difference. So, what we are saying is that we have an issue where you can make a difference, and that is that donating blood can help save lives. So, we are trying to first get their attention to issues that they know about. They know about global warming; they do know about world hunger so these issues have relevance to them. Yes, they would rather work on issues like Habitat for Humanity where they can look and turn around at the end of the day and say I built a house. They want to know that the volunteering that they are doing is having an impact in their community.

So, I think the challenge we have is (a) to get their attention with something that is relevant to them that they have heard of and part (b) is to make sure that they know that our issue is relevant to them and that they can make a difference in their local community, and that we are not wasting their time. We are not asking them to go out and protest and nothing at the end of the day will have an impact to them and their

community.

DR. BRECHER: Marc, maybe I missed it but when are these going to start running?

MR. PEARCE: Mid-September. The campaign will be distributed in mid-September. That doesn't necessarily mean that TV and radio stations will immediately pick it up. Usually they work on a quarterly cycle so you could see them pick it up immediately but it also could take a quarter for it to have an impact.

DR. LOPES: I hope these work. I think though probably the high point in blood donations came from a sense of citizenship. You didn't give blood because you supposed that your unit would save a life; you didn't vote because you thought that your vote would make a difference. I think the kids now do want to have that assurance that what they do matters. We may need to focus on something that goes back to a sense of community and citizenship in giving blood in some other social areas.

DR. BRECHER: Right. It does seem to fit

what a lot of new commercials seem to be like. My girls have always commented that watching an advertisement, we don't know what it is about until the very end.

MR. PEARCE: I think that is a good point. This is the first set of distribution of materials that we have. This is a three-year campaign. We are going to have another round of production of PSAs and I think we will certainly be looking to doing lessons learned after this campaign and possibly even focus on some of the issues that Jerry mentioned with minority donations in the next round, but certainly those things will be determined later.

DR. BRECHER: Thank you, Marc.

MR. PEARCE: Thank you.

DR. BRECHER: We are going to move on to the Give Life Foundation, Bart Fisher.

Give Life Foundation

MR. FISHER: Thank you, Mr. Chairman. I don't have a Power Point presentation so I prefer to address you directly, if that is all right.

My name is Bart Fisher and I am chairman of the Give Life Foundation. I am also a lawyer so I can go on Jerry's list also--a rogues gallery of lawyers in the room here--and probably even worse than that, I am a lobbyist. So, that is two negatives I guess. Most importantly though, I am a parent and I am here really in that capacity more than anything else today.

What we are trying to do at the Give Life Foundation is to focus on the availability of the blood supply, not the safety issue because we leave that to others but we think that becomes academic if you don't have the blood to work with. So, we think the first order of business is to get the blood supply to where it should be, and we have all heard today the problems that are there.

Just a few words about the Give Life Foundation, we were started last year; we are just a start-up. Patrick Hughes and I started it. He is an entrepreneur and he regrets that he can't be here today to talk with you. The purpose of the Give Life Foundation is to promote the donation of

blood, blood products, organs and tissues. So, we set upon ourselves a very broad mandate. We intend to support the activities of the Department of Health and Human Services to create Donation Nation, and for more information about our foundation you can go to our web site at www.givelife.org.

What I would like to do is just address a few points as to what our activities are going to be, and you might wonder what we could possibly be doing following these three august organizations in the blood area who have told us of their plans for the Ad Council campaign and what our niche could be. Basically, we are looking to New Year's Day. We have a focus which is that we want to harness the power of reaching that younger demographic that they were talking about but do it with a focus on New Year's Day.

We have a very simple idea which is based on the life experience I have had, which is as a former teacher and baseball fan also. The three times of hope, it seems to me, are spring training

when everybody can make the team; the first day of school when everybody can get straight As; and New Year's which is the time of hope. So, we intend to have every American make it his or her New Year's resolution to give the gift of life, whatever it is; whatever you can do--blood, blood products, organs, tissue.

This is very simple and yet it can be very powerful, and it can be a powerful adjunct to what you just heard, in fact, because we intend to have a New Year's Eve special on CBS which will feature celebrities--and that was an interesting discussion before about the power of celebrity in our culture and we probably have a difference of opinion on that. We think role models are very important for young people. But we believe that this can be a celebration of life and we believe that we will get public service announcements flowing out of our New Year's Eve special that will go through the whole year and that, in fact, are many days of giving through the year. You could give your New Year's resolution and say, well, I will do it on my

birthday; I will give blood on my birthday, whenever that is through the year. We think New Year's Day is a very powerful day because January is typically the worst month for blood donations. They are down and that would be a good time to have visibility.

So, the first activity is the New Year's Eve special. The second activity is working with a group called DECA, Distributive Education Clubs of America, which is to marketing what Future Farmers of America is to farmers. It is marketing students. There are 300,000 of them across the country in high schools and colleges and they are going to work with us to do dance marathons. Again, that will help us capture the younger demographic. We agree totally with the thrust of the prior presentation. We are also in discussions with NCAA about trying to use ball games at half time for the Gift of Life New Year's resolution idea, again using celebrities and athletic personalities to do that.

So, that is our New Year's program and we

are very focused on that. It may work or it may not work but we intend to capture New Year's Day the way Jerry Lewis has captured Labor Day for his charity. We think the association with New Year's--hope, optimism and giving the gift of life, celebration of life--is going to be very powerful. We are working with Hill and Norton, which is a public relations firm, on this campaign and we are very excited about it.

As I mentioned before, I am a lobbyist so I also want to talk for a minute about the national blood reserve issue because the Give Life Foundation will operate in the public policy arena as well as advertising and we are very concerned about the situation in terms of the national blood reserve. We want to endorse the comments made this morning by the AABB representative to encourage Secretary Thompson to publicly endorse the national blood reserve. I have distributed a letter to the committee from the Department of Homeland Security where they have endorsed the national blood reserve, and that needs to be supplemented because

what we are working on, on the Hill, is trying to get appropriations for that, and at least getting committee report language that calls for the creation of a national blood reserve.

So, any advice this committee gives should focus on this national blood reserve recommendation to the Secretary to publicly take a leadership role. He has been so great on so many other issues, including organ donation, that this can be another feather in his cap.

Basically, those are my comments. I think my background might be of interest. I founded the Aplastic Anemia and MDS International Foundation in 1983; was a co-founder of the National Marrow Donor Program and I am on the board of directors of the Marrow Foundation. So, I have been on the organ issue side more than the blood issue up to this stage but what I have seen and heard today has made me, if anything, more concerned. What I have seen is fragmentation. I have seen an indication that there are no platelets today in the area, at least that we know about, know where to find. We see NIH

doesn't want to be a depository for that and they have their own resource agenda. So, I speak as a parent of a son who died of aplastic anemia in 1983 who was living on platelet donations. And, the idea, a parent, is if there aren't platelets sitting out there ready for use by people in need, to me that really points out the problem.

We look out over the land and we see a country where fewer than five percent of the people who could give blood do so. We see blood down last year 20 percent. We saw less blood given last year than four years before. We see a crisis. And, we see an issue that has gone beyond being a public health issue; it is a national security issue. So, if this committee does not advise--as its function should be--the Secretary to take a leadership role to publicly call for the national blood reserve I think it will be remiss in its duty. It is very important for the country, and how we do it and get from A to Z needs to work out on the Hill. But we have not waited. We have submitted an unsolicited proposal for FY-2004 monies to the Department of

Homeland Security seeking 17 million dollars for this national blood reserve. But we don't think we can wait for the 2005 funding cycle. We don't think terrorists think in terms of funding cycles. We need this now and half of the money we requested would be for an awareness campaign and the other half for the acquisition of blood supplies.

So, we are working diligently at DHS. DHS is in discussions with HHS. But we need to move this issue at work speed and it is not moving at work speed right now. Thank you very much.

DR. BRECHER: Thank you. Any comments, questions? If not, we are open to public comment if there are any public comments. Mark?

DR. POPOVSKY: Mark Popovsky, Haemonetics Corporation. I want to go back to the Ad Council comments. I thought I heard a slight but perhaps material discrepancy between the first two presenters regarding the target group. Is it 17 and above or 18 and above? If it is 18, I think that would be a mistake because in almost every state in the United States 17 year-olds can donate

blood, and as one of the committee members indicated, what we do know, and we certainly have precious little data about the social science of blood donation, is that donations started early tend to become a habit. So, I am wondering if someone could respond to that.

MR. PEARCE: It is 17 to 24.

DR. POPOVSKY: Thank you.

DR. BRECHER: We are actually ahead of schedule. We could take a break but I think it is pretty close to lunch so I would suggest we move on to the next topic, which is transfusion-related acute lung injury, and Mark Popovsky is going to give us an update.

Transfusion-Related Lung Injury (TRALI)

DR. POPOVSKY: Good afternoon. I am going to wait for a pointer but I want to thank the committee for inviting me, Mr. Chairman and Mr. Secretary. I have been asked today to address an issue that has certainly grown in interest and importance to the U.S. and, in fact, world transfusion medicine community, that being

transfusion-related acute lung injury.

As all of you in this audience are aware, the lung has not traditionally or typically been viewed as a target of injury from transfusion. However, a physician who is confronted with pulmonary complications in the setting of transfusion will need to compile a diagnostic list that would include some or all of these entities and perhaps even more, and time does not allow me to go into the rationale for distinguishing these entities but all of you are certainly away of anaphylactic and allergic transfusion reactions and circulatory overload as being conditions that can manifest with pulmonary symptomatology and signs and symptoms. Hemolytic transfusion reactions can, in fact, frequently present with pulmonary complications, as can bacterial contamination. However, the subject of this presentation--really the sine qua non, is the presentation with respiratory distress, that being transfusion-related acute lung injury.

This slide has been adapted from an

excellent review paper by Drs. Webert and Blaichman that was published last year in Transfusion Medicine Reviews. What they did for us was to cull the literature and ask the question of the various signs and symptoms that have been associated with transfusion acute lung injury what is the frequency in relative terms for these various symptoms and signs. So, several of them are very common, and you can read this table as well as I. So, the first five, the dyspnea, hypoxemia, pulmonary edema and hypotension, as well as a febrile response, are all viewed as being very common. Slightly less common but still happening with some frequency are tachycardia and cyanosis.

Hypertension is sort of on the cusp between common and uncommon, and then three other phenomena, leukopenia, hypocomplementemia and mono cytopenia, have all be described but, frankly, they have been described so infrequently that it is hard to associate them with some type of relative term.

However, if you are a physician or are a nurse who is administering blood and you are in the

operating room or, in fact, at the patient's bedside, what are the signs and symptoms that you are most likely to see? So, in one retrospective study of a rather sizeable cohort Dr. Becky Haley and I looked at this and asked the question what was that presenting sign or symptom that called attention to itself that ultimately led to the diagnosis of TRALI? There were three. There was respiratory distress, hypotension and, interestingly enough, hypertension which then subsequently became hypotension.

What is the time line for the clinical features associated with TRALI? We know that from the onset of a transfusion the vast majority of cases fall within a window of one to two hours. In my view at least, the literature tells us that 100 percent of the cases will occur within six hours. Secondly, this always occurs in the setting of plasma-containing transfusions.

This x-ray which really I have pulled from my cases series is certainly not diagnostic but it is also extremely typical of a patient who now has

been diagnosed with TRALI. It is certainly non-specific but it is severe in its acute form, with the presence of acute pulmonary edema that eventually involves the entire lung fields.

Actually, I apologize to the Chairman. I did not adhere to his request this morning, which was to declare any potential conflicts. I am actually presenting to you today as a subject matter expert in the area of transfusion-related acute lung injury and not as an employee of the Haemonetics Corporation. I should have done that at the outset and I apologize.

What are the clinical features associated with TRALI that are important or helpful to the clinician? One is that the hypotension that is often seen both outside the operating room and in the operating room does not respond to intravenous fluids.

Secondly, there is often a discrepancy between the severity of the symptomatology and the findings on oscillation. So, although rales have been observed, they are often not very impressive.

Diminished breath sounds are not very impressive. Also, in most cases but not all, because this does not involve fluid overload, one would not see the other stigmata associated with overload, that being that one would see normal jugular venous pressure, absent third heart sound and, if available to you, one would see either normal or low pulmonary wedge pressures.

The blood products that have been reported in the literature associated with TRALI really run the entire gamut, of those available to us, over the last half century beginning, of course, with whole blood to fresh frozen plasma and red cells of every type preparation anticoagulant preservative combination, granulocytes, cryoprecipitate which is important because of what it doesn't contain, a lot of plasma, so illustrating, even though there have been only one or two cases in the literature, that in fact a small volume of plasma is sufficient to trigger the reaction. The same holds true for platelet concentrates and, to round out, platelet pheresis has been commonly associated with this,

and there are few well-documented cases of IVIG.

The most frequently implicated blood products, again culled from the literature, are red blood cells, fresh frozen plasma, apheresis platelets and platelet concentrations, of course, the three or four most commonly used blood products today and over the last 20 years.

I guess one last point is that several investigators have shown that, even though I pointed out the association with reports of infusion of cryoprecipitate, there is an association between volume of plasma and the frequency or incidence that has been reported in the literature. So, there is some association there between volume of plasma in the units and the presentation of the condition.

TRALI has been known to us as a described syndrome really for 21 years now. The definition that Brendon Moore and I used is as follows, and it was done with some care in that we recognized that this was, in fact, an example of acute lung injury. We felt that it fell within a spectrum of acute

lung injury that was, at one end, as mild or somewhat more severe in certain instances as noncardiogenic pulmonary edema to the adult respiratory distress syndrome at the other end. Because we wanted to define an entity that would be clear to the user, the clinician, and be helpful, we deliberately chose not to include other confounding factors that might in fact get in the way of reporting. So, the instances of patients who are overloaded or who have other underlying respiratory disease certainly could develop TRALI but for the purpose of this first definition, and we published it in 1983, we chose to use this, if you will, more narrow definition of acute respiratory distress, severe hypoxemia, acute bilateral pulmonary edema, hypotension typically moderate in severity, and fever, all occurring within six hours of a plasma-containing transfusion, and we excluded these other factors, cardiac disease and respiratory disease.

Now, we were impressed in our early studies with the severity of the syndrome. A

hundred percent in our first large series required oxygen support; almost three-fourths required mechanical ventilation. There appeared to be two paths of courses for these patients. The majority, 80 percent or more, followed a course of rapid radiographic, physiologic and clinical improvement, such that within 96 hours these patients were well on the way to full recovery.

There was a second group, about a fifth of these patients, who in fact took longer to recover. If they did recover--or, I should say if they did not die from the condition, then they followed one of these two paths. However, about six percent in our first series, in fact, died. However, to underscore the point of recovery, unlike ARDS, which often leaves permanent pulmonary sequelae, when these patients were retested physiologically six months later or a year later, in fact, they showed no evidence of any underlying disease.

I owe this slide to Dr. Honess, and I apologize for not having the reference here. But he presented data from FDA at the recent TRALI

conference in Toronto that shows why perhaps we are as interested in this condition as we are today, which is that over time, with increasing recognition, TRALI has moved up the list of important complications, such that at least for these three fiscal years TRALI is now the most common reported transfusion-associated death, with ABO hemolytic transfusion reactions and bacterial contamination close behind.

Supplementing what I just showed you is that from four different sources we can get a sense of the mortality rate which for transfusion is very high, 6-23 percent that has been reported in the literature. So, what is the incidence? Well, this is one of the major questions that we attempted to answer at the recent Toronto conference. The fact is that we don't know the incidence. From the Mayo Clinic from the early studies that Brendon Moore and I published, we found that 1/5,000 plasma-containing products was associated with acute lung injury.

However, you need to know two important

points that could have had an impact on the data. First is that this was a medical center that was highly educated to TRALI over a very short period of time because of, first of all, the influence that the transfusion medicine department had at Mayo, and the kind of broad announcements and education that we gave to the nursing and medical staff at the Mayo Clinic. Secondly, Mayo is a unique institution in that it has specially trained nurses who administer all of the non-operating room transfusions, at a huge medical center. So, we had a group of nurses who, in fact, were as well trained in transfusion reactions as any physician. So, we don't know. That said, I think it is fair to say that we do not know the current incidence.

This table summarizes and illustrates the wide disparity in reports of incidents. The two important columns here are the risk per 100,000 units and risk per 100,000 patients. Just scanning both columns, you see that there is a 100-fold and actually in some cases several 100-fold difference between the lowest reported incidence and the

highest, and including some of the differences shown from the SHOT data from the U.K., showing the difference between red cells and platelets risk per 100 units. So, it illustrates the problem that we have as a community in trying to understand the frequency.

One thing that is clear though is that this is under-reported. So, from Pat Kopko, Paul Holland and myself, a paper that we published two years ago, illustrates, again through a retrospective study, looking at a case in which 50 patients received blood from a donor linked to fatal case of TRALI. Without going into the detail of it, looking at various outcomes and then looking back and reviewing the charts, I found from the charts that were still retrievable that there were as a spectrum of symptomatology that had respiratory symptoms--some mild, some severe--two patients, interestingly enough, had two reactions, but only two of the eight severe reactions were even reported to the transfusion service, illustrating a lack of recognition and

under-reporting, and that was the point of our paper.

So, who is at risk? What we can glean from the literature is that there appears to be no difference in gender in developing TRALI; no particular age predilection; no particular disease or diagnosis predilection, and I will come back to that in a minute; no medications. A question arose from the literature and from the Toronto conference as to whether or not multiple transfusions or even a single transfusion is, in fact, a risk factor for TRALI and we really were not able to resolve that question at the conference.

Now, from Les Honess' recent paper in Transfusion Medicine Reviews looking at admitting diagnoses of TRALI fatalities reported to Food and Drug, the point here is to illustrate that nothing really pops out at you. Again, this is through the filter of cases that by themselves were selected, recognized and then reported to Food and Drug, with various underlying diagnoses. So, they run a full spectrum of conditions that most hospitals would

confront.

