ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY
DEPARTMENT OF HEALTH AND HUMAN SERVICES

THIRTY-FIRST MEETING
May 10 &11, 2007
GEORGETOWN UNIVERSITY CONFERENCE HOTEL
3800 RESERVOIR ROAD, NW
WASHINGTON, DC 20057
THURSDAY, MAY 10, 2007

AGENDA:

08:30 Doors Open Open to the Public

09:00 Call to Order
Arthur W. Bracey, M.D.

09:05 Introduction of New Members Roll Call
Conflict of Interest
Jerry A. Holmberg, Ph.D.

09:10 Chairman's Comments
Arthur W. Bracey, M.D.

09:15 Introduction of the Assistant Secretary for Health
Swearing in of new members
John O. Agwunobi, M.D.

09:30 Committee Questions to Dr. Agwunobi Committee

10:00 Committee Updates:
Update on ACBSA Charter and Previous Recommendations
Jerry A. Holmberg, Ph.D.
Update on FDA's Risk Communication on Plasma Derived Factor VIII Factor IX
Mark Weinstein, Ph.D., OBRR, FDA
Update on FDA Immune Globulin, Intravenous (IGIV)
Jennifer Scharpf, M.P.H OBRR/CBER/FDA

10:45 Break

11:00 Continuation of Committee Updates
Update on the Blood Product Advisory Committee's discussion on Chagas Testing
Robert Duncan, Ph.D., DETTD, OBRR, FDA
Update on BPAC discussion on Transfusion Related Acute Lung Injury (TRALI) (15')
Leslie Holness, M.D. OBRR, DBA, CBER, FDA

Update on BPAC discussion on WNV Testing (15')
Maria Rios, Ph.D., DETTD, OBRR, FDA

11:45 Open Public Comments
Immune Deficiency Foundation
Marcia Boyle, President and CEO
Abbie Cornett, Alliance for Plasma Therapies
Arthur W. Bracey, M.D.

12:00 Committee Discussion
Arthur W. Bracey, M.D.

12:30 Lunch

01:30 Global Status of Transfusion and Transplantation Safety
Luc P. J. Noel, M.D.

02:00 US Status of Transfusion and Transplantation Safety
Arthur W. Bracey, M.D. AABB
D. Michael Strong, Ph.D., BCLD (ABB)
Americas Blood Centers
Celso Bianco, M.D.
American Red Cross Richard Benjamin, M.D., Ph.D.

03:00 Committee Discussion
Arthur W. Bracey, M.D.

03:30 Break

03:45 Status of Transfusion and Transplantation Safety continued
Arthur W. Bracey, M.D.
Joint Commission Klaus Nether, MT(ASCP)SV

04:15 Committee Discussion
Arthur W. Bracey, M.D.

06:00 Adjournment for the evening

PARTICIPANTS:

DR. JERRY HOLMBERG

CHAIR: DR. ARTHUR BRACEY

MEMBERS

ANN MARIE BENZINGER
JULIE BIRKOFER
DR. GREGG BLOCHE.
DR. WILLIAM DUFFELL, Jr.,
ANN MARIE FINLEY
DR. CHARLES HALEY
DR. PETER KOUIDES
DR. ILEANA LOPEZ-PLAZA
DR. DAVID MATYAS
JOHN MCGUIRE
DR. GLENN PIERCE
DR. GLENN RAMSEY
DR. SUSAN ROSEFF
DR. GERALD SANDLER
LINDA THOMAS
DR. DARRELL TRIULZI

NON-VOTING EX OFFICIO MEMBERS

DR. MATTHEW KUEHNERT
DR. JAY EPSTEIN
DR. HARVEY KLEIN
CDR MICHAEL LIBBY
DR. JAMES BOWMAN
DR. JIM BURDICK

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P R O C E E D I N G S

(09:00 a.m.)

DR. HOLMBERG: I just have to go through the roll call and as we come to new members of the committee, and the old members, I would like you to give a -- maybe two to three sentence description of what you bring to the committee; your position for Dr. Agwunobi so that he becomes familiar with your background and also your role on the committee here. Ms. Benzinger.