So, is there a spectrum? There would appear to be, and that spectrum runs from something that is mild with dyspnea and fever to the full-blown syndrome originally described in the 1980s.

It is of importance and I think of interest to show that before 1983, 1985 there were other entities that were almost certainly TRALI but were given other names across the spectrum of the clinical literature. I think that is one of the reasons why it wasn't recognized. There were few case reports in the critical care literature, anesthesia literature, surgical literature, internal medicine and even blood banking literature. But the common theme here with regard to laboratory findings was the presence in either donor units or implicated donor serum or plasma or in the recipient prior to transfusion of either or both leukoagglutinating or lymphocytotoxic antibodies.

To go to the first papers that actually

described transfusion-related acute lung injury from the Mayo Clinic, we found a very repeatable observation, that whether it was a very small study or a much larger one, there was the presence of Class I antibodies in at least one donor unit given to the patient in the prior six hours for the onset of symptoms, and/or the presence of leukoagglutinating antibodies and, interestingly enough, a correspondence between antibody and antigen in a very high proportion of these cases and, as other investigators saw prior to 1983, recipient HLA or leukoagglutinating antibodies in a small but not insignificant number of cases as well.

So today, to understand the pathogenesis, I think most people would agree that this is a condition that involves increased microvascular permeability in the lung, and that perhaps there are two pathways to get to the same point. One is through leukocyte antibodies, typically in donor units but perhaps in the recipient, and, as Dr. Silliman and Ambruso have described, the notion of

a two-hit model involving biological response modifiers and bioactive lipids.

To just briefly summarize the pathogenesis of the literature, I think it is fair to say we don't know the precise mechanism but there is certainly overwhelming observation of, as we saw in the Mayo studies, the presence of donor HLA or granulocyte specific antibodies of any one of the antibody specificities that are found and a high degree of concordance between HLA antibody antigen in at least half the cases. We know that these antibodies activate complement, and we also know from experimental lit and from the clinical literature of ARDS that C5A promotes neutrophil aggregation and sequestration in the microvasculature of the lung. We know there is margination of neutrophils in the pulmonary microvasculature. We know that when these neutrophils are activated they are going to release their biochemical substances, and we know from experimental literature that that fact results in endothelial cell injury and pulmonary edema.

From elegant studies a decade ago, from Seeger in Germany, in which in an ex vivo lung model of TRALI he and his team used cocktails of either 5B positive polymorphic nuclear cells with or without the presence of an anti-5B source, with or without the presence complement, and then ran this profuse it through a rabbit lung to see what changes would be observed.

To summarize, basically over time the only combination that resulted in significant increases in lung weight, which was the parameter being measured, was having the presence of antibody antigen and complement. To add more support to this antibody-mediated model, from Drs. Kopko and Holland we know that their important contribution was the identification of Class II antibodies, as well as Class I, in a large number of these cases. So, they found an antibody antigen correspondence, either Class I or Class II, in a very large proportion of their cases and they found that in six cases, if you took monocytes from patients who had TRALI and incubated them with serum from

implicated donors with TRALI, you found that there was significant expression of cytokine in tissue.

From Europe there is another interesting study, one of the only prospective studies in the TRALI literature, in which patients were randomized to receive plasma in an ICU setting, either from multiparous donors, defined as having three or more pregnancies, or non-multiparous plasma. These are 102 ICU patients. They received FFP. Five of these patients had clinical reactions, one of which was clearly transfusion acute lung injury. That donor was multiparous.

Then, interestingly, he observed that there was suppression of the PAO2-FIO2 ratio in the recipients of multiparous donor plasma, raising the question of what is in multiparous plasma that would, in fact, cause this expression.

From Dr. Freedman, in Canada, at the Toronto conference, he presented some intriguing data looking at the presence of antibody in their cases and clinical severity. So, of patients who recovered without the need for ventilation, 45

percent had antibody identified in the workup as opposed to 69 percent in those who recovered but needed ventilation, and those who succumbed and died had an even a higher percentage of antibody positivity.

If we go back and look at this two-hit model that Chris Sillman has described very elegantly, in his model you have underlying pulmonary endothelial activation due to some condition, whether it be surgery or infection. Then there is a second event with the infusion of biological response modifier from stored blood which results in acute lung injury.

Now, in the U.K. there have been developments that I think we need to take note of. This was again presented at the recent ISBT congress, and they found that 89 percent of their cases that they were able to work up through the SHOT hemovigilant system were associated with leukocyte antibodies. They found excess of deaths attributed to either FFP or platelets, 47 percent for the two, compared to the total number of units

that those two blood components represent. They found that FFP and platelet cases, 91 percent of those cases included a donor, a leukocyte antibody female donor. As a result of these data, they made the policy decision that they would divert female plasma--so plasma from female donors--away from the mainstream production that led to fresh frozen plasma production. In essence, they are creating FFP from males only.

So, what needs to be done? What are the things that we as a community need to consider in making policy? Clearly, if we knew who was at risk this would go far to being able to identify and ultimately prevent this problem, but today we can't. But we clearly need data in that regard.

Secondly, we need to identify the hot donors. Clearly, there are many donors every day who have these antibodies in their blood which are transfused to recipients who do not develop any signs or symptoms of TRALI. But we still have this body of data that I just shared with you regarding the presence of these antibodies in association

with the condition. So, one possibility would be to screen multiparous donors who are going to be destined for either platelet or FFP products for HLA and/or granulocyte antibodies.

We also could develop, in conjunction with or separate from the preceding, a product management scheme in which we defer the donor who has been implicated in a TRALI case--most blood centers are doing that today, or we could identify those donors; let them donate, but limit their donations to plasma-poor products so we would wash or freeze red cells from implicated donors but not make platelets or plasma. Or, we could, as in the U.K., divert plasma from females who are antibody positive. These are all choices that we have before us.

In conclusion, TRALI is an under-diagnosed, under-reported but very serious problem in transfusion medicine. It clearly represents a spectrum of lung injury from the very mild to the very severe. It appears that antibody-mediated injury is the primary mechanism

but not the sole mechanism because I believe several pathogenic models may, in fact, be operative. We clearly need prospective, multi-center studies. Finally, in my view, we need to take proactive steps to reduce the risk. Thank you very much.

DR. BRECHER: Thank you, Mark. We will open it for questions.

DR. LOPES: During World War II an awful lot of plasma was used. I am sort of surprised that TRALI was not recognized back then and wonder if it is something that you don't see where the primary problem is trauma and bleeding, or if something has happened since that has increased the level of the antibodies to be found in plasma.

DR. POPOVSKY: It is an interesting observation. The first case report is from 1951, clearly after the end of World War II. I am sure TRALI has been with us every since the beginning of transfusion therapy and we simply were not focused on it because we were really focused on prevention of hemolytic transfusion reactions and other

complications and so it was probably obscured by other concerns.

DR. KLEIN: Actually, during World War II most of it was albumin; it wasn't plasma that was used, and it was in patients who had a lot of chest wounds and pulmonary complications. As Dr. Popovsky pointed out, in his definition he has eliminated those from analysis because one is never sure whether their pulmonary condition is, in fact, due to TRALI. That is one of the weaknesses in the various definitions that have been proposed, that is that in the intensive care unit we do a lot of transfusion, especially with plasma-containing products, and you won't see TRALI because, by definition, anyone who has underlying lung disease is not going to be considered TRALI any longer, at least by the Canadian definition and the definition that Mark proposed.

DR. EPSTEIN: Mark, in many parts of Western Europe solvent detergent-treated pooled plasma is used in lieu of FFP. I wonder if you could comment on any reports of that affecting the

rates of TRALI. I have heard anecdotally that it has significantly reduced the rate of TRALI in some countries.

DR. POPOVSKY: I have never seen a well-documented case that linked the two.

DR. BRECHER: Mark, let me ask a quick question. What is being done with the diverted plasma in the U.K.?

DR. POPOVSKY: It is discarded.

DR. BRECHER: Celso?

DR. BIANCO: Mark, your last line is very provocative, proactive steps are needed to reduce the risk. We know from the mortality reported to FDA that we have a dozen, two dozen cases a year that are reported but we don't know the overall incidence, as you said. But if you go to the previous slide and look at what needs to be done, could you estimate the impact of each one of these measures on the incidence of TRALI? What would you expect, if you defer implicated donors, in terms of reducing the overall incidence of TRALI, or diverting plasma from females or antibody positives

in the overall incidence of TRALI?

DR. POPOVSKY: Well, I don't want to give a flip response to your question. I think that to me it is intuitive that if we can remove or diminish the number of antibody positives who are contributing to the entire pool of blood donation that we would reduce the incidence. By how much? We have made attempts, you know, in various publications that I have been involved with we have attempted to calculate that. I think we will know the answer to your question within a year or two from the SHOT experience. If they are right, they should see--and, granted, there are weaknesses in their system because it is a voluntary reporting system but no different than it is here, in the United States in which even though they are mandated to report to Food and Drug we know for a fact that many hospitals, for whatever reason, do not report. So, I think we will see a decrease. They believe they will. Their data would strongly support that.

As far as each one of those steps, each

should have an impact. I would say the weakest of those suggestions was the one that is practiced today, which is you find a donor; you identify that donor as being the likely source of the problem; you now say thank you, Mr./Mrs. Donor, but we don't want you to donate anymore. But that probably is the weakest because now you are doing that, you know, after the fact.

DR. SAYERS: Mark, is this transfusion-related acute lung injury because by convention we transfuse intravenously and the pulmonary vascular bed is the first vascular bed that the transfused product greets? If we transfused in, say, the descending aorta might this be transfusion-related acute kidney injury?

DR. POPOVSKY: I don't think we know the answer to that question.

DR. BRECHER: There is a study.

DR. SAYERS: What is that?

DR. BRECHER: There is a possible study.

DR. SAYERS: I thought you were going to suggest a subcommittee.

[Laughter]

DR. BRECHER: Thank you, Mark. We are going to move on. Also on the topic, Steve Kleinman is going to summarize the meeting in Canada.

Review of TRALI Consensus Meeting in Canada

DR. KLEINMAN: Hi. Good afternoon, everyone. While Jerry is setting up the slides, let me give you some introductory comments about the conference in Canada. This conference occurred in April of this year, and it was set up along the lines of an NIH consensus conference format. There was a steering committee that prepared questions for the panel. The panel consisted of 11 members. I chaired that panel. Many people on the panel came from different expertises--immunology, transfusion medicine, critical care, etc. The conference went for two days and I think we had about 20 speakers and about 200 participants. We tried to come up with a statement to answer those questions the first evening and got feedback from the participants on the following day, and have

subsequently been working on refining our recommendations.

What I am going to show today--in the interest of time, I am not going to cover the issues of incidence and pathophysiology, both of which were questions to the panel but have been covered you the previous speaker. We agree that we don't know the incidence and we agree that pathophysiology is multifactorial. I would just say there seems to be good evidence for both the antigen antibody-mediated pathway and there seems to be good evidence for the neutrophil priming pathway independent of antigen antibody.

But I will cover the other questions. In one sense, one of the crucial questions asked of the panel is how should TRALI be defined and what processes should be implemented in order to develop objective criteria for use in the classification of TRALI reactions?

Basically, this gets down to definition, and I think it is clear that the reason that definition is important is because if we are all

not using the same definition internationally, then we can't compare studies and we have difficulty in defining things like incidence, severity, clinical presentation, preventative measures because we read conflicting reports from people who have defined cases in different ways. Secondly, a standardized definition is obviously important if we are going to go forward in research protocols so that we are enrolling the same kinds of patients.

Basically, here is the definition of acute lung injury. The international consensus group adopted this definition in 1994. This is not in the transfusion setting but acute lung injury of any cause, and this is slightly modified from their definition, I will point that out, but acute lung injury is an acute onset syndrome characterized by hypoxemia, which can be documented either by PaO2 for FIO2 of less than 300 mmHg or an oxygen saturation that is less than 90 percent on room air, and we have modified this slightly as it applies to TRALI because we recognized that both of these measurements are not always available in

every hospital. So, we are saying that other clinical evidence could be used to document hypoxemia, at least with regard to making the diagnostic. Clearly, if you are going to enroll a person in a research study, I think you want to document hypoxemia by standardized measurements.

Third criteria, bilateral lung infiltrates on chest x-ray and, fourth criteria, no evidence of circulatory overload. So, in the TRALI situation from other causes this is usually circulatory overload due to congestive failure or preexisting conditions. However, in the transfusion setting, obviously, the overload may be as a consequence of the transfusion itself. So, since all TRALI patients are transfused, the issue of volume overload in the differential diagnosis is important and it is sometimes difficult to exclude circulatory overload in suspected TRALI cases.

Here is our proposed definition of TRALI. I really need to acknowledge the NHLBI working group on TRALI and Pearl Toy, who gave a presentation to the conference, because essentially

we would not have been able to come up with a definition in the limited amount of time we had, had not a group already spent months working out a framework. So, this really is very similar to the NHLBI working group's definition of TRALI which they presented and which I think is in the manuscript that is somewhere in press or submitted for publication.

Using the same format as their definition, we said that in patients who have no acute lung injury prior to transfusion you can make the diagnosis of TRALI if there is now new acute lung injury--and remember, I gave you the definition of that on the previous slide--that occurs either during the transfusion or within six hours of the transfusion's completion and, secondly, that there is no other temporally associated risk factor for acute lung injury. The difference between our definition and the NHLBI's draft working definition is that they didn't have the words "temporally associated risk factor;" they just said no other ALI risk factor. Let me go on and make that point

later.

So, we also have said, similar to the NHLBI working party, that while we can have cases that we call TRALI--the point I wanted to come back to is that you will notice there is no laboratory diagnostic test required for the diagnosis. It is clearly a clinical syndrome. It may have multiple etiologies. We may have a mixture of cases due to a variety of mechanisms. But to restrict the definition to persons who have antibody, for example which has been used in some previous publications, we thought was unreasonable because you can only find what you are looking for so we would be restricting TRALI to one mechanism, whereas we think there are multiple ones.

Now, also similar to the NHLBI, we had cases that we would like to call possible TRALI, and I will get back to why we make this distinction but you can see the distinction basically is that these are patients who have a temporally associated ALI risk factor and so they develop acute lung injury but you don't know whether the acute lung

injury is from this other risk factor or from the transfusion. What do you do with these cases? You could say, well, they are not TRALI because there is another risk factor and never capture those cases, but then again, how do we know that it is the other risk factor that caused the case and not the transfusion unless the case is investigated? So, we proposed this possible category.

What are ALI risk factors? Well, these are ones that I think are commonly accepted by persons involved in critical care. Although these are all risk factors, the incidence of TRALI associated with these various risk factors varies markedly. It is up to 40 percent for patients with septic shock and as low as 2 percent for patients on cardiopulmonary bypass, that being one of the lower ones that is on the list.

The column to the left are direct lung injuries and the column to the right are injuries that don't directly affect the lung but lead to acute lung injury. Acute lung injury is a less severe manifestation of ARDS so acute respiratory

distress syndrome is acute lung injury that is even more severe.

What about TRALI in the setting of massive transfusion in critically ill patients? If you look at the critical care literature, you will find massive transfusion as a risk factor for acute lung injury. Here is some data. In four studies of ARDS, again the more severe form of ALI, occurred in 21-45 percent of massively transfused patients. Each of the studies used definitions for massive transfusion but essentially they came down to somewhere between 8-15 units transfused in 12-24 hours. As I mentioned, is this ALI due to an underlying condition? Is it due to some other preexisting condition? Is it due to massive transfusion? Or, is it actually mediated by transfusion? Well, if it is mediated by transfusion, then it is transfusion-related acute lung injury.

So, our proposed definitions would consider these cases as TRALI unless the transfusions were temporally associated with an

ALI-associated condition. So, if it is multiple trauma patient who receives massive transfusion then, obviously--to go back to the other slide--that is a TRALI risk factor and that person would be considered a possible TRALI. If, on the other hand, it is a GI bleeder who receives multiple transfusions and turns out to have acute lung injury we would suggest classifying that as a case of TRALI.

Why would we distinguish TRALI and possible TRALI? Actually, we have several potential options. One is we could choose not to even capture the possible TRALI cases at all and say we don't think those are significant. We feel they should be captured in some way because they need to be studied. However, we really don't know what their correct diagnosis is so to lump them in with definite TRALI cases would really confuse reporting. So, we would recommend that they both be reported but that they be separated as different entities in surveillance systems and then in research programs they can both be targeted or

either group of cases could be targeted for studies. We also propose that you might want to manage these cases differently so, as I will get to in a moment, we have recommendation for how to work up a case of definite TRALI, and if it is a case of possible TRALI we really haven't made a recommendation. We have said that the institution should decide whether they want to work up a case of possible TRALI the same way they would work up a case of TRALI.

Another issue in possible TRALI is if you were compelled to try to capture all of the cases you would need to have much better reporting from your critical care unit because most of those categories of risk factors are going to put the patient in the intensive care unit. So, we are not advocating now that every hospital needs to capture all of these cases. We are really thinking that is more likely to capture these cases in certain surveillance studies or tertiary care systems that are attuned to the problem.

What is excluded? Actually, it is

interesting that if you look at this definition it is really not remarkably different from the one that Mark talked about that he proposed 20 years ago. It excludes mild TRALI cases. As he pointed out, look-back studies suggest that such cases exist but the reason we have excluded them is that we really can't come up with any criteria to categorize a mild TRALI case. So, since we can't be precise we think that trying to include these in any categorization will only make things more confusing as we try to accumulate data about incidence and about prevention and pathophysiology.

It is probable that cases of TRALI can coexist with circulatory overload, that it can happen in the same patient. It is certainly true for acute lung injury from non-transfusion caused, that you can have both circulatory overload and acute lung injury. But we think that that is a difficult diagnosis to sort out. There was a lot of discussion about this point at the consensus conference and no solution is perfect. We recognize we might be excluding some cases but we

think that if we include these we will be gathering cases that other people will criticize and say, well, that is really not TRALI.

One of the observations we made is that if it really is a patient with circulatory overload and that is recognized and the patient gets treated, if that patient in fact also has TRALI and the TRALI is severe enough, then presumably you may be able to still diagnosis after there is no longer circulatory overload.

It would seem that if transfusion is a condition that can harm your lungs and you already begin with lung injury, that would be a circumstance where transfusion could be even more problematic because you are already set up for a bad outcome. So, the concept of worsening lung injury after transfusion in a patient who already has preexisting TRALI is I think an important one. But we chose to exclude it from this first level definition because really there are no diagnostic criteria to be able to know why the lung injury got worse and so, again, I think we would be gathering

information that we couldn't evaluate well.

The definitions that we proposed, and they have been talked about at various meetings up until now--so the definitions proposed by the consensus panel we believe--because who is the consensus panel? It is 11 people who came to a consensus; it is not a consensus of the world, obviously, at this point--but we think there at least should be a starting point where this could be harmonized with definitions that are being proposed by other groups. As I mentioned, it is not too different from the NHLBI working party. We have already proposed these definitions in various forums to the ISBT committee, the BEST committee, the AABB Clinical Transfusion Practice committee and the European Hemovigilence Network. Essentially, all of these groups pretty much think that this is the right framework for a definition; there may be some fine tuning.

So, I think that we are much further towards a standard international definition than we were six months ago, and I expect that once this

gets published and people comment on it we probably can get to some fairly standardized definitions. Clearly, this definition is a starting point, or these definitions for TRALI and possible TRALI are where we begin. We expect they will evolve as we get some more data that allow us to refine them.

I want to now go on to a crucial question that we were asked, what options are available for managing donors implicated in TRALI reactions? For those people in the room who were at the conference, and there are a few, I want to mention that when we gave our statement the following morning, after working late into the night, we really hadn't sorted this out very well because we were really overwhelmed with a huge amount of information in a short time and we really spent a lot of time focusing on the definition question since we felt that was important. So, some of what I am going to say has actually occurred in subsequent discussions of the panel, after the conference, so it is a little different than what we presented, although fairly in line with it.

Secondly, we weren't able to make a recommendation that we thought would be binding on everybody so part of what we have done is to try to highlight the important issues involved in this question, and then to propose some potential solutions.

Well, our definitions are that it is important to distinguish between donors associated with a TRALI case and donors implicated in a TRALI case. Since people have used the word "implicated donor" in various publications a bit sloppily sometimes we start with this, that an associated donor is a donor whose unit was transfused into the recipient who develops TRALI within six hours of that TRALI developing. An implicated donor is a donor who has been demonstrated to have an anti-HLA, either Class I or Class II, antibody or an anti-HLA neutrophil antibody with a specificity that is directed against an antigen on recipient cells. So, that is either established because you have done antigen typing of the recipient and the antibody is specific against one of those antigens,

or because you have done a cross-match between recipient cells and donor serum. I will come back to that.

Now, what are the donor management options in a case of TRALI? Well, obviously the premise is that we want to manage donors in a way that we can protect recipients of future donations or even recipients of co-component donations. We didn't really deal with the co-component issue in the committee at all but we dealt with should the donor be eligible for future donations.

As I mentioned before, we think that, again, you would need to decide whether you want to apply this to the possible TRALI cases where the implication of transfusion as the etiology is not as strong. So, you can obviously do one of two things. You can either decide that all of the donors associated with a case will be handled the same way, or you can try to do a laboratory investigation to decide which donor is culpable.

If you are going to handle all donors the same way, you have one of three choices actually.

You can defer them all from a future donation. You can allow them, as Mark said, to make a future donation but essentially either only used washed red cells or frozen cells so there is no plasma transfused. Obviously, you would have to defer them from apheresis platelet donation. Or, as was proposed by some at the conference, maybe you put a flag in the donor record and you say all of these donors, these five donors, were involved in a TRALI case so we will put a little flag in the computer record and if one of these donors is involved in the future in a second TRALI case we will say, gee, that is stronger evidence and so now we will know that is an implicated donor or we will infer that is an implicated donor and we will defer that person; we will take an action on that person.

We had an ethicist on the panel, the consensus panel, with some legal background. He said this would not fly in the current informed consent situation in Canada and in many countries--I don't know about the U.S.--and the reason it wouldn't fly is because as soon as you

flag that donor record that donor is different from every other donor and you, as a transfusion recipient getting a medical therapy, would have the right to know that you were getting a unit of blood from somebody who was suspect as being less safe than other donors you were drawing. We didn't used to think this way obviously. We used to do this for post-transfusion hepatitis 20 years ago, but I think he made some persuasive arguments to our panel to make us at least raise this issue and say that we don't think that this is a viable alternative in the consent climate. Now, whether it is reasonable or not you can argue but we don't think it is viable. But that, again, would be for every jurisdiction to decide on its own.

Anyway, this blanket approach to handling all donors in the same fashion is something that the panel didn't think was a good idea and the panel basically said we do have some tools to do laboratory workup so we think a laboratory workup should be done in cases of TRALI, the purpose being to try and identify an implicated donor and,

therefore, protect future recipients.

We also said if you are going to do a TRALI workup in donors there is a prerequisite, at least one prerequisite, and the major prerequisite at the blood center--remember, you are not the one who has the TRALI patient; that is at the hospital--you, at the blood center who can call the donors back need good clinical case information before proceeding. We heard from the participants in the conference that often they get a report from a hospital that says we have a case of TRALI and that is it; they don't get any evidence so now they are left with relying on the diagnostic acumen of the hospital and deciding whether they should initiate a protocol. That protocol is expensive. It requires access to specialized laboratories and, importantly as well, it involves calling donors back and getting another sample and, therefore, notifying donors that they may have done harm to a recipient. Certainly, that is something that is necessary to do if, in fact, that is the case but the point is that if you can't get good clinical

case information as a blood center medical director you shouldn't be obligated to go ahead and do a workup. So, this means better interaction between hospitals and blood centers.

Secondly, we believe that there should be a requirement for obtaining a recipient specimen or, in the absence of a specimen there may be patients, oncology patients, who may have preexisting HLA antigen typing already done. Now, we know that in reality sometimes you can't get a specimen and so the question that needs to be asked is--I guess how I would like to phrase this is that every attempt should be made to get a specimen from the patient because it is a vital part of the workup. However, if you can't get a specimen from the patient, then really you are going to have to ask the question if I find antibody in a donor without being able to link it to a patient and know if it is antibody against an antigen directed to that donor, would I defer that donor? If the answer is no, then don't do the workup if you need to have the antigen antibody matched. If the

answer is yes, then do the workup in the absence of the recipient specimen.

Now there are a couple of other questions that come up about doing the workup, and I will show you what that workup is in a minute. If you have multiple donors in the case, we heard several strategies that were proposed. One is that you workup all the donors simultaneously. Your second strategy is what I would call an incremental strategy. Because it is an expensive workup and you may not want to work up every donor, you start with the donors who are more likely to be the donors who caused the reaction. We heard several different strategies along that line. One approach is to workup your female donors first since we know a lot of them have HLA antibody.

A second one is to work up the donors whose unit was the one most recently transfused prior to the symptoms because, although six hours is the time limit of symptoms, in many cases the symptoms occur concurrent with the transfusion or within one to two hours. So, you could start that

way. Call donor A back first; test donor A; then go and call donor B; and then go and call donor C. The third is you might take the donors of FFP before red cells.

We heard all of these approaches presented. The panel really couldn't say that one is better than the other but we did think that the incremental strategy was a viable strategy where you didn't necessarily have to work up all donors. It is really up to an institution to make that decision.

I think you might get the impression, which we got from what we heard, that workups are not really standardized right now. Although many centers may work up donors, there really isn't a standard way that everybody has accepted as being part of the workup.

The other mechanism of TRALI, other than the antigen antibody mechanism, is what we have heard called the two-event model but I don't like that name personally so I have decided to call it the neutrophil priming model because it says

neutrophils adhere to endothelial cells and get primed and then they get activated, and presumably they get activated by biological response modifiers that get infused which could be antibody, on the one hand, or could be these lipid substances. We heard that it is possible to test for neutrophil priming activity but that this test has really so far only been from a single laboratory, a single group of investigators. So, we felt that it was premature to say to people that they needed to do this neutrophil priming activity as a workup in TRALI, although there were many people in the audience who thought that this should be done. So, we encourage it to be done. It is certainly a vital research test that needs to be done in a more widespread format but we were not recommending that it be a standard test done in working up donors.

So, what is the workup we are recommending? Well, donor testing for each of the donors you work up would be for HLA Class I and Class II and anti-granulocyte or anti-neutrophil antibodies. Clearly, Class II has been implicated

more and more over the last few years so that is a vital part of the workup and so you would start with a broad screening test and if found antibodies you would get the specificity of the antibody. One other point I should make here is that we recognize that it is sometimes hard to identify granulocyte antibodies. That technology is not as widely available.

For recipient testing, HLA Class I and II typing; neutrophil typing if possible; then, thirdly, if an antibody is found the most definitive thing to do would be to perform a cross-match between recipient cells and donor serum but that means that you need to get recipient cells sent to you in a timely fashion after you have identified the antibody. So, how practical that is remains to be seen.

Again, by our definitions of an implicated donor, recipient antigen testing or cross-matching is necessary to come up with a definition of an implicated donor.

So, what to do? Now you have done the

workup, what action does this lead to? If you have a positive cross-match or you have a cognate antigen--our British colleagues use that term--so you have an anti-HLA, say B27, and, in fact, the recipient has a B27, now you have said that is an implicated donor so you would take action. Remember, that action would be either to defer the donor or to only use washed red cells in the future. So, that is how you would handle that donor.

What do you do with the other donors in the case? Well, if you had donors whom you worked up and they had no antibody, it should be safe to allow them to continue to donate. If donors were not called back, you have already found an implicated donor so they should be safe to reinstate.

The question mark though is what do you do suppose you have worked up a few donors and more than one has antibody? Maybe one has antibody against the antigen on the patient cells but another has an unrelated antibody that you think

probably didn't cause the TRALI in this case. We could not decide how to handle this, and this has been a controversial issue and I will give you the two sides of it. One side is, well, you haven't proven this donor caused TRALI in this patient so the donor is fine. The other side is now you have an antibody, whether it be HLA or anti-granulocyte and we know that HLA and anti-granulocyte antibodies can cause TRALI, so how can we allow this person to continue to donate? But we don't test everybody for antibody. We are allowing people, multiparous women, 17 percent of whom have antibody, to continue to donate anyway but they weren't implicated in a TRALI case. So, I can go around in circles, which we did at the panel and we couldn't really come to a uniform agreement. What we are going to publish though, and I think what we finally agreed on is that because of the severity of TRALI with anti-granulocyte 5B, renamed HNA3, nobody is comfortable if a donor like that is found in allowing that donor to continue to donate. So, we have decided, in generalizing a bit, to say if

we find an anti-neutrophil antibody that donor should be deferred regardless of whether that donor was implicated, whether the recipient had the antigen. However, if we find an HLA antibody, which is much more common and many of our donors have it, this is where we couldn't come to an agreement whether that donor should be allowed to continue to donate or not. The preference of the panel was that that donor should be but there were strong dissenting opinions.

Now, suppose we don't find any donors who are implicated in the case, we do the workup and we haven't found the donor? We work up every donor in the case and we don't find a donor whose antibody matches the recipient's, what is the explanation? Well, there are several possible explanations. Maybe the antibody is in the recipient. That happens sometimes. We haven't recommended that you need to work up recipients because then you would have to HLA type every donor to really do the workup to match the antibody to the antigen. So, that is a possibility.

Secondly, maybe the TRALI was due to another mechanism and it wasn't antigen antibody mediated at all. That is what the group from Denver says and they say they never find antibody in their cases, or very rarely. So, we don't know what it means if you can't find an implicated donor. Again, you might find a donor with an antibody that doesn't match an antigen or you might not even have the recipient sample so what do you do in those cases? There are lots of permutations and it is very hard to spell out a policy that covers them all. But this is kind of how we formulated the question.

The last question--well, next to the last question but the last question I will discuss thoroughly was is there sufficient evidence at this time to recommend that any laboratory screening tests and/or other deferral measures be implemented to exclude donors in order to reduce the risk of TRALI? In other words, it is the same questions that were asked Mark at the end of his talk. What can we do to reduce the risk of TRALI?

Well, the first is a motherhood statement, adherence to current guidelines of blood component utilization, especially FFP, don't transfuse a patient when he doesn't need it and, obviously, you prevent complications. So, we have said that in the statement but I think that is kind of an obvious one.

Defer donors implicated in a TRALI reaction by the previous definitions. Why do we do that? Because of the two look-back studies in the literature that say that donors can cause TRALI in multiple cases. Although there is another look-back study from the U.K. that has shown a donor caused TRALI case and they found actually a number of donors. They have tracked previous recipients and there were no TRALI cases. So, not every donor who causes a TRALI case in a given recipient is going to cause it in other recipients but, since some do, we believe that you should defer these people because this will err on the side of recipient safety even though we may defer some safe donors. There is obviously not a big

impact on blood supply here.

Then we get to the one that is most controversial, should you divert plasma or defer selective groups of donors based on demographic or other characteristics? This is what the U.K. has started to do. In descending order, you could say, well, we won't use plasma from any female or any transfused male donor. We won't use that for transfusion; we will divert that to fractionation. Or, the next one down, you could just take all females--not use plasma from all females. Or, you could say let's be more restrictive and we will get a pregnancy history from people and not use plasma from previously pregnant females--ever pregnant, multiparous, you can take your choice. Or, we can actually test the female donors. These are all more inclusive but with less impact on availability.

These were all presented as possibilities and I think our consensus was that actually TRALI is a serious problem so we can't dismiss these solutions which seem to be excessive, on the one

hand, and have large side effects. We can no longer say, okay, we have talked about it here for five minutes; these are not viable. The U.K. is admittedly in a unique situation in that they don't fractionate their plasma so they have lots of choices of what to do with their non-used plasma, but we think that you can't dismiss these out of hand. You actually have to look at what the implications would be so we suggest that each blood collection agency or each national system evaluate the benefit or the impact on their system regarding blood availability for adopting these strategies.

But having said that, we certainly didn't come out and say that the time is now to actually implement any of these but it just says that you need to consider them and have some sort of analysis to say this won't work.

Now, that analysis could be a two-pronged analysis. One is what is the potential benefit? You know, the U.K. showed that 91 percent of the cases presumably would have gone away if they had that policy in place. But that same data doesn't

hold for cases in Canada where many more cases didn't have antibody. It certainly doesn't hold for the case series that was reported in the U.S. from the Silliman group. So, you have to evaluate your data to see what the impact on safety would be based on your own data. Then, secondly, you would obviously evaluate the impact on availability.

Additional proposed strategies--one proposed was that since the neutrophil priming activity hypothesis implied that units were older, you might consider using younger units for at risk patients, but we don't know who at risk patients are.

Secondly, it may be that platelets, if we get to platelet storage solutions with less plasma, that might reduce the risk of TRALI. Thirdly, but not on the slide, we did hear the anecdotal evidence that maybe solvent detergent plasma would be better than FFP but that is not a product that is produced in the U.S., nor were there any real data to support that premise which might be theoretically true.

Finally, we were asked about future research. I am only going to show two slides on this. We have more recommendations but selected research issues, and there are a lot more than these that need to be done in the epidemiology clinical format; better characterize the epidemiology of TRALI; determine its incidence and severity with various components; study the possible TRALI cases in detail in research settings; try to ascertain if there are recipient factors; and look for mild forms of TRALI.

Pathophysiology--again, there is still a lot of work to be done there; continue working on animal model systems. Can we see TRALI in severe neutropenia? We think we can. There have been some case reports. If so, what is the mechanism? If it is supposed to be the neutrophil that damages the endothelial cell, what happens in severe neutropenia? I just threw another one up here, we don't really know what causes the hypotension and fever in TRALI.

That is the summary. We now have a

manuscript that has been accepted in Transfusion that will come out in December. So, there will be a full publication of these recommendations or at least statements in December, in Transfusion, and there will be a conference proceedings published in Transfusion Medicine Reviews in the January issue. So, there will be ample time I think soon to see these things in writing and see them sort of worked out but I think I have given you the essence of it here.

DR. BRECHER: Questions for Steve?

DR. PENNER: Just a quick question, would it be practical to test all multiparous donors for leukoagglutinin?

DR. KLEINMAN: Practical, meaning defer them? I mean, if you are going to test them, then you would defer them.

DR. PENNER: If they are positive, defer them. That would remove perhaps some of the potential risk for TRALI.

DR. KLEINMAN: Well, you would remove somewhere between 7-15 percent of your female

donors, at least from studies that have been done. So, if they are multiparous, more than three pregnancies, it may be as high as 24 percent, but if you just say, you know, I am going to test all female donors it is somewhere in the 7-15 percent range for HLA antibodies. So, can you afford to lose 7-15 percent of your female donors from the whole blood pool? I don't know, but you would also lose them from your platelet apheresis pool which I think is probably not something that is practical at this point.

DR. PENNER: What is the reduction though of the TRALI?

DR. KLEINMAN: Well, we don't know. That is the whole point.

DR. PENNER: Would you estimate?

DR. KLEINMAN: They are estimating it is 90 percent in the U.K. but nobody has looked at what it would be in the U.S. because we don't have a database. We don't get the cases reported to us with the right information.

DR. PENNER: This would be with just

simple leukoagglutinin tests.

DR. KLEINMAN: Well, they are not simple; they are quite complex actually and expensive. But this would be with HLA antibody tests and anti-granulocyte antibody tests. But, yes, that could be done. I mean the technology exists. They are simple in the sense that it can be done. You know, there are a number of laboratories.

One thing I didn't talk about is what would be the best tests to use and how are they are standardized. That is a whole separate set of issues that would have to be worked out but, presumably, they could be worked out. So, if somebody said tomorrow you need to test all of your female donors for HLA and granulocyte antibodies, and we had the money to do it, I think it could be done but it has lots of implications.