MS. BENZINGER: Hi, I am Anne Marie Benzinger, President of the Alpha One Advocacy Alliance. I am a patient with alpha-one-antitrypsin deficiency and also have -- had a single lung transplant. And am on the recipient list again at (inaudible).

DR. HOLMBERG: Thank you, Ms. Benzinger. We will go alphabetically.

MS. BIRKHOFER: Good morning, I'm Julie Birkhofer. I'm the industry representative for the Plasma Protein Therapeutics Association PPTA. I believe I am on this committee for my expertise in reimbursement, and coalition building, and advocacy. And I really appreciate all of the work that Dr. Holmberg and the attention you've

given our issues Dr. Agwunobi. Thank you.

DR. HOLMBERG: Dr. Bloche, as you come in. Would you -- Dr. Bloche, would you like to introduce yourself and give us about two sentences so that we stay on track here. If you could just go to a microphone.

DR. BLOCHE: All right. I'm Gregg Bloche, and the parking gods don't like me. I tried to use my faculty parking here at Georgetown and that is not making them happy. But it's good to be on -- I am on the law faculty at Georgetown and a visiting fellow at the The Brookings Institution and I teach and write about health policy issues.

DR. HOLMBERG: Right, Dr. Duffell, from Gambro is a vendor representative and unfortunately he is in the midst of two FDA inspections and he could not attend. So, he sends his regrets. Ms. Finley.

MS. FINLEY: Anne Marie Finley, health care consultant in the Washington D. C. area and a trustee of the Hemophilia Association of New Jersey. In previous -- my previous lives I have been a Congressional investigator for the House government (inaudible) reform committee and the author of several (inaudible) reports on blood

and hepatitis issues. I've also served at the FDA.

DR. HOLMBERG: Dr. Haley could not be with us today he's from Texas and represents Trailblazer. He's a medical director for Trailblazer, which is a contractor or for Medicare. Dr. -- I am going to mispronounce --

DR. KOUIDES: That is okay we will cut it. That is Kouides.

DR. HOLMBERG: Kouides, okay.

DR. KOUIDES: I actually have a PowerPoint slide with my name in like 15 different pronunciations. So that is a new one, I guess. I'm Peter Kouides, I'm a hematologist at Rochester, New York. I direct the medical centre at Mary M. Gooley Hemophilia Center. I am a medical director and I'm also on the National Hemophilia Foundation Medical Advisory Scientific Committee for The Hemophilia Treatment Centers.

DR. HOLMBERG: Dr. Lopez-Plaza.

DR. LOPEZ-PLAZA: My name is Ileana Lopez. I am the medical director for (inaudible) Medical Center. And I'm responsible for (inaudible) the transfusion services and the stem cell processing lab.

DR. HOLMBERG: Thank you. Mr. Matyas.

MR. MATYAS: Hi, I'm David Matyas. I'm a partner with the law firm Epstein Becker & Green, specializing in health regulatory issues and in particular medical reimbursement. I'm also a member of the board of directors for the American Health Lawyers Association. And in its public interest endeavors. I'm here kind of in a non-partisan way here for reimbursement and advise and the like.

DR. HOLMBERG: Very good, thank you. Dr. Pierce.

DR. PIERCE: My name is Glenn Pierce. I'm a past President of the National Hemophilia Foundation and on the medical and scientific advisory Council for that foundation. And I am -- currently run research at hematology research at Bayer Healthcare in Berkley.

DR. HOLMBERG: Thank you Dr. Pierce. Dr. Ramsey could not be with us today Dr. Ramsey is from Chicago at Northwestern University. Dr. Roseff.

DR. ROSEFF: Good morning, I'm Sue Roseff and I am the medical director of transfusion medicine of Virginia Commonwealth University in Richmond, Virginia. And prior to that I spent about seven years working for

the Red Cross.

DR. HOLMBERG: Thank you Dr. Roseff. Dr. Sandler.

DR. SANDLER: I'm Gerry Sandler, I'm formerly chief medical officer at the American Red Cross blood services. Presently direct transfusion services here at Georgetown University Hospital. I'm a representative here, nominated by the American Hospitals Association.

DR. HOLMBERG: Thank you Dr. Sandler. Ms. Thomas.

MS. THOMAS: Good morning. My name is Linda Thomas, I'm the Director of the Marc Thomas Sickle Cell Foundation. My late husband, after 28 years, passed away with sickle cell disease. I am honored to be here. And I'm for patient advocacy.