DR. KLEIN: You almost never see an anti-granulocyte antibody in the absence of HLA antibodies. I mean, it is almost reportable.

DR. KLEINMAN: That is interesting. I didn't know that.

DR. KLEIN: Really? You learned something!

[Laughter]

DR. KLEINMAN: Thanks. I always learn something from you, Harvey.

DR. SAYERS: Steve, the national blood service in the U.K. also has the strategy of using imported plasma for transfusion of patients under 18 months. That plasma comes from the United States. The argument being that in a group of patients with a longer life expectancy you reduce the theoretical risk of transfusion-transmitted variant CJD if you use plasma from people that haven't exposed themselves to British beef. So, I am wondering now if the NBS is going to insist that that imported plasma come from male--

DR. KLEINMAN: They already do. That is in their contracts.

DR. SAYERS: Well, that is startling because we really have set the stage then for a two-tier blood supply, safe plasma going overseas and less safe plasma staying here.

DR. HOLMBERG: The 90 percent which you just quoted, is that from the British?

DR. KLEINMAN: Yes, from the British experience. To set the background, I think the British have done the most thorough workups of their TRALI cases in the last few years that have been reported. There may be other institutions that have done them in the past in the U.S. but it seems like the British have had a program in place to carefully work up all the donors in TRALI cases with a very complete workup, and in those cases that they have captured as reported to them, first they do a screen and the cases get reported. They sort out whether they really think it is a TRALI case or not, or a mis-report. Then they do a workup of all the donors in a centralized laboratory, and I think the case series is about 100 cases over the last four years, and they found that in about 90 percent of these cases they find a donor with an antibody. That donor, I think in every case, has been a female donor. So, they assume that that donor caused the TRALI and that is

where they get the 90 percent.

DR. HOLMBERG: Is it too early for them to report? Are there any preliminary reports out from the U.K. as far as how their incidence has dropped?

DR. KLEINMAN: No, because they just started this a few months ago. I think that they may have a little bit of confounding because they really increased clinical reporting of TRALI cases over the last couple of years so the trend of reported cases has been going up because they have got more clinical recognition. Now they have made an intervention and so perhaps they may capture more cases at the same time that they are preventing cases. I don't know. But if it turns out that the cases go down considerably after the policy, I think that would be good proof that the policy had an effect. If the cases don't go down, then I think it is hard to tell whether the policy failed or whether it had partial success but we were capturing more reportable cases at the same time.

DR. BIANCO: Just one clarification

regarding the question that Dr. Sayers asked, the plasma that is exported from the United States to the U.K. is not segregated by gender.

DR. KLEINMAN: That wasn't my understanding but I may be wrong.

DR. BIANCO: Steve, unless somebody is doing it very secretly, but none of the software that is available for blood center management of inventories can segregate by gender. So, it would have to be a very special project, a very special way.

DR. BRECHER: Jay?

DR. EPSTEIN: Well, it occurs to me that if the data from the U.K. suggests a decrease in TRALI we are going to be considering very seriously whether to adopt a similar measure in the U.S. I wonder if we can't prepare ourselves for that possible debate by examining the feasibility of a similar system in the U.S. Specifically, the question is do we need to have female donors to have an adequate supply of FFP. My understanding is that we do not, that only a small fraction of

the plasma collected is made into FFP; the larger proportion goes to fractionation and, in any case, there is still a predominance of male donations, roughly 60 percent to 40 percent. So, those figures, if still correct, would suggest that there is more than enough plasma to make FFP from male donors only but I would like to hear what some blood bankers think about that, putting aside for the moment, you know, how one would manage the inventory.

DR. BIANCO: I can tell you, Jay, that it varies. Between 20, 25 percent of the plasma from whole blood donations goes to the manufacture of plasma products for transfusion. Now, the other item that I think is important is that we are focusing on plasma but I think that the majority of the plasma transfused or a lot of the plasma transfused is transfused with platelets, particularly single-donor platelets, to have more plasma than a unit of plasma normally has. I don't know in the incidence what is the relationship between plasma and platelets as a relationship. I

understand in the FDA series and Holness series it is about half.

DR. KLEINMAN: Jay, one other thing that I think would come up from the FDA's point of view is if you were to institute that type of policy, then obviously you would be inputting more female plasma and less male plasma into the fractionation pool and the question is would the FDA consider that a change in the characteristics of starting material for fractionated plasma now that the gender mix is changed. I don't know the answer to that.

DR. EPSTEIN: Well, we have no gender bias.

[Laughter]

DR. BRECHER: I guess the other question is would you then start to see more cases with IVIG?

DR. SANDLER: Steve, I am looking at the four categories that you are considering for diversion of plasma and the fact that there is no recommendation, and my question is I take it that the committee would agree that if there is a bona

fide case of TRALI and there are one or two donors that future plasma from those two donors would not be collected and transfused to other persons. Is that correct, or does your committee not have a recommendation on that?

DR. KLEINMAN: Well, the two questions were different. The first question is if you have a donor involved in TRALI, what do you do? That was question four. If you have a donor involved in TRALI and you prove that person is an implicated donor, you don't use their plasma.

The second question, question number five was what do you do as a preventative measure? Do you not accept the whole category of donors because they might be at risk? That is where I listed those options, and they were listed because they came up at the conference. This is the list that different people talked about. If you wanted to, you could theoretically adopt any one of those strategies because if you are looking for where leukocyte antibodies are, then the maximum group is all females and transfused male donors. Well, in

the U.K. they said we don't need to do that. Even in the country where they have implemented a preventative strategy they said, well, we don't think that there are many HLA antibodies or granulocyte antibodies in transfused males so we are not going to go to that extreme. Then we would have to ask a different question, well, they don't have transfused males anymore because after their policy, you know, they changed their VCJD deferral question. But at the time they put that into place they still had that transfused males were eligible to donate. So, it is just a hierarchy of possible options.

DR. BIANCO: They will resolve their problem by excluding all donors that were born in the U.K. and import everything that they use.

DR. SAYERS: This is in follow-up to what Jay asked about can we maintain a national fresh frozen plasma inventory without female donors contributing, and I think the question is really larger than that. Goodness knows, there are sufficient number of disincentives to donate these

days and I suspect that for a significant number of women the knowledge that we were recruiting them for their red cells only and we are going to be discarding their plasma might well be a disincentive to donate. So, the question would be can we study how many female multiparous donors could we convert to, say, exclusively red cell donation by apheresis. So, that is just a point that it is not just can we manage the inventory, but it is also can we manage the donors who are now getting a new message which many of them might find difficult to understand?

DR. KLEINMAN: But why would we discard their plasma? Wouldn't we use their plasma for fractionation under that scenario?

DR. SAYERS: Well, you know, we heard some comments earlier that what we might be then doing is enriching that pool for the complication that we are avoiding with lipid plasma transfusion.

DR. BRECHER: Jay?

DR. EPSTEIN: Yes, but again there you deal with the issue of dilution because if the

presence of the antibodies is a sufficiently low proportion and you have these very large pools we would expect it could still be diluted out. Again, anecdotal evidence suggests that the problem is not there with the pooled product.

DR. BRECHER: Although I imagine if you had one donor with a sky-high titer--

DR. EPSTEIN: That can happen now.

DR. BRECHER: Right, but it wouldn't go into a lot that then went to hundreds of patients.

DR. EPSTEIN: It could happen now.

DR. BRECHER: Yes, it could happen now but you would be stacking the deck more that way. I guess there's more reason to go after the generation Y donors before they become multiparous.

[Laughter]

On that note, why don't we take a ten-minute break?

[Brief recess]

DR. BRECHER: Committee members, please take their seats. A quick question for committee members, we can choose to make a recommendation

about TRALI, about the discussion we just had, or we could table it until later in the day. I would prefer to table it until later in the day and move ahead. So, we are going to start hearing about therapeutic plasma issues, economics and reimbursement. The first speaker will be Jan Bult, president of the PPTA.

Therapeutic Plasma Issues, Economics and the Role of Reimbursement

MR. BULT: Thank you very much, Mr. Chairman. I would like to walk you through some of the issues that we are facing right now. I would like to explain at the beginning that when we were approached to address this issue it was around summertime when there was some question or concern whether we were facing a potential shortage or not. I think it is important to lay that out in the beginning.

Why is that so critical? Because all of you remember what happened in '98, the late '90s, when we were dealing with a serious shortage of immune globulins and we saw a few years ago a

shortage of recombinant Factor VIII. But I think it is important to explain right in the beginning what is different than in '98.

First of all, we do have a pretty good monitoring system in place that helps us to understand the changes in the supply dynamics. This is publicly available information that is on the web site. Everybody has access to that information. The industry as a whole is much better positioned to meet consumer demands. We see more companies. We see product portfolios, which is a good thing. But the other important change, and it is a reality of today, is that we have to address the current economic challenges. We have said it in the past and I will repeat it today, that is, if we talk about the long-term viability of this industry we need to make economic adjustments. There is no other way around it.

Now, if you go back to 1998, for me, it was a remarkable year. It was the year that I moved to the States, lived here and started to work, and within a few months I had the honor to

testify before a congressional hearing, to do an interview with Mike Wallace on "60 Minutes," and present for this committee. I leave it to your imagination which was the toughest one.

The commitment that we made at the meeting was that we will come up with a monitoring system about our distribution. We committed to do this every quarter. What has happened is that we have done it now on a monthly basis. It is published on the web site. And, in cases where we had some concerns we communicated this directly to the consumer organization. However, what we need to do is we have to ask ourselves continuously do we still have to do it today? I would say yes. Is it still the case next year? I don't know. We have to be critical and make sure we do the right thing.

The next question that comes up is, is there anything we can say about future supply? We need to realize that there are very strict laws in place that prohibit an industry, certainly as concentrated an industry as hours, to talk about certain aspects. What I say is that based on what

we know today we do not see a near-term short supply but we will see--and that is my prediction--that individual companies, in response to their economic challenges, will tighten supply.

Now, I am not going to go into a legal exercise here. I just want you to know that there are certain things that we as an industry cannot talk about. The issues that are listed in red is I think the critical one here. So, even when we would like to do it, we can't. There are laws in place and we respect the law.

Now, what I am going to do is I am going to talk about what the economics are for this industry, and I am going to deal with some of the products that are listed on this slide where you can see the average yield that we obtain. I am not going to walk you through the details of the fractionation process, the combination of temperature, pH, alcohol and time to fractionate the different products. That is not the purpose of this meeting.

In the summertime the questions came about

supply of the therapies and, as all of you know, we have seen significant changes in the marketplace. We have seen consolidations. We have seen companies making a decision to divest and leave this business. We have seen the closure of collection centers. We have also seen closure of fractionation plants. As a result, we also see that there is reduced volume of fractionated plasma and, not another surprise, we have also seen a significant reduction in staff.

The good news is we have seen new companies entering the market since '98. I must say FDA also worked on that to make sure that companies could get into the market. We have seen new product approvals. Company did serious work to work on facility enhancements. We have also seen the introduction of new technologies that allow the industry to get higher yields which, of course, translates into the need for reduced volumes of plasma. And, we see utilization of both source and recovered plasma.

Now go back to what we saw in '98. If you

look at this beginning, the annual distribution in the United States of immune globulins, as an example, was about 40,000 kg per year. If you see where we are today, it is about 26,000, 27,000 kg. Of course, there is an enormous fluctuation because this is monthly reporting but I think the message here is very clear. The industry took the message seriously and has worked very hard to increase the volume of immune globulins and other therapies in the market.

The question now is do we have the right balance? In '98 we had the situation where demand exceeded supply. Is that still the case? If we have increases supply, is this balanced with demand or are we building and filling inventories?

So, what I am going to do now is I am going to explain with a model that is based on these five therapies what is going on right now. The first thing we need to know is that the driver for the collection of plasma has changed. If we go back in history, we see a situation where albumin was the driver whereas today volume of needed

plasma is determined by immune globulins that are needed in the market.

If we take this model and we look at the economics of plasma fractionation, if we take immune globulins as the basis where you can see this is the fractionation capacity of a company, this is the volume that is brought to the market. You see the volume of liters that are needed to manufacture the therapy. Look at albumin, less liters are needed in this model. We do the same if you look at Factor VIII, other proteins and alpha-1.

If you then translate the income out of these products you can calculate the revenue per liter. There is a certain cost price, cost of manufacture. It is true of every company. There is no company that is able to recover the cost of manufacture with the sales of one therapy. You need multiple therapies in the marketplace to do that. As you can see, the best revenue comes from the first liter of plasma that is manufactured and the further you get into the system the more

problematic it becomes.

So, what happens--I made a change, Mark Skinner, based on your comment. What happens if you are a manufacturer when you have no other proteins or no alpha-1 in your product portfolio? It means you have to recover your cost on the other therapies that you are manufacturing. Or, what happens when you have other therapies and you have no plasma-derived Factor VIII? The point I want to make is that it is different for every company but the model as such is helpful to understand the situation.

What also works is if you look at immune globulins that are needed, it also results in more albumin. This is the volume that is sold on the marketplace so this volume goes in inventory, goes on a shelf. Nobody knows when it is going to be bought. But, as you can see, everything is still below cost price. So, in this particular situation you are losing money.

Now, if immune globulins are the driver and if there is any concern about immune globulins

and, as I told you before, we don't see a near-term threat for immune globulins, but you can ask the question why don't you make more? Just make more so you avoid all the problems. Well, if that is the case this is going to happen. You can make more but you can't sell it. So you put it in inventory and also you get more albumin and it is still below your cost of manufacture. That leads to a situation where this industry is going to lose a significant amount of money and, as we have seen with the changes in the marketplace, we are not in a position to do that. So, this will not happen, especially not if you look at the revenue that we have seen over the last years that has come down significantly. All the changes that you see in the marketplace right now are a clear response to the economic pressures.

We have said on other occasions that we are different. The fact that we use starting material of a biologic nature, human plasma, is completely different than a pharmaceutical industry. If you look at the different cost

components, about two-thirds of the costs of plasma-derived products are the result of the manufacturing process which is quite different than pharmaceuticals. There are implications of these differences.

The other thing that we need to remind ourselves of is that this industry is basically serving small patient populations compared to the pharmaceutical industry. But we get caught into measures for pharmaceuticals time after time. There is not that differentiation that we would like to see. These therapies are not easy to make. We cannot get a patent on a human protein. The only thing you can do is work on your technology and continuously improve the technology as a result of regulatory requirements but also as a result of new knowledge, especially to deal with the risk of emerging pathogens. The investment capital for this industry is huge. It takes an enormous amount of time to manufacture these therapies. It takes about seven months between collection and delivery of the product on the market. The up-front

investment is huge.

Since we are serving small patient populations it is very difficult to met the clinical trial requirements, especially when you have to look at the large number, and I am very happy that I learned that FDA is willing to organize a workshop to look at the aspects of harmonization in clinical trials, which I think is a good step in the right direction.

But what we also know is that a further reduction in reimbursement is not going to be helpful for a variety of reasons. If we are going to be confronted with a situation that companies have to decide to further consolidate or divest, that will limit choice and that is the last thing that we need.

So, what we are looking at is revenue factors, and I am not going to go into any of these issues. Julie Birkhofer will do that as the next speaker. But I think one important message that we need to understand is that the reimbursement is not what goes to the manufacturer. The reimbursement

goes to the provider and it works its way through the system and reimbursement is not equal to manufacturer revenue.

So, what we have to do is to look at two aspects. We have to look at cost challenges and at the revenue challenges. The cost challenges are mainly of a regulatory nature. Almost a similar topic was discussed a few weeks ago with the Blood Product Advisory Committee, and we have identified a couple of examples of things that we can look at. I am not going to go into detail here but, as I mentioned to you, we are in dialogue with FDA and I hope that we can move on this.

When it comes to the reimbursement policies, I think the most important message that we need to bring to stakeholders is that we are different than PhRMA. We cannot be compared to the pharmaceutical industry for the reasons that I mentioned, and I also I will repeat one more time that reimbursement is not equal to industry revenue. So, what we need to do for the future is that we need to continue to make sure that we

understand what is going on in the marketplace. We also need to remind ourselves that, as a result of what happened in '98, companies have committed to build an emergency supply so that when it is needed there is access to therapy for patients in significant need. And, we need to continue communications with our stakeholders, and we try to do that.

In conclusion, we believe there is no near-term threat of a shortage. We believe that the current inventories and the use of new technologies will help us to really get a better situation where demand and supply are in better balance.

We will continue to make the point that economic adjustments are needed because look around and look at the companies that were in place in 1998--let me just give you a couple of examples, Alpha Therapeutics Corporation no longer exists. Biopharma has decided to divest and Baxter has significantly reduced its activities. Aventis Behring or Cention is now part of CSL. So, that is

the reality. At the same time we have seen Octapharma coming to the U.S. marketplace. We have seen Grifols coming to the U.S. marketplace. But just look around you and you will see what has happened as a result of the economic challenges.

The most important thing is we will continue to fight for access, freedom of choice and recognition for innovation. Thank you.

DR. BRECHER: Questions or comments for Jan?

DR. PENNER: With respect to the IV gamma globulin, I think there is almost unlimited potential use for IV gamma globulin, primarily for non-labeled use, in a variety of the immune deficiency disorders--lupus, ulcerative colitis, hemolytic anemias, and so on. These are non-labeled usage. The labeled usage is for a very select group, immune thrombocytopenias and the immune deficiency disorders. I have not seen that we have been able to proceed in treating patients with these immune disorders even though there is a sufficient number of studies that would at least

indicate the potential positive effects of immune globulin in those conditions, and I don't see industry coming up, trying to support studies that would at least push or encourage this use of the product. I could see doubling the use of intravenous gamma globulin for most of the patients that I am seeing with respect to the immune disorders. That area I think could be pursued a little bit more aggressively than just sitting back and accepting what the insurance companies now will say is labeled use only.

MR. BULT: I can only say thank you for this comment.

MR. SKINNER: John, first to your comments, Donna is going to speak actually to your point I think in terms of the hemophilia products and similar kinds of situations in a moment.

The question I have for Jan is one that I have asked before and I will ask it again and see where we go. I appreciate your presentation and I recognize the problems. There have been new market entrants and there have been market leavers in the

U.S., but if you look exclusively at the Factor VIII component of that equation, recognizing that multiple products are needed for profitability of industry, in the U.S. market plasma-derived Factor VIII is not a growth market. In fact, it is relatively static. Globally, you know, there are a number of major countries that have moved, and others like Australia that is attempting to move right as we speak, to recombinant Factor.

So, the revenue side of the equation is not a solution for the economics of the industry, at least as far as Factor VIII is concerned, in the U.S. market. Revenue might help with the other factors but in terms of Factor VIII that is disappearing, that is not going to help the problem. Those other countries in the world that are less developed aren't going to pay U.S. prices for Factor VIII. You would have to sell at a much lower rate, which would only compound the problem on the revenue side.

So, I guess what I am trying to figure out is can the economic woes of the industry be solved

solely on the cost side? Is there enough regulatory change that can occur that will ensure that it will continue?

I guess the second part of the question is that would ensure that those Factor VIII products, the plasma-derived Factor VIII products, be available for the rest of the world that can't afford the recombinants perhaps, let alone the plasma-derived, at the current price.

MR. BULT: Thank you, Mark, for bringing this up. As you know, we have spoken about this several times and I know it is going to be the topic of our presentation in Bangkok in a few weeks where we will talk about it. The first thing that I want to say is that freedom of choice is important, which means that we have to respect the decision of the physician and the patient for the therapy that he or she wants to use.

If you look at the market situation in the United States, if I just focus on Factor VIII 70 percent of the U.S. marketplace is provided with recombinant therapies, 30 percent is plasma

derived. If I look at the other big regions, Europe is about 50-50; Japan is about 50-50. What I see in the world is that there are different opinions about what therapy should be used and, again, we respect freedom of choice. But if I think for example about a huge, important group of patients, von Willebrand patients, they cannot be covered by recombinant therapies. I am not saying that plasma-derived Factor VIII should only be used for this indication. There are more indications, as you know, but I don't think I should go into further detail here.

The other thing that we need to understand is that, whether we like it or not, there is an economic reality and a company cannot just exist from one therapy. That means that you need to have multiple therapies in place. It is up to the individual company, based on the product portfolio and the technology being used, what the right mix is and what prices can be used to put these products on the market.

I agree with you that the developing world

cannot afford U.S. prices, but I also believe that the developing world has a long way to go. If I look at the current supply of Factor VIII, we know that about 70-75 percent of the world hemophilia population has not treatment at all and I think there is a long way to go between nothing to six or seven units per inhabitant, which is what we are seeing in current Third World countries. So, I believe if we do it step by step there is a way to work. As you know, we have had several meetings with WHO in the past where this issue has been addressed, but we are all aware that affordability today is a much bigger issue than quality and safety.

MR. WALSH: Thank you for the presentation, Jan. I just wondered is the industry doing anything or considering any changes in the distribution channels. You know, you had that chart up there that really demonstrated what could be considered a disproportionate margin for fees or rebates to distributors. What is industry actually doing about that if that is an issue?

MR. BULT: Well, I would like to clarify that when you talk about industry we, as PPTA, are not doing anything in this regard. So, when you talk about industry, you talk about individual companies. Individual companies may decide what is the best way for them to bring the products to patients. Some of them use home care providers. Some of them have different distribution systems. That is up to the individual company to decide. But I do believe, and I am absolutely sure, that companies are looking right now to find the most optimal way to bring their therapies to the patients.

As I said before, we are facing significant economic challenges and we try to identify in the whole value chain where there is the most added value and recognition for the innovations that have been developed.

DR. BRECHER: Last comment?

DR. HAAS: I think the economics I can understand quite clearly but in the economic literature there is a distinction made between

demand and need. When we identify need--and I think I can probably do it here in the United States but certainly globally there is a need for these products that can't be afforded so it doesn't fit--getting to the demand model, we get into a terrible situation where in a system like ours the revenue is necessary to drive the system but when the revenue is not coming in individuals don't get the product. I suspect that if any of us were in the Third World right now and wanted or needed access to product and heard an answer which said, well, we will allow this to happen incrementally we wouldn't accept that as an answer to ourselves, all of us sitting around the table.

So, I think one of the things we need to be thinking about, we, this group, is that if the market, the private market is driving what gets produced and not enough is getting produced to meet the need, then we have a significant problem in terms of how to address that need. We can't just simply say, well, the market is not going to do it so it is not going to be there. I think that is

inadequate; we have to be much stronger than that.

MR. BULT: Let me clarify one comment that I made when I talked about incremental uses here. In my response to Mark about what is happening in the developing world my point is that if you look at the use of Factor VIII and you use as a basis the units per inhabitant you have a fair comparison per country, and we know that there are countries where the use is about 0.5 units, which means you can treat acute bleeding for some patients. But there are also countries where the use is about 6 or 7 units per inhabitant, which is optimal preventive treatment and basically giving patients a normal life. My point was that you cannot go from zero to seven in one step. That is what I meant by the increments.

DR. BRECHER: Thank you, Jan. We are going to go on to the second speaker, Julie Birkhofer, also from PPTA, discussing reimbursement.

Role of Reimbursement in Therapeutic Plasma Treatments

MS. BIRKHOFER: Thank you, everyone, and good afternoon. Thank you for the opportunity to be here on behalf of PPTA. I appreciate coming before you and sharing with you a brief overview of the role of reimbursement in our industry. I know this is a complex topic. We heard earlier today from Dr. Hambrick. I wish he were here now. Clearly, these issues that I will try to bring to your attention today will serve as an outline for our comments and reflect our concerns regarding the proposed rules.

We all know the MMA passed in December of 2003 and with that there has been a host of implementation issues that have come out in the form of various proposed rules in the past month. I would like to briefly discuss with you today PPTA's role in health policy; give you again a synopsis of our industry challenges; talk briefly about the Medicare/Medicaid and share with you some conclusions. I think we heard from Dr. Hambrick this morning the complexity and the web that the Medicare and Medicaid systems bring upon us. I

don't propose to be an expert so, please, if you have questions I would be happy to entertain them.

The purpose of PPTA's health policy department is, as Jan mentioned, to assure access and choice to plasma-derived recombinant analog therapies. We very much appreciate the advisory committee's recommendations with regard to reimbursement and your recognition that reimbursement does impact availability in terms of access. The major way that we are successful in our endeavors in Medicare in the States is that we expand and we work with our stakeholders. All of PPTA's successes are achieved in coalition with our stakeholders. The goal is to create a greater community and political awareness.

I would briefly like to talk about the inpatient, outpatient, physician office and home care settings. You heard an environmental and economic analysis from Jan. Just to reiterate, we have a consolidating industry. We have declining product revenues. I would just highlight that the challenge for industry is to continue to meet

consumer demand and to fund predictive development given the increasing regulatory and economic constraints. For an industry under these pressures, I think it is remarkable and noteworthy that in 2003 we had four new entrants to the U.S. market.

We are different. We talked about that. These are unique therapies, small patient populations, very complex and lengthy manufacturing processes, the cost of the starting material. You all recognize the precious material that plasma is. There is no plasma bank. We are concerned with the applicability of generic biologics. We feel that this could stymie innovation and could slow the industry's ability to respond to consumer demands. We urge policy makers to differentiate plasma-derived and recombinant analogs from traditional pharmaceuticals.

The therapies that I would like to focus on are what I would consider to be our core therapies that treat chronic disease. There are others. There are hyper-immunes or specialty

immunes. But what we would like to talk about are the blood clotting factors, the IVIG and the alpha-1 proteinase inhibitors.

The key message that I would like to leave with you is that the MMA has put into place a variety of new reimbursement methodologies, most of which are unproven. Congress, under the wisdom primarily of Bill Thomas, Chairman of the Ways and Means Committee, put forth a lot of policies in the Medicare Bill to rely on the private market. Most of those are theoretical and unproven. We don't feel that the fragile patient populations that use these life-saving therapies should be subjected to unproven private market methodologies.

Furthermore, if you really look at the politics of it, it is uncertain in the 109th Congress, if there is a change in administration, that the MMA will be opened up. We all know that there have been assertions from the democratic candidate that, if given the opportunity, they would re-explore funding for Title I, Part D drug benefit. So, whether it is a viable benefit

remains an unknown.

Basically a brief overview of the sites of service and the various rates for blood clotting factors--this was discussed by Dr. Hambrick. I don't want to be repetitive but I think, in particular, the concern for factor is under the part B, physician office setting. I believe earlier today a consumer advocate from Hemophilia, New Jersey, shared with you her feelings on the adequacy of a five cent add-on for factor to sustain access to care for individuals with hemophilia.

Furthermore, it was also expressed that the current first quarter ASP, as published in a 32 listing of widely used drugs, demonstrates that there would be a 29 percent reduction in recombinant Factor VIII. Clearly, given the economic challenges of the industry and the need to sustain access, a reduction of almost one-third is not what we need to sustain access.

With regard to IVIG, I think the flash point here is under the hospital outpatient. We

are unsure again of what AWP information CMS used to calculate the rate. It is not as troubling and problematic as factor but, again, we will be going into CMS. We will be urging our companies to supply verifiable data to challenge the rate. The good news in IVIG is that we were able, through the legislation in December, to exempt IVIG from competitive bidding.

With regard to alpha-1 proteinase inhibitor, again the flash point is on the hospital outpatient side. It does have an orphan designation. There is a unique blend of flexibility where it can be reimbursed at 88 percent of AWP or 106 percent of ASP, and it would be capped at 95 percent. However, even given that special treatment, we again experience an almost 20 percent reduction for the alpha-1 proteinase inhibitor. In the 109th Congress, we would like to reach out and collaborate and work with the alpha-1 community to have home care coverage for them.

Again, the gaps in site of service really don't make sense. If individuals with hemophilia

can home infuse and individuals that are PID can use IVIG safely in the home, why shouldn't a person with alpha-1 that has difficulty breathing or has mobility issues, why shouldn't they also have the dignity and the quality to infuse in the home? These are inequities that, again, we would like to work with the community, work with Congress and work with CMS to address.

Furthermore--I mentioned some of this earlier--the alpha-1 rate, as Jan noted, really doesn't recognize innovation--the two new entrants to the market, the millions of dollars per patient invested--and we feel that the reduction of 29 percent represents a drastic cut in reimbursement.

On the Medicaid side, because CMS, as you know, does have Medicare and Medicaid publicly funded programs, there is a lot going on in the states. The picture really hasn't changed. Economic downturn, budget issues--really no politician wants to raise taxes so we see revenues plunging. This is what is driving the debate.

With regard to Medicaid, states continue

to look for a quick fix--prior authorization; preferred drug list; shifts to managed care; PBMS; very restrictive in terms of access to care and price controls.

In general, federal and state reimbursement policies impact access choice and innovation. They are also serving as models for the private sector. What Medicare does private insurers soon follow. Competitive bidding that is a Medicare tool is, again, an unproven private market methodology. Sole-source provider contracts are what we are seeing in the States. They are intended to control utilization; to limit access; and they very much restrict consumer/physician choice. The trend is that reimbursement is steadily declining across all sites of service. That is the intent. It is more than a trend; it is an intent. Prospective payment and the private market methodologies in the MMA are very deliberately designed to control cost, to reduce spending, to control utilization.

What I am arguing is that when I talk

about how our therapies are different, very basically these methodologies should not be applied to the plasma-derived and recombinant analog therapies that consumers with life-threatening conditions--they should not be subjected to these types of methodologies.

In conclusion, PPTA will continue to conduct outreach to consumer and provider organizations, to work in coalition, to educate policy makers, to come before your committee. I very much appreciate the fact that you have invited us here today. We need to continue to work together on reimbursement issues to assure access and choice. The recommendations of the committee are invaluable. I cannot stress to you enough the importance of those and I am very delighted with your actions this morning to form a task force to work to get some synergy with CMS, to get their attention on these issues. Simply put, reimbursement drives access, choice and innovation. Thank you, and I would be happy to entertain any questions.

DR. BRECHER: Questions or comments?

DR. LOPES: I want to come back to the question that Mark asked about driving down cost. I have been sitting, trying to figure out what kind of a process could take seven months from collection until the end. Is the plasma literally in kettles and test tubes and passing through pipes for most of that time?

MS. BIRKHOFER: If you think of it conceptually as from vein to vein, from the time the plasma is collected, frozen, stored, shipped, received, thawed, processed, manufactured, heat treated, pasteurized, nano-filtered, whatever the process is in that fractionation process, which was on Jan's slide when he tried to outline it, it is a lengthy process.

Now, it doesn't stop with the manufacture. It then continues. Plasma-derived therapies are subject to lot release. We have done a great job working with the FDA to tighten the time frames for lot release. But these therapies aren't just released onto the market. Everything is tested and

retested, submitted to the FDA. Lots are tested; they are controlled; tracking numbers. This is very, very complex stuff. Incidentally, we have a virtual tour. If you are interested, I would be happy to share it with you. It is a little digidisk that will walk you through and show you some of the complexities of this process. But, believe it or not, it is a six to eight month process.

DR. HOLMBERG: Julie, if you will give that disc to me I will try to get that to each one of the committee members.

MS. BIRKHOFER: Sure, I would be happy to.

DR. BRECHER: We are going to move on to Michelle Vogel, on consumer access.

Consumer Access

MS. VOGEL: Thank you, Dr. Holmberg and Dr. Brecher for inviting me today to testify on behalf of the primary immune deficiency community and to share with you the reimbursement issues affecting us. I would just like to take a minute to introduce IDF's new president who is here today

with us, Dr. Richard Birkel.

IDF was founded 24 years ago by parents of a patient and their physician. Since our beginning we have had an active medical advisory committee which is now made up of 20 prominent immunologists. In addition to our nationwide network of volunteers, we have a full-time staff and a medical director. The picture there is actually a snapshot of our community. It is a patient's family members and caregivers. That gives you a little picture, a face of primary immune deficiency diseases.

Immune Deficiency's long-term goals--we continue to improve state-of-the-art medical care for primary immune deficiency diseases. We work hard on early diagnosis and we are striving for newborn screening tests to be developed and implemented. We are continuing to provide life management programs to the primary immune deficiency community. We are working to develop new cutting edge scientific and medical research. We work to help to reach more patients through education and advocacy.

The World Health Organization now recognizes over 140 primary immune deficiency diseases affecting approximately 50,000 people in the United States. The diseases are the result of genetic defects that involve the immune system and its responses. The exact action of each of these diseases is known only for a minority of these conditions. Primary immune deficiency diseases are characterized by an increased susceptibility to recurrent, poorly responsive, severe and unusual infections.

Affected individuals have abnormalities of cells or proteins of the immune system. The cells include B cells, cells producing antibodies, T cells, cells that coordinate the immune system's responses and leukocytes, the white blood cells and cells that fight infections. Some of the proteins are immunoglobulins, the gamma globulins, complement proteins and blocking agents such as C-1 esterase inhibitors.

This is a list of the most common primary immune deficiency diseases. I am not going to read

all the diseases to you but as the common variable immune deficiency is our most common disease and severe combined immune deficiency tends to be the one that most people recognize, also known as "bubble boy" disease.

Back in 2002 we did a survey of our primary immune deficiency community to really look at the diseases and to try to pull together data. We had 1,526 respondents in one study. Then we did another study looking at the treatment and experiences or preferences of patients with primary immune deficiency diseases, which had 1,186 respondents.

The next slides are just going to give you a little picture of some of that data before we get into the reimbursement issues which will help you understand.

Dealing with the patient age of primary immune deficiency diagnosis, as you can see, a third of all the patients are younger than 18 years old but a quarter of them are 45-64 years old. So, they are being diagnosed later and later in life.

Time to diagnose after symptom onset--the average time is 9.2 years. What happens with that is that the longer it takes to diagnose a patient, the more susceptible to chronic and permanent impairments which end up leading to disability. That is what is our finding. The people who are being diagnosed later in life are the ones who are needing to apply for disability. So, this 9.2 years is not acceptable.

As you can see, primary immune deficient patients, 67 percent of them use IVIG. You can see that the majority of patients are being infused once every three to four weeks, about 80 percent. The length of time of infusion on average is three to five hours, which I mentioned earlier, but we have patients that are infused over eight hours. If you think back to the infusion pump issue, if you take those patients off the infusion pump and switch them to a gravity drip bag you double the time. That is a long time for an infusion.

This gives you a little information. When a patient receives an infusion it is typically

during the week, nine to five on weekdays so people have to take time off from work or kids are missing school for their infusions.

This gives you a little snapshot of where they are receiving their infusions. When we surveyed we saw that 40 percent are receiving it at home. This does not address the Medicare community. This is what led to researching the safety issues in the home which then led to the home infusion benefit. That number is not increased by much right now because of the way the Medicare law is but that number needs to grow, but we are really hitting in every site of service.

As you can see, the majority of patients, almost 70 percent, are employer coverage but if you go to the blue, there are your federal programs, your federal and state. For your Medicare we have 15 percent. The majority of those patients are disability patients but, as people are living longer on IVIG, we are going to start seeing that elderly population growing.

Health insurance problems--64 percent of

primary immune deficient patients have health insurance problems and some of these reasons are because of denial of coverage; exceeding lifetime caps; prior authorization causing treatment delays; IVIG is just not covered; the states prefer drug lists, the formularies that Julie was talking about; and policy cancellations.

Reimbursement, hospital outpatient--let's go to 2004, this year. CMS classified IVIG in the lowest possible classification of generic, non-innovative, multi-source therapy. They were paying $37.95 per gram. That is less than what the product costs. So, what happens? Patients are denied access to life-saving therapies. Hospitals can't administer the IVIG. So, where do the Medicare patients go to receive IVIG? Right there we were starting to see a shift in site of service. Things worked out in this situation where CMS reclassified IVIG as a sole source and move it up and said 88 percent of AWP and brought it up to $72.60 per gram. Just kind of remember that number, $72.60.