DR. HOLMBERG: Thank you, Ms. Thomas. Dr. Triulzi.

DR. TRIULZI: Good morning, I am Darrell Triulzi. I am Professor of Pathology and Medicine at the University of Pittsburgh and director of the division of transfusion medicine there. And I'm here as a nominee representing the AABB to the committee.

DR. HOLMBERG: Thank you. Dr. Kuehnert.

DR. KUEHNERT: Hi, I'm from the Centers for Disease Control and Prevention. I am the Assistant Director for blood safety. I'm also the head of the working group on blood organ and other tissue safety. And so we're reorganizing to form the office of blood organ and other tissue safety. So, we're very excited about that. And I'm representing the CDC as a liaison to the committee.

DR. HOLMBERG: Thank you and Dr. Epstein.

Dr. Epstein: Good morning, I'm the director of the Office of Blood Research and Review at the Food and Drug Administration. I'm your liaison from the FDA. I'm an infectious diseases physician by training but I have been a career scientist and bureaucrat since 1981. My mission here is to give bureaucrats a good name.

(Laughter)

DR. HOLMBERG: Than you Jay. Dr. Klein.

Dr. Klein: Good morning I'm Harvey Klein, I am a hematologist by training. I direct the Department of Transfusion Medicine at the clinical centre at the National Institutes of Health. I have been involved in

blood transfusion issues for almost 35 years.

DR. HOLMBERG: Thank you. Commander Libby.

CDR. LIBBY: I'm Mike Libby I am the Director of the Armed Services Blood Program. I'm a Specialist in blood banking. I'm here as the active duty liaison.

DR. HOLMBERG: Thank you Mike. Dr. Bowman.

DR. BOWMAN: Hi, Jim Bowman, I'm a physician with CMS.

DR. HOLMBERG: You can give a little bit more of your background.

DR. BOWMAN: I am a junior bureaucrat. I've had prior experience as transplant surgeon and with Blue Cross and other commercial healthcare payers.

DR. HOLMBERG: And I know that Dr. St. Martin was not able to attend but Dr. Solomon is she here? I don't see her. Okay, also representing FDA. And we also have Dr. Burdick from HRSA.

DR. BURDICK: Hi, Jim Burdick, I have a background as a transplant surgeon. Also I direct the division of transplantation in a HRSA, which has oversight of the National Systems in organ transplantation and blood stem cell transplantation and I'm here representing HRSA.

DR. HOLMBERG: Okay, thank you.

DR. BRACEY: Good morning, I am Art Bracey the medical director of transfusion services at St Luke's Hospital in Houston. Social Professor of pathology at the University of Texas. And in my lifetime in medical practice I guess I have overseen transfusions of about a million components to various patients. So, I'm very interested in ensuring that what we do is safe for those patients. Thank you.

Well, what I would like to do then is to start off with just a brief comment from the Chair. And first, welcome to the new members and the warmest greetings to those returning committee members. The time that you commit to this effort is deeply appreciated by me. And in the long run it's clear to me that your efforts will promote the public health. As a point for clarification I thought I would briefly review the scope of the activity of this committee for the new committee members.

The history of the committee dates back to a recommendation from the Institute of Medicine in its report to the Secretary on the decision-making process in the early phase of the HIV epidemic. One recommendation

that stemmed from that report was to establish a position in the Department with the lead responsibility for promoting the safety of the blood supply. And it's been deemed by some as the Blood Czar. That individual is sitting next to me, Dr. Agwunobi, and we're certainly pleased to have him here today and he's going to swear in members of the committee and also field the questions.

But he's got a tremendous job in terms of coordinating all the agencies within the committee -- within the Department to make sure that we have the safest blood supply. Now, our task, as members of this committee, is to advise the Assistant Secretary on a broad range of policy matters, including parameters related to public health, associated with blood use. But again our point is not only from a perspective of scientific considerations but broad policy concerns with a particular focus on the ethics, legal issues, and economic considerations.