Let's go to 2005, and $68.48 cents was proposed. So, we are dropping $4.12 per gram. I am bringing this issue up because this drives me crazy and it is going to be an issue again. You guys have come out with language and have been tremendously helpful. Dr. Holmberg, I am going to ask for your help again. CMS does not recognize IVIG as a blood product. I can't understand it. Right now they are not dealing with the dampening effect but once they do the acquisition cost in 2006 may come back. I am going to be proactive right now and say let's try to solve this problem and get them to recognize it as a blood product.

So, what do we need to do? IVIG should be at least back to where it is in 2004. I mean, there is no reason for it to be reduced. I have mentioned the blood product issue so I am going to move on.

Let's go into the physician fees. Remember, $72.60 in the hospital. In the physician's office the reimbursement is $66 per gram but, remember, 80 percent of that is covered.

Originally it was really supposed to be covered at 95 percent of AWP but there was a mistake in the bill so it is covered at 80 percent. So, what happens there? Physicians start calling and saying they can't treat the patients anymore; they are losing costs. So, patients are being denied access to the treatments and being turned away from these treatment sites. Again shift from site of service.

Luckily, the hospital situation was fixed so then the patient can go to the hospital. But if that wasn't fixed, where does the patient go? Again, reimbursement is dictating site of service, not the patient and the physician but the reimbursement.

Also in Part B CMS classifies IVIG as a generic product. So, it needs to be changed and we don't know what it is going to look like for 2005 yet, what the ASP plus 6 percent is going to be. But a very alarming situation just happened a few weeks ago where AMA was looking at coming out with recommendations for CPT codes and they recommended classifying IVIG as a low complexity administration

procedure, which is a category including saline and antibiotics. No training is needed, no oversight, no nothing--easy product to administer. Luckily, last week AMA reversed its decision but there is this disconnect of understanding IVIG and understanding the community that uses it. So, this is continuing to be a problem. Providers are very concerned about the switch over to ASP, and we are getting calls from physicians' offices that are looking not to continue to treat this community.

The home infusion benefit--I spoke a little bit about this, this morning but the benefit covers the drug only supposedly, not the administration of IVIG and not the use of durable medical equipment. So, right there it is not an adequate benefit. But it was a start. Once it went into effect we thought, okay, if the hospitals aren't going to take the patients and the doctors aren't going to treat them, we have the home care now, a new benefit. Well, most of the home care companies said, no, we are not going to take your patients. We are being reimbursed at 80 percent of

$66 and we can't get reimbursed for the nursing services and we can't get reimbursed for durable medical equipment.

But a few did on a case by case basis. Some of them said, okay, we will do it if the patient pays for the nursing services. Some patients did that for a little while but, you know, a patient who is on disability and living on a disability check can't really afford those nursing services for very long. Then what happened, all of a sudden they started to submit the claims and found out that if they were infusing through an infusion pump Medicare was not reimbursing it because they were deeming the infusion pump medically unnecessary, therefore, IVIG was medically unnecessary. Problem.

So, we are working with Congress. We have met with CMS and we are trying to fix the infusion pump problem and trying to get this to be a whole benefit. We look to the committee to help us in this situation and help work out the problems in the different parts of CMS and try to get some

parity. But, you know, to kind of bring a conclusion to this, primary immune deficiency diseases are chronic, life-threatening diseases and with the introduction of IVIG therapy patients have been able to live productive and near-normal lives. Without this therapy they have no chance. Primary immune deficiency Medicare patients are being shifted from treatment site to treatment site and this is dependent upon reimbursement.

We recommend that there be equal and adequate reimbursement for all sites of service. The new home infusion of IVIG site of service is definitely needed for our community. Congress saw that and most of our Medicare patients are on disability. They do not need to be exposed to additional infectious agents by visits to hospital and doctors' offices so we do need to fix that situation.

IDF has recently met with MedPac who is conducting a study on IVIG reimbursement for the primary immune deficiency community, and we stress the importance of patients having access to this

life-long, life-saving therapy and the best site of service for the patient, determined by the patient and their physician, not based on reimbursement.

MedPac is also reviewing the need to separate the different IVIG products by giving each product its own HCPC code so that CMS does not continue to classify IVIG as a generic, and IVIG should continue to be exempted from any competitive bidding model. That concludes my remarks and if you have any questions I would be happy to answer them.

DR. BRECHER: Quick questions or comments? If not, we will move on to the last speaker of the day--

MS. VOGEL: Thank you.

DR. BRECHER: Thank you. Donna DiMichele, on licensure issues for rare bleeding disorders.

Licensure Issues of New Advances in Replacement Products for Rare Bleeding Disorders

DR. DIMICHELE: While the presentation is coming up, I will start the discussion. I want to thank the committee for inviting me to present

today on the issue of replacement therapies for rare bleeding disorders. What I am, hopefully, going to be talking about today is the fact that the lack of availability of such therapies is really, indeed, a safety issue and, therefore, I believe that this is an important committee to present to.

I am presenting broadly on behalf of the Medical and Scientific Advisory Council of the National Hemophilia Foundation that sort of started this initiative and, more specifically, on behalf of Dr. Amy Shapiro who couldn't be here today.

Sensitive to the fact that this is the last presentation of the day, I am going to do this as quickly as I can. The aims of the presentation are pretty much three-fold and I will go through them right in the beginning. The first is that with this presentation we would like to highlight the issue, as felt in the bleeding disorder community, that there is a discrepant therapeutic standard when you compare persons with hemophilia and the standard of care that they have and those

affected by the rare bleeding disorders.

In this presentation we would like to propose several approaches to develop these very necessary therapeutic options for these individuals, and we would like to ask for the support and the endorsement of this advisory committee on blood safety in our global efforts.

With respect to the overview of the presentation, I would like to begin with a definition; give you some background infection on the issue and some examples of some of the clotting factor deficiency; and then go through our proposals for moving forward with respect to solutions to this problem that include coalition building among organizations with a mutual interest in finding solutions for this issue; what we are doing to highlight this issue through presentations, not only this one but others; and what we propose to present to the FDA and industry with respect to developing mechanisms to improve access to required therapies.

So to begin with the definition, as most

of you probably know, the legal definition of a rare disorder in the U.S. is a disease or condition that affects fewer than 200,000 Americans. Certainly, the hemophilias qualify. With an incidence of 1/10,000 individuals even hemophilia A and B are considered to be rare disorders, but the ones that I am talking to you about today actually have a frequency in the general population of somewhere between 1/500,000 to 1/in a million so we are really talking about rare.

With respect to background and the therapeutic issues, there are several issues that come to bear here. The first is problems with respect to treatment and product availability and expertise, the first involving the availability of safe and effective therapies and, the second, the knowledge within the medical community of appropriate replacement strategies. I am not really actually going to address the second of these but, hopefully, we are going to talk a lot about the first.

The second issue that comes to bear on

this is the fact that there are barriers to developing adequate replacement strategies. With a limited market for licensed products the issues really involve cost, the cost of research, the cost of clinical trials and, to a certain extent, regulatory burden with respect to bringing a product for a rare disease to market.

With respect to clinical trial development even, the fact that there are very few study subjects really impacts on clinical trial design that is currently generally mandated by the FDA in bringing these products to market.

So, what happens is, you know, we still have this problem, of course. We don't have the available therapies or the optimal therapies but we still have these patients to treat so what do we do? Well, we give them non-virally inactivated plasma products in general, and sometimes we use products in an off-label capacity that are already licensed for another indication, and occasionally patients are even faced with the fact of importing products that may be licensed in Europe for

personal use. You have heard a lot about reimbursement issues and certainly they impact in this arena as well because, as you can imagine, drugs that are imported for personal use or are used off-label are frequently not reimbursed, and these issues are only getting worse, as has been highlighted in many different ways today, so that none of these options are really long-term solutions.

What we are really faced with as a consequence is that patients with rare deficiencies have limited options for care. There is a lower standard of care when compared to their hemophilia counterparts and, because of that, there is the potential for increased morbidity and mortality.

I would like to talk a little bit about Factor VII deficiency as an example. Factor VII deficiency is an autosomal recessive disorder. In general occurs at a frequency of about 1/500,000. Actually, because of some registry data we have, both North American registry as well as the international registry, we have data on about 650

such patients. Actually, if you include heterozygosity for this disorder, what you find is that this is a rare disorder but it is one of the more frequent disorders that we encounter. In the North American registry, for instance, you will see here that it basically encompasses 46 percent of the patients that are in that registry if you exclude Factor XI deficiency.

Now, 35 of those patients would be considered severe, with levels under 20 percent, with limb and life-threatening hemorrhages that have been reported with quite a bit of frequency. The fact of the matter is that even given the prevalence of this rare bleeding disorder relative to any of the others, we still don't have a licensed replacement product for factor deficiency in the United States.

That doesn't mean that there aren't any. In fact, there are two plasma-derived Factor VII concentrates that are manufactured and licensed in Europe, and the recombinant activated Factor VII product that is licensed in Europe and in the

United States for the treatment of hemophilia inhibitors does not have an approved indication for Factor VII deficiency in the United States at this time.

If that is the case for the more frequent of the rare bleeding disorders, the question is what else is going on for some of the others? Indeed, with respect to the other rare deficiencies, we have situations in which there again are potential specific replacement products that already exist worldwide and that is, indeed, the case for Factor XIII deficiency for the A fibrinogenemias and hypofibrogenemias for Factor XI deficiency and these products, like I said, are concentrates that are actually made and approved in Europe for the treatment of these deficiencies but not here, in the United States.

We also do have therapies that exist here in the United States that can be used to treat other deficiencies, symptomatic as PAI-1 deficiency but we don't have a licensed indication to do so. Then we have the situation in which some of these

deficiencies are so rare--Factor V, X, II, plasminogen--that basically we don't have any products at all anywhere in the world to specifically treat these deficiencies.

So, that is the scenario. The question is how do we move forward? I would like to tell you a little bit about the efforts that we have made so far. The first, as I mentioned before, is the formation of a coalition of organizations that have a mutual interest in solving this problem. I am happy to say that the coalition is actually becoming, indeed, quite broad. Through the initiative of the medical and scientific advisory committee of the National Hemophilia Foundation, which actually has resulted in a recommendation, recommendation number 143, advocating for the use of specific replacement therapies for individuals with rare disorders, this issue has since been highlighted by the blood safety working group of the medical and scientific council with respect to its long-term goals.

Most recently, there has been a working

group created as part of the Factor VIII/Factor IX subcommittee of the International Society of Thrombosis and Hemostasis that is specifically going to focus not only on scientific issues related to the rare bleeding disorders but also access to care.

Finally, the World Federation of Hemophilia, thanks to Mark Skinner, is also going to be bringing up this issue in terms of some of the discussions that are going to occur with respect to blood safety and availability in Bangkok, in October. We have not actually approached NORD, National Organization of Rare Disorders, yet but we plan to include them in this consortium.

With respect to highlighting the issues, I am here today and this presentation has also been given, as I said, internationally both in 2003 which stimulated the formation of this working group and, most recently, our actions are continuing to be presented on a global scale.

With respect to moving forward, we feel

that an integral goal of our efforts is going to be, and this is a process that was first initiated in December of 2002 but still does need to move forward in an important way, is working with the FDA and industry to develop mechanisms to allow improved access to these therapies. We feel that there are three main mechanisms that we need to work on. The first is to obtain additional licensed indications for products that are already available in the U.S. for other reasons, for instance prothrombin complex concentrates for Factor X and II, NovoSeven which is the recombinant activated Factor VII for Factor VII deficiency, and some of the anti-fibrinolytic therapies for PAI-1 deficiency.

Another strategy is to obtain products licensed in other countries for use in the U.S., particularly where we have no virus-inactivated plasma-derived or recombinant alternative. Again, there are several of these, including the treatments for Factor XIII and Factor XI deficiencies and the fibrinogens. Finally, a goal

of our discussions with both the FDA and industry would be to get new product development in the area where there isn't any yet.

The talking points that we feel need to be presented to the FDA and industry with respect to improved access include some harmonization of regulatory processes for biologics between Europe and the United States. Right now these two agencies are frequently very far apart in terms of what they will accept for licensing requirements. Also, looking into alternative mechanisms for drug importation for rare disorders, and also the issue of industry incentives for either new indication applications or new product development. I am going to spend a few minutes at the end of this presentation talking about potential for modified clinical trial designs and data requirements for product licensure which we feel is at the crux of this problem.

To this end, we highly recommend a workshop that is sponsored by the FDA and co-sponsored by other interested agencies to

actually begin to discuss this problem. Again, we are also excited about the October 7th workshop. I am not sure if this issue fits in there and, if it does, we would love to participate. If it doesn't, then maybe a separate workshop might need to be organized to discuss this issue where interested parties can at least come together to begin to discuss issues and start fleshing out sort of the critical pathways to getting what we need.

As I said, the real crux of the issue here is what is the data? What is the clinical pre-licensure data that we are going to require to get some of these products licensed? And, it is not easy. Due to the rarity of these disorders and in general the lack of global availability of a single therapeutic product, trials such as those that are performed in hemophilia are not likely to be feasible. So, the question is if that is not going to work, what will? We are not a hundred percent sure and that is why we believe that a dialogue needs to happen. But we do feel that there probably are some minimum requirements for

pre-licensure data collection that need to be satisfied, and how it is done I think is going to be an interesting question that needs to be hashed out.

Of course, these minimum requirements include safety issues, both with respect to adverse events and viral safety efficacy determination. Establishment of dosing guidelines is very important with respect to these rare disorders and it has to be done in a way that is consistent and verifiable. Of course, everything needs to be ethical and comply with regulatory requirements. And, as much as possible, we would like the collection of data to actually meet existing regulatory requirements and, of course, we endorse fully the commitment from industry and clinical investigators to commit to post-licensure Phase IV studies which are often required in this situation.

Now, how do we do it? Well, there is the potential of going the industry-sponsored trial route, with potentially modified regulatory requirements for data collection. There is the

possibility of encouraging investigator-initiated IND processes, but a lot of streamline and investigator support is necessary, more than is currently available. I already know of one situation in which an investigator went through all of the hoops to get an IND for a fibrinogen concentrate and still got into some issues institutionally which he is still trying to sort out. So, this is not easy when an investigator tries to do it on his or her own.

Finally, the question is whether the registry data that we have and can collect and can provide a significant amount of data would, if it were restructured, be sufficient to actually encourage product licensure data collection, preclinical data collection and whether that would be sufficient. Indeed, there is a precedent for this, especially if it is encouraged through non-industry, independent groups such as the Hemophilia and Thrombosis Research Society of North America which is currently doing this for recombinant VII-A.

With respect to industry incentives, we highly encourage orphan drug status, the conferring of orphan drug status on a lot of these concentrates because there are certainly incentives for industry if they do obtain orphan drug status for some of these products. You can see them there. With respect to off-label use applications, there are also incentives to manufacturers in terms of small business innovative research grants and patent extensions which are possible, and we would like to encourage industry to take advantage of those.

Of course, crucial to this we think is harmonization because of the repetitive work and financial burden on manufacturers to go through two different regulatory processes. Once again, we think that the regulatory requirements that have actually worked for hemophilia may not work for these rare bleeding disorders, and there are precedents which do exist for products being licensed for rare disorders on the basis of studies involving very few study subjects, and they include

Gaucher's disease and the PEG-ADA.

In summary, I would like to finish off by basically summarizing and saying that persons with rare bleeding disorders--and I hope I have made that point--have limited and generally unsatisfactory treatment options and, consequently, they have what we believe to be an inferior standard of care when compared to persons with hemophilia.

A well-coordinated multi-organizational, international effort is going to be required to find solutions to improve and optimize care. We would like this committee to, hopefully, endorse these goals and endorse the goals of this campaign and we feel it would be beneficial to the global effort already in existence. Thank you very much and, once again, I thank the committee for the opportunity to present this.

MS. LIPTON: Thank you very much. That was really educational for me. Could you elaborate which specific goals you would like us to take a look at? You didn't call anything a goal

specifically. Is there something in writing?

DR. DIMICHELE: Thank you for asking me to clarify that. That is probably very helpful. I think actually there is a resolution that has actually been drafted by Mark Skinner and that might be helpful in terms of the discussion in terms of what actually we want. I don't know if you just want to discuss that resolution but in essence, very briefly said, the goals of this campaign are obviously to secure safe and effective therapies for the rare bleeding disorders. I think, you know, if that goal is endorsed by blood safety and availability I think that would be very important with respect to our discussions on all levels.

MS. LIPTON: Thank you.

DR. EPSTEIN: I just want to comment. First of all, Donna, thank you very much for a very elegant overview of a significant health problem. A lot of what you focused on has to do with necessary actions by FDA, product approvals and approvals of extension of labeling. I am sure you

are well aware and I hope that everyone else is well aware that someone has to apply for something.

DR. DIMICHELE: Yes.

DR. EPSTEIN: To my knowledge, there have been no submissions to the FDA by sponsors of candidate products, whether or not licensed abroad, and we certainly are willing to entertain requests for categorizations for orphan drug and to review applications, and we have an open mind in dealing with the problems of study design in the face of rare disorders. As you yourself pointed out, that is not actually a new problem at FDA. You know, we have found the wherewithal to deal with it. So, I guess my point here is that we do have an open mind. We are partners in the public health, and what is really necessary is to bring the parties together for constructive dialogue.

DR. DIMICHELE: Right, and we know that. I think what I am trying to do on behalf of all of us who are thinking about this is to highlight how difficult this issue is because, certainly, there are few subjects for pre-licensure clinical trials.

On the other hand, we still have to have efficacy and safety data and this is not an easy problem to solve to everybody's satisfaction, and it is going to require mechanisms that are quite different than what we have used for products for hemophilia. We know you know that, and we also know there haven't been applications for a lot of the cost-based reasons that were also outlined. That is why we really advocate that the discussions are with FDA and industry and all of the invested parties because I really think that the dialogue is necessary to bring those applications and to discuss what those applications are going to involve with respect to preclinical data, and how much money it is going to cost to get that product to market--I mean, everything is so intertwined that I think a discussion on the table is going to be necessary even before you get those applications out. That is what we are sort of sensing.

DR. BRECHER: Celso?

DR. BIANCO: Donna, this was superb.

DR. DIMICHELE: Thank you.

DR. BIANCO: I think you convinced Jay; he is all excited about it--

[Laughter]

--but how are you going to convince industry with the bleak picture that they presented to us today? It was so bleak that maybe I shouldn't say what I am going to say, but it almost encourages government intervention or the approach that certain European and Asian countries can use for setting up their own fractionation plants, and all that, because the industry is not presenting viable solutions. So, how do you marry that?

DR. DIMICHELE: Well, you know, I don't know that I have all of the answers today but we did hear from Jan today that multiple products are frequently necessary for revenue generation. We also did hear that every manufacturer's cost-based structure is a little bit different so this, obviously is not going to be a feasibility for every manufacturer right now of fractionated plasma-derived products.

On the other hand, it seems to me, maybe

in a very simplistic way, that, yes, there isn't much revenue to be gained here. The question is how can we diminish the cost of getting this product to market? And, it seems to us that that is the only way we are going to be able to do it so a lot of what I have been proposing, I am hoping, is going to be methods--you know, regulatory burden, financial burden due to regulatory, financial burden due to requirements for clinical trial design, all of these can be effected and we can affect the cost side so that the revenue side, if not revenue producing, at least hopefully can be revenue neutral. But, obviously, that is where industry's input into all of this is required in this dialogue.

DR. KLEIN: Donna, are there industry data from Europe or subsequent experience from Europe that might be sufficient for someone simply to apply for licensure in the United States based on what they have?

DR. DIMICHELE: That is a good question. Again, that is some of the information and some of

the discussion that we would like to have with the FDA. I have to tell you it is unclear, since these products are licensed, how much post-licensure data is actually being collected from Europe. But the question is if post-licensure data collection would be something that would be useful and that could be included in an application here, in the United States, then maybe these companies could be encouraged to start collecting this data in a post-licensure fashion and actually submitting it to the FDA, but I don't know if Jay wants to comment on that.

DR. EPSTEIN: As in many things, there is a simple answer and a complicated answer. The simple answer is that there is nothing in our laws that prevents us from recognizing and accepting non-U.S. data. The complicated answer is that when such data are submitted to the FDA, and they sometimes are, we need to determine whether they satisfy our criteria and that can include things like were human subject protections respected in a clinical trial? Can data integrity be validated?

Were the study designs scientifically appropriate? Is the documentation complete? Things like that. Companies often are not able to satisfy our requirements because they have not structured their trials or they have not retrieved data in such a manner that they could submit it to the FDA.

At the present time, what you said is true, that the EU standards and the FDA standards are not necessarily the same. It is also true that there is no current mechanism for automatic mutual recognition of licensing. So, we have separate licensing authorities and we have separate licensing criteria despite the fact that many of the formats of applications have been harmonized under the ICH process, the International Community on Harmonization.

There are also evolving infection sharing agreements whereby the respective regulatory authorities around the world are beginning to engage in bilateral memoranda of understanding that will permit us to share confidential, although not trade secret, infection, but with the permission of

companies we can also share trade secret information. So, there are steps toward harmonization but the bottom line is that independent sovereign states still make their own decisions on product approvals and that is not changing any time in the near future. So the question is whether data gathered abroad could satisfy our standard but nothing precludes submission of such data.

DR. DIMICHELE: But the other side of the coin there is the standard that the FDA is currently holding this data to, can there be any compromise there without compromising the safety of patients here, in the United States? You know, there is class one data and then there is the data on which we already make a lot of medical decisions and treat patients. I guess what we are trying to say is that the high quality of data that has reassured us with respect to the licensure of products in the United States for our bleeding disorder community heretofore just may not be doable for the rare bleeding disorders, unless we

can figure out a way to make that happen. I don't know.

MR. HEALEY: Thank you again. I think it was an excellent presentation. To Celso's point, I think there is motivation on the part of the companies--ff course, I can't speak for any of them individually--to explore new proteins out of a single liter of plasma and I think that fits into the economic structure and what it will take to bring the industry around to a more favorable economic position. Part of managing the cost downward, what Donna is speaking about, I think is essential.

I think the other piece that is kind of missing here is the revenue piece, the payer side. I think there are a lot of good suggestions about a workshop and bringing FDA to the table, but I think CMS is missing in this picture and I do encourage Donna and MASAC to consider that and make sure that whatever dialogue occurs on this topic also includes the payers.

DR. DIMICHELE: Thank you. That is am

important suggestion.

DR. BRECHER: Last comment, John?

DR. PENNER: Maybe I will take this back to Jay. The Gaucher's data, does that fit in with the potential for perhaps looking at these things a little differently?

DR. EPSTEIN: I can't speak to that specifically because it was reviewed in the Center for Drugs and I don't know the details. But what I could say more generally is that it is our goal to do what is scientifically sound and practical and reasonable. What is needed here is a dialogue and we have the ability to be flexible as appropriate. You know, we are not unimpressed with the EMEA acts on a European product but still we need to look at data.

That said, we have approved products with very, very small trials and we do have the ability to make reasonable judgments between how much data are needed prior to approval versus can be gathered post approval in some organized surveillance, and we are sometimes willing to make that tradeoff.

So, there are in fact a lot of options open and I really think it is just a question of dialogue.

But, again, I cannot emphasize enough that material dialogue occurs when a sponsor, a manufacturer brings in a product and requests approval, and that has never happened for these products in these disorders to my knowledge. So, it good I think to talk about the framework issues and we certainly have already signed on to the workshop, and I think, you know, you have heard around the table that looking toward the revenue stream is important. I would put on the table that maybe trying to get public funding for development is another piece of the equation. Anyway, the bottom line is we share the interest in making progress because it is not our goal to leave any patient group behind.

DR. DIMICHELE: Thank you.

DR. BRECHER: Is that the new motto, no patient left behind?

DR. PENNER: Would an RFA be suitable in a situation like this?

DR. EPSTEIN: FDA doesn't issue those.

DR. NEMO: You know, we would consider targeted initiatives in this area. The Blood Division, particularly, deals with a lot of diseases that fit into the rare category, as you know, Donna, and we have initiatives and they are not necessarily development of products per se but a lot of initiatives dealing with rare disorders. Again, like Jay, we don't have people knocking down our doors to do these kinds of studies. In fact, there are other issues that will be discussed tomorrow. We still don't have people knocking down doors to do these larger studies. So, I think my advice would be to come to the Institute if you have some good ideas and just discuss it with us.

DR. BRECHER: Would you give us your name?

DR. NEMO: I am George Nemo, NHLBI.

DR. BRECHER: Thank you, George. We are now open for any public comments before we move into the discussion.

Public Comments

MS. O'DAY: Good afternoon. I am Miriam

O'Day and I am senior director of public policy for the Alpha-1 Foundation. We did want to weigh in with some comments because we have come before this committee many times on reimbursement issues and I want to make sure that we have kept you updated and gave you our opinion here as well.

As many of you know, alpha-1 is a pediatric and adult liver disease. The only treatment is transplantation. In the adult onset it is chronic and progressive emphysema. The treatment is a weekly infusion of augmentation therapy. We have prioritized for many years access and choice, and we think that reimbursement has to sustain that.

In 2003 we had two new products introduced into the marketplace. Remember that we have for alphas no home infusion benefit, only a physician's office or a hospital outpatient setting available for Medicare recipients. In 2003 our HPS rate was $3.43 and we believe that that rate recognized other products beyond just the sole-source product that had been in the market prior to 2003. The HPS

rate that is proposed for 2004 has gone down to $2.46 and that rate seems to be based solely on one product. So, why in 2003 did we see a rate that was based on multiple products and in 2004 we see a rate that is proposed based on one product when we have now three products available on the marketplace?

The comments that we will be making to CMS and that we wanted to share before the committee today are that we believe that in 2004 all products should be considered in rate setting. Also, in the area of access and choice, the Foundation is seeking an exemption from competitive bidding that looks very much like IVIG received in the MMA. We are doing that because we also believe you should have access to all products there and an exemption from competitive bid. We are also working with the U.S. Congress and the committees of jurisdiction to expand our sites of service. Thank you very much.

MR. CAVENAUGH: My name is Dave Cavenaugh. I am on the government relations staff for the Committee of 10,000. I want to take this

opportunity to comment a little bit on the overall situation we find ourselves in.

People in the hemophilia community are very saddened to hear that the last major genetic trial that has proven very effective at increasing the amount of clotting factor in the bloodstream has been terminated, and still look very much to the field of genetics for the kind of cure that we have found through simple transplants. Those in our community who received a transplant, for whatever reason, of their liver and ended their hemophilia have just been given a whole new license. So, we continue to look toward that sort of success rate.

Our job at COTT has really been more looking out for some of the other incoming fire that we have faced in our community, given the nature of plasma and its sources of course, and most recently that has been CJD for the most part. We have seen a number of years of work now, by both the FDA and the industry, on inactivation through the fractionation process. But just this week we

have learned of our first case of a person with hemophilia, HIV, HCV and CJD, and it is in England. It is from a person who was notified by the government that there are 12 documented exposures that he has been a party to in the process of receiving factor from lots made from a donor who subsequently developed a disease. So, we just have to continue to pay attention to it.

That is the sort of thing that we can't stop doing, but the Medicare Act has required a shift of focus and a lot of energy on keeping up with where we are on reimbursement. Not very many people in the hemophilia community are covered under Medicare. Many more are under Medicaid and private insurance a larger number still. Changes in Medicare happen to be used as a template by state Medicaid agencies in terms of coverage. You all remember when AWP first broke as a scandal about three years ago and the fraud abuse work group of the National Associations of State Medicaid Directors found out about this Florida example and exposed the drugs that were being

greatly over charged for. The major fear in Washington among the community was that all of Medicare would prohibit instantaneously any kind of AWP-based reimbursements at once. It took a resolution in Congress to stop that from happening until GAO studies had been done.

In this case, although the Medicare Modernization Act is sweeping, the numbers may be small in our already small community but we have to look at it as a source of danger and revisit this issue of the 20 percent co-pay. We are in a club of a very small number of disease communities facing such high medical costs per month, per family or per case, if you will, very small. I think some of the other drugs involved, Cerezyme for Gaucher's--very few others--and, therefore, we think we do have--I don't want to say a right because CMS doesn't listen to "right" but the 20 percent co-pay is not possible in our community.

Past arrangements of using increasingly home care for distribution as a cost effective measure have permitted that not to be a barrier to

care. If that is discontinued other arrangements must be made. We have trouble talking to Congress talking about this because they, in their current party control, really hold any kind of exemption from co-pay as anathema. If there is a government program, there has to be private shouldering of some of the burden. I understand that. But we know the people who are (a) on Medicare, (b) possibly on disability as well, (c) living with hemophilia and HIV and/or HCV are hard-pressed to pay any kind of a 20 percent co-pay. So, we have to tackle it right away.

As you all well know, states have increasingly been working to simplify their own budgets in the face of escalating prescription drug costs, if you will, through measures that do not take into consideration the nature of the disease. Single-source providers are very dangerous if they should come up with one manufacturer's product for a disease community where inhibitors can be found with one product that aren't found with another, and people have come to know that in the treatment

of their own diseases.

In addition, in the case of a natural disaster, if that one provider goes down what is the source of the healthcare in that community? Some of these other things--preferred drug lists. It requires at lot of vigilance at the state level, plus whatever Medicare changes may be used as templates in the future. So, we are quite concerned about it and I just need to say this hasn't been a Medicaid session and this morning's session was the Medicare session but if you look at the larger disease threats, these immediate reimbursement issues and what the last presentation just talked about, which is our desire to get on with taking care of those with still further--I want to say remote but that is not the right word, smaller and equally deserving disease populations within the bleeding disorders community it is a very large agenda. Thanks for your time.

DR. BRECHER: Thank you, David. We are going to move on now to committee discussion, and what I would like the committee to focus on is I

would like to put this day behind us today. Tomorrow we have a lot of other issues and we have a record of losing our quorum at the end of the day.

MS. ROGERS: Is the public session over?

DR. BRECHER: Oh, I am sorry, are there any additional comments?

MS. ROGERS: I will be very brief. I think there are a few more of us.

DR. BRECHER: Oh, I am sorry, I didn't realize there were any more. Go ahead.

MS. ROGERS: My name is Anne Rogers and I am the executive director of the Delaware Valley chapter of the NHF, which is based in southeastern Pennsylvania, but in addition I am president of the United States chapters for the NHF, the chapters staff organization, so I really have quite an influx every day of information around the country as to how our patients and their families and their families are being affected in the climate that we are in right now, and I would like to say this, we have fires going on right now in America and across

the United States in hemophilia delivery but they are basically focused in a few areas. Right now we need, as always, access to our medicines and we do not have that in every area of the United States.

In Pennsylvania right now we have had a situation of a preferred product through our HMO Medicaid approved insurance companies. We snapped that out when we got really aggressive but we have no access to the newest medication at all.

I will give you another example that benefits the only recombinant product for the treatment of hemophilia B this last week. Our two biggest commercial individual insurance companies reduced the reimbursement rate for that only product to 67 cents and 70 cents when the lowest sales price anywhere for that product is 80 cents. It can be higher but never lower than 80. So, we cannot have dispensed BeneFix anymore.

What I am trying to say is that right now in America, I believe, for a disease such as hemophilia that is so expensive we have to really watch that our payers are in line with what we

need. I am going to read you just very briefly two communications from two different hemophilia organizations, and they are very short.

Beginning in January, 2005 hemophilia therapies will be reimbursed at cost plus six percent plus the dispensing fee yet to be determined. The 20 percent co-pay that most families cannot afford remains intact. Home care companies that have been absorbing the co-pay will no longer be able to do so. The likelihood is that those individuals on Medicare, usually the most vulnerable of our community, will be forced back to the emergency room for treatment. Keep in mind, Medicare sets the standards for reimbursement. State Medicaid and private pairs follow suit.

This is another one I would like to read from another chapter of the NHF. By limiting our providers, our dispensers, to one there is greater vulnerability to supply shortages. As recently as 2001 there was not enough of the medication needed to meet the medical needs of our community. Factor was rationed to all providers. The shortage lasted

over a year and was felt throughout the country. By allowing more than one, it spreads the risk to ensure that if we experience a shortage again all persons will have the best possibility to receive the medications they need.

The recent hurricane Charlie also brought to light the vulnerability of having only one pharmacy in a state to be able to dispense factor. If that pharmacy happened to be in the path of any disaster, natural or otherwise, persons with hemophilia would not be able to get their medications in a timely manner. Thank you very much.

I would like to say I am sure that the NHF will be making comments as well today.

DR. BRECHER: Thank you. Next?

MR. ROMANO: Thanks. I won't take that long either. I am here representing the Hemophilia Federation of America, which I am a consultant for. However, in another role in my life I am the nephew of three hemophilia acts, the cousin of two hemophilia acts so hemophilia is a big part of my

life.

If you look at the last 20 years and the role of treatment and a cure, we have made tremendous strides. However, if this rule goes forward the Hemophilia Federation feels like treatment and access and availability, which this committee is all about, will be cut back. Dr. Holmberg mentioned the book "The Journey" yesterday. I think sometimes for Medicare patients it may be back to then in emergency rooms.

The Hemophilia Federation is against this rule. We ask that this committee comes out very strongly with recommendations, making sure that the co-pay especially is treated fairly with home care. My uncles would, if they could, pay up to 30,000 of the co-pay. I say "could" because two are dead, one of HIV and others are infected with HIV. So, I will say this, this committee should take a high stand on those issues and this rule is bad for this community. Thank you.

DR. HOLMBERG: Your name?

MR. ROMANO: Jim Romano.

DR. BRECHER: Thank you. Next public comment?

MS. STINGER: My name is Sue Stinger, and I have a 21 year-old who is a severe hemophiliac, college student, honor role. His medicine for one year is half a million dollars. So, a 20 percent co-pay isn't possible. So, that is just to give you some perspective of what we are talking about.

Committee Discussion

DR. BRECHER: Thank you. Any other public comments? If not, we are going to move along to the committee discussion. As I started to say, I would like to put today's business behind us today. As I see it, we have three areas to discuss, TRALI, rare disorders and reimbursement. I think the TRALI is probably the simplest so maybe we can get that out of the way first.

We had two relatively short presentations. We have discussed TRALI in this committee before. With Karen Lipton, I have put a few words together for a possible recommendation, which we are going to put up on the screen, but it reads with respect

to transfusion-related acute lung injury (TRALI), the committee recommends research into the etiology, epidemiology, treatment and prevention, including the impact of deferral or screening interventions prior to implementation. I open this for comments or suggestions.

DR. PENNER: Do you want to be more specific? Harvey and I were discussing very briefly some possibilities of just--why don't you go ahead, Harvey--one of two very simple options.

DR. KLEIN: Well, one of the things that we have considered is we don't have much data, as Jay asked for, for what it would mean to the blood supply if, for example, one were to defer multiparous women, defer them from plasma donation or defer their components from plasma use, or how we would define multiparous women.

It seems to me that before one could even think about what kind of strategies one could use, you need to have those kinds of information, which are relatively easy to obtain. So, perhaps that kind of initiative might be a first cheap and

effective step to take.

DR. BRECHER: I think the last sentence on the screen would cover that.

DR. KLEIN: It does cover that but I think what John was getting at is that maybe we need to be a little bit more specific perhaps on what we wish to do because that certainly does cover it, but it really covers a universe of things.

DR. BRECHER: Karen?

MS. LIPTON: I was just going to say the reason we put in the words "research" and "research prior to" was specifically to make sure that we understood the data that were out there and really the full impact of anything before we would even introduce the concept. I think there are a lot of issues we need to think about. I think we have the data; I think we could do it quickly. I think one of the reasons we framed it this way is because to try to go through every single possible deferral strategy or intervention strategy is hard to list.

DR. KLEIN: Certainly I don't disagree with that. I always worry though that when you put

up something that broad--you know, that is a program project--is George still here?--where someone will say, okay, let's put together our grant now and in three years maybe it will be funded, and in ten years maybe we will have the answer. Perhaps there are some intermediate kinds of things that one could look at. Again, I don't want to put specific issues or words in anybody's mouth but it could be done--I won't say quick and dirty but certainly a lot more quickly that might have some impact on public health.

DR. SAYERS: I think one of the things the committee could also recommend is the development of a standard definition. We certainly heard that there was no standard definition for TRALI, or generally accepted definition.

DR. LOPES: I think that maybe adding the words "including modeling the impact of deferral." The research into etiology and such will take a lot more time than figuring out the deferral issues.

DR. BRECHER: We can certainly add that.

DR. KUEHNERT: I wasn't here for a lot of

the TRALI discussion; I was following up on some West Nile stuff. But I think that what has happened time and time again, with leukocyte reduction, bacterial contamination and now we are talking about TRALI, is the issue about clinician recognition and reporting, and the issue of under-reporting. It just seems like a very recurrent topic, but it seems I would be remiss if I didn't mention the need to have some sort of statement on adverse event surveillance and strengthening that because if you don't know whether you start from and you make an intervention, you don't know what the impact is.

DR. BRECHER: Our thought was that the term epidemiology would encompass surveillance.

DR. KUEHNERT: I mean, you could read the tea leaves but you would have to work pretty hard.

DR. BRECHER: We could certainly insert the word "surveillance" after epidemiology.

DR. KUEHNERT: Well, that might be enough.

DR. HOLMBERG: Where do you want to insert "surveillance?"

DR. BRECHER: Epidemiology, surveillance, treatment.

MS. LIPTON: Well, perhaps that is not research though. Maybe you want to recommend surveillance, and research.

DR. BRECHER: Yes, that would be better, surveillance and research. Other than the specific example that Harvey--

DR. KLEIN: Again, I hate to be too specific but I think the idea of giving people a notion of what it is that you want early and what it is you want late--and I like the idea that you would agree upon a definition; develop a method to survey or detection perhaps and reporting; and then, finally, to analyze some strategies and their impact on availability of blood, safety and availability of blood. When you start talking about looking at research into etiology, I agree, it is extraordinarily important but, again, I am trying to think of things that might be done without a program project.

MS. LIPTON: Harvey, could I ask a

question? We are talking about definitions, and I agree what is a little difficult is that these definitions are not all within our control and we do have a number of organizations. We have the Canadian conference and then I have no idea whether FDA is contemplating a definition. So, I think we could encourage the development of a common one. I think it is going to happen but I am not sure how we cross borders doing that or, you know, within our committee.

DR. BRECHER: Celso?

DR. BIANCO: Following what Karen just said, we heard from Steve Kleinman and we know that there is an NHLBI working group, working on those definitions and all that. I think that we could encourage the process and could encourage the working group through NIH and actually research project directly link to that. The surveillance is something that will have to come some other way.

DR. BRECHER: So, do we want to add a sentence that we encourage the NHLBI working group to establish a definition of TRALI?

MR. NEMO: Well, they are really in the process of doing that. This whole activity has picked up some momentum. So, it is sort of ongoing right now. I don't know if it needs a shove from the advisory committee at this point, but there is certainly interest in continuing to work on the definition and working with the other groups.

I also can add that there are a number of potential applications that may be coming to the NHLBI dealing with the issue of TRALI. That is what we have heard and we have gotten some preliminary information from investigators. They are putting together, for example, center grants. We have a specialized centers of clinically oriented research, or SCCORs, and I know that a couple of the investigators are considering having that as a main topic. There is no guarantee that they will get a good enough priority score to be funded but there is activity out there. Also, in our REDS-II program which is about to be funded, within the week, there also have been proposals dealing with looking at the prevalence of TRALI.

Again, that is going to have to go through some strict review within the steering committee. But there is a lot of thinking and activity going on. Plus, we have our own internal initiative that we hope to push through the Institute dealing with TRALI, looking at those kinds of issues but that is still fairly preliminary.

DR. BRECHER: That is very helpful. All right, is this wording agreeable to the committee?

DR. HOLMBERG: I had put standardization in the definition but you want that out?

DR. BRECHER: Yes, it sounds like the NHLBI does not need to show that at this time.

DR. KLEIN: You know, first of all, a shove never hurts, Mr. Chairman and, second, I think, as a non-voting member, that the committee may want to go on record as saying that they think that is important. Maybe they don't.

DR. BIANCO: Instead of saying "encourage" I think that we could say we support the NHLBI initiatives regarding TRALI.

DR. BRECHER: Well, do you want to put the

word "definition" in there?

DR. BIANCO: Well, we support the efforts in terms of standardization of definition and funding of research.

DR. BRECHER: I think that sounds good. Jay?

DR. EPSTEIN: Of course, I agree with the statement but exactly what kind of advice is this to the Secretary? In other words, it is sort of like a sense of the Congress, just saying we agree with what is happening. But is there something stronger that we should be saying about, you know, that the Secretary should lend support or the Secretary should expand initiatives or, you know, something on those lines? I am just not clear what our message is to the Department here because we are advisory to the Department. It is interesting for us to state what we think but our purpose here is to advise the Department.

DR. SANDLER: I am wondering whether the missing piece is a preamble that would say something to this effect, that the committee had

reviewed the available data and did not find sufficient scientific information to recommend a specific donor deferral policy. What I am getting at is I think that is the ball out there. Do we think that we should do one of the four things that Steve had on his list? I think what is inferred here but not stated specifically is that we don't think that an intervention along any of those lines can be made from the available data.

DR. BIANCO: But what I hear from Jay is that we also want to say that we want to do something about it. So, we need the studies, the data and the effort, particularly in NHLBI, to get there.

DR. SANDLER: Yes, I am saying with the language I used I was thinking as a preamble to explain why we are recommending this.

DR. BRECHER: Right, so at this time there is insufficient data to form any recommendations regarding donor deferral vis-a-vis TRALI, and go on to the second part, something like that.

DR. HOLMBERG: Dr. Sander, did you have

that written out?

DR. SANDLER: I will restate it.

DR. HOLMBERG: I will try to copy it.

DR. SANDLER: The committee reviewed the available data and did not find sufficient scientific information to recommend a specific donor deferral policy. I am sure Jay can edit that to make it more concise.

DR. HOLMBERG: And did not find?

DR. SANDLER: Sufficient scientific information to recommend a specific donor deferral intervention.

DR. EPSTEIN: I don't think we should focus on deferral because, you know, there is donor management; there is an alternative--

DR. SANDLER: Agreed.

DR. EPSTEIN: It is a specific intervention at this time.

DR. HOLMBERG: Sufficient scientific evidence to recommend--

DR. EPSTEIN: A specific intervention at this time.

DR. BRECHER: Now we will go to the second sentence. We don't have to say "with respect to TRALI." We can just begin the sentence with "the committee recommends," although we have to put "TRALI" somewhere.

MS. LIPTON: Harvey, this whole issue of the timeliness of what is going to happen here. I mean, without saying, you know, we would like to hear back on this data in this committee or as soon as we get a standard definition as soon possible, it could just go--

DR. KLEIN: Yes, I would think that we would like the Secretary to help expedite the NHLBI's efforts to develop a standardized definition, and the efforts to develop a surveillance system, and the efforts to model the impact of the various strategies proposed on the safety and availability of the U.S. blood supply.

MR. ALLEN: Pardon me for asking this, but is any part of one of these initiatives or working groups going to be a component for public awareness or education? Because the minute this comes

out--it is not just about deferrals--we are going to have people refusing transfusions. Is that going to be part of any of this at all, or should we include that? Or, is it too early for that?

DR. BRECHER: I don't think we have done that with many of the other recommendations that we have made, for example bacterial contamination. So, I was not anticipating that there would be an effort in that regard. It is still a relatively rare complication. Most people are not aware of it but it is one of the major causes of fatalities from transfusion.

DR. PENNER: In the meantime, do we want to increase the educational aspect at the moment to alert at least the scientific community or the medical community that this is an issue? Because, as you say, it is not well recognized and that certainly will help in the surveillance.

DR. KUEHNERT: I think this might get into the broader issue of adverse event surveillance. I mean, when you educate clinicians about post-transfusion adverse events you educate them at

the same time as to the possible causes, which include TRALI and bacterial contamination. So, it is sort of a package deal. It seems like to would be the best way to do that. We could start here and now but it seems like it would be best done as a comprehensive educational package.

DR. BRECHER: Jay?

DR. EPSTEIN: It is another point but I think we have left out the issue of diagnostic methods. There is really a need to support the basic scientific development of the tools that would be needed to either detect these anti-HLA or anti-granulocyte antibodies and/or facilitate some kind of cross-matching process that could be expeditious in selecting the donor for the recipient, and maybe we don't have to, you know, understand the etiology but if you can do a cross-match and prevent a risk donation, that might suffice. So, I think there is a technology piece missing here.

DR. BRECHER: I think we can probably address that by just inserting the word "diagnosis"

after "etiology."

DR. PENNER: We already have "screening interventions."

DR. EPSTEIN: I guess most people would think we are just talking about this risk factor screening, whereas there is a whole technology infrastructure. It is assumed; it is now you read it. We can be more explicit or not.

DR. LINDEN: Yes, I just think that diagnostic testing is much more complicated than screening if you are just asking how many children they have had, or whatever. Also, I was just going to add that I think we are modeling the impact; we are not modeling the intervention. I think we lost that word "impact" somewhere.

DR. BRECHER: So, we have included diagnostic testing and I think that will address that.

DR. HOLMBERG: I am just concerned that we may have overlooked Dr. Klein's comment. Dr. Klein, did you want to add something to that last sentence?

DR. KLEIN: I think the way I read it now it almost looks like Heart, Lung and Blood is doing everything, as Matt Kuehnert pointed out. I think what we want to do is recommend that the Secretary support the expeditious development of a definition; the development of a surveillance system; and, in my opinion, the impact of various screening interventions on the safety and availability of blood in the U.S.

DR. EPSTEIN: I think it would be helpful to make these same points as a set of bullets so that they are stand-alone items for action and support.

DR. BRECHER: Rather than separate them by comments, make them bullets.

DR. EPSTEIN: That is right because it is not clear what is a subset of what, and if you set them off by bullets you have your categories.

DR. BRECHER: Yes, we can do that.

DR. KLEIN: The first bullet would start with the expeditious standardization.

DR. HEATON: I guess the question I have

is what do we want NHBLI to do? Do we want NHBLI to assign expert staff to this or do we want them to fund it? You know, it is not very specific the way it is written.

MS. LIPTON: Well, we were actually thinking of taking out NHLBI and just leaving it to the Secretary so "to support the expeditious development of a standardized definition." That activity is going on. That would be the logical place that it goes to support the development of effective surveillance mechanisms and support research into the etiology, diagnostic testing--I don't know. I think we don't need to reference any specific agency within HHS. The Secretary is going to know where it should fit.

DR. KLEIN: I think the third thing I would put down would be the modeling of the impact on safety and availability, and the final thing I would put down is research into all of these things, which is somewhat longer term but equally important. I also take Jay's point, which I think is an important one too. Whether that is engulfed

in the research or whether it has a separate bullet, but the idea of developing a diagnostic approach to this issue is obviously extraordinarily important.

DR. BRECHER: The next one would be modeling, modeling the impact of deferral or screening interventions.

DR. LINDEN: If we put that next aren't we getting ahead of ourselves?

MS. LIPTON: I think what we are recognizing is that if you put research in, then the expectation is this is all going to come in an orderly fashion. It is not. And, I think the message there is before you do anything, at a minimum, model the impact of what is going on. I think this is going to overtake us faster than--

DR. KLEIN: Well, we are seeing it already happening. We are seeing what is happening in the U.K. and they are going to have some data. I suspect something is going to happen very quickly in Canada. And, I think before we do anything here we might want to know what percentage of the

population would be eliminated; what the impact might be; and what we would guess, given the best available data, the reduction on TRALI might be, knowing that we are still giving platelets and red cells that have some plasma involved. Those things could be done without a basic science approach.

DR. LINDEN: Maybe say "possible." Because these are things we know about that have been proposed. I agree with that, we don't need research first. But it kind of comes out of left field.

DR. LOPES: Maybe if we pull epidemiology out of the last part about surveillance and epidemiology.

DR. KUEHNERT: I would suggest on the surveillance if you say implementation of active surveillance and epidemiology--well, I am not sure, it may be lost on some people but active surveillance means that you actively seek out, in other words, not just waiting for fatality reports to come in or other reports but actually asking have you seen the following, whatever TRALI is

defined as. That is what active surveillance is and you get, you know, much better numbers with active surveillance as opposed to passive. So, that is what I would recommend.

DR. PENNER: Do we want to add any development of the educational programs?

DR. KUEHNERT: You could include that in there.

DR. BRECHER: I think we are trying to throw in everything and I think we have plenty there.

DR. KUEHNERT: Again, it is such a comprehensive thing, the education part, it almost seems like it should be part of a separate resolution.

MS. LIPTON: What if we just say implementation of effective surveillance? I would be very reluctant to say that we are recommending an active surveillance. You know, we have an adverse event reporting mechanism. What we are really talking about is education about looking for this so it just makes me very nervous. It sounds

like we are asking for a whole separate surveillance mechanism and I just don't think we should go in that direction.

DR. BRECHER: Yes, a good passive system might be sufficient if we set it up right. Then I would take epidemiology out of the last sentence because we already talked about epidemiology above.

DR. EPSTEIN: I think leave it where it was.

DR. BRECHER: Yes, I am sorry, leave epidemiology.

DR. EPSTEIN: And strike it in the second bullet.

DR. BRECHER: Yes, you are right. All right, last commentary?

DR. SANDLER: Yes, I kind of like Dr. Penner's insistence on the word "education" and what I would like to see is the second bullet begin with "educate healthcare providers about this newly recognized entity to support..."

DR. BRECHER: How about let's keep it simpler, "effective surveillance in education?"

DR. KUEHNERT: Whom are you educating? Clinician education?

DR. HOLMBERG: You need to do education before you do surveillance.

DR. BRECHER: That is fine, clinician education and effective surveillance.

DR. PENNER: And do you want to put in any kind of a time line since we are concerned about that expeditious? Is that like two or three years from now? Harvey was saying next month the U.K. will have its stuff and the Canadians will be doing it.

DR. BRECHER: Speaking of time, it is now 6:30. So, I think we will let the Assistant Secretary or Secretary decide about what the time will be.

DR. BIANCO: You said this was the easy one, right?

DR. BRECHER: I had no idea. So, all those in favor?

[Chorus of "aye"]

All those opposed? It carries. Let's go

to the harder one. Let's at least put it up there so we can see it and we can think about it overnight, at a minimum. Mark had recommended wording for the rare disorders so at least look at it.

MR. SKINNER: A lot of this comes straight out of comments that Donna made, and my thought is it fits very well with the discussions of plasma industry economics as well as the reimbursement issue, and that has really been, you know, beyond the issue of the need to treat to be able to treat these individuals with new and safer products. I think it fits well within this area of discussion. There has been a lot of discussion about the FDA's plans to hold a workshop and so a lot of what I have put in this resolution may well be already under way, but I think it just lends the support of this committee to that effort for the need to further explore these issues. So, it is actually on the screen; you just need to open it. It is already there.

Whereas the HHS advisory committee on

blood safety and availability recognizes the lack of licensed treatments for individuals with rare bleeding disorders, for example Factor V, Factor VII, XI and XIII, present a significant health risk in the discrepant therapeutic standard from that for persons with hemophilia, and whereas the committee notes importation for personal use and off-label use are not adequate long-term solutions or acceptable alternatives, and whereas the committee concurs that there is a need to enhance the development of licensure of treatment products for these individuals, the committee recommends that the Department of Health and Human Services encourage the development of products to treat individuals with rare blood disorders, including facilitating obtaining additional licensed indications for an already licensed product, obtaining a licensed indication for products licensed in another country for use in the U.S. developing new products, the committee also recognizes the importance of industry collaboration with regulators, both pre and post market approval,

and the licensure of potential new therapies, and the committee encourages the government to invest in research and the regulatory authority to optimize treatment for rare bleeding disorders.

I think this covers most of the highlights. One, two, three are basically off the slide that Donna had presented. The next item references the importance--really what I am getting at there is the importance of Phase IV trial participation from the industry. The last, of course, is that ever-important money.

DR. BRECHER: Celso?

DR. BIANCO: I think it is very good but it is mixing both sides. There is one role that is for the Department of Health or the Secretary. There is another role that is for industry, and obviously the bridging role is the treaters, the developers and the scientists. I think that that is a little bit mixed up here. As Jay emphasized, they have to apply for a license before anything starts.

DR. BRECHER: I think we are going to have

to discuss this one. Also, sometimes it is blood disorders, sometimes it is bleeding disorders so we have to sort that out as well. Is it possible that we could start half an hour earlier tomorrow, at 8:30 instead of 9:00, and address this at that time? Jay, you have a comment?

DR. EPSTEIN: I just wanted to comment that regulators don't optimize care; we approve products and establish product standards. So, there is something a little wrong with the last sentence.

MR. HEALEY: I didn't know if you were getting ready to close the meeting. It looks like you are. I also had a recommendation. Obviously, the time is not right now but I wanted to see if I could preserve some time in the morning to introduce a recommendation as well.

DR. BRECHER: So, we are going to start tomorrow at 8:30 and we are going to continue with looking at our recommendations at 8:30. We are adjourned for the day.

[Whereupon, at 6:38 p.m., the proceedings

were adjourned, to resume on Friday, August 27, 2004 at 8:30 a.m.]

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