It was interesting to look at the meetings of past minutes and I looked at the minutes from the very first meeting, some 10 years ago, and then Assistant Secretary, in the minutes, stated the following. "The job

of this particular committee is to assess consumer and societal factors as they compare the risks and benefits of various actions." We are unique in terms of our configuration, having a diverse composition of various members with a background of those -- including those with a need of blood therapies, those that have experts in -- the experts in medicine, people with experts in the legal issues and also representatives of industry.

So, again our task is to consider the broad range of what we do, and what we will be spending a great amount of time on today, will be looking at issues, and tomorrow, issues related new charges that we have in our charter related to transplantation. So, without further ado, I would like to introduce the Assistant Secretary Dr. Agwunobi.

Dr. Agwunobi, was confirmed as the Assistant Secretary in December of 2005. Dr. Agwunobi has a long history of involvement with the health issues. He comes to us from the State of Florida, where he had a tremendous impact in terms of the public health there. And he's done much to forward our efforts for this committee. And so without further ado, Dr. Agwunobi, I will open the Chair

to you.

DR. AGWUNOBI: Thank you Mr. Chairman. I should start by thanking you Dr. Bracey for your leadership, your willingness to serve and to sacrifice, in the way that you do in order to keep this moving forward, is deeply appreciated.

To old members and new, I thank all of you for your commitment to this issue. It's quite clear that many of you live and breath these issues. You all do. And that you recognize that the outcome of your work isn't a part of that bureaucracy that Jay holds so fondly. You are above that. Your work is, I hope, a part of the process that truly makes a difference over time. My name is John Agwunobi. I'm a pediatrician by background, although I have spent a large chunk of my career working in public health policy at the state and federal level now. I'm struck over the years by a commonality that exists in every level of bureaucracy and public health policy. And that is that we tend to be reactive more than we are proactive, it is the nature of the beast.

Indeed the Chair in his comments mentions that this committee was formed in response to something. In

response to the HIV AIDS threat. All too often, in fact usually, policy and major interventions in pursuit of quality follow some event, some tragic event typically. As I look out into the future I envision, and hope, and pray for a day where we are more proactive in policy than we are reactive. We've learned so much in the areas of blood safety, particularly over the years, that risk benefit equation that balance that the Chair alluded to that was mentioned by my predecessor way at the beginning of this committee's life. It's a very real premise that today is used in making decisions in your world and in the world of blood and blood safety, every single day. And the equation changes, with time, as we learn. I'm very proud of the scientists in HHS, CDC, NIH, FDA and other places HRSA. I'm very proud of the work that they do every day to try to get ahead of the of the question to be proactive, to look out onto the horizon.

I would urge you as you do your work going forward to not just focus on the issues of the day which are critically important. What happened yesterday and what are we going to do about it. But to spend a lot of time focusing on, and so what did we learn from that, and

how can we get in front of the next event? How can be prevent the next event? How can we build a system that is constantly a head of the issues? I'm prompted by the introduction from my colleagues from CDC to urge you to start thinking about the commonalities that exists across blood, organ, blood component, tissue at cellular therapy. The safety issues that link all of those things are quite tangible.

As you look at science and scientific therapeutics, it's quite clear that we are marching, we are accelerating, towards the use of ever sophisticated biologics, cellular therapies, genomics, proteomics. And it's quite clear to me that the issues of safety that we deal with on a day-to-day basis today, regarding blood, expand out into the future, across so many more aspects of therapeutics related to all of these things I have just described. It's a funnel, and we are somewhere in the middle, and it gets bigger and bigger overtime. And yet the solutions, I will wager, are very similar across all of those fields. Whether it’s whole-organ transplantation or the use of biologically derived proteins in therapy, and everything in between, including blood.

The work that you do will have application across all of those fields. I would urge you Mr. Chairman and members of the committee to consider building upon the expertise that you possess in blood safety and in protecting individuals from infectious disease and other problems related to blood and blood products use. To see whether or not there aren't commonalities that can be applied across all of these fields. And to draw in experts from those other areas into your discussions, to try and figure out if we can invent wheels once rather than multiple times.

In this proposed vision Mr. Chair I would hope that at some point we would consider whether or not there isn't a way that we could predict where cellular therapeutics might encounter trouble in the future and try to assist them in preventing that now; by helping them build systems, helping them build a plan, helping them build a strategy. The same thing with proteomics and genomics and all of these other advances in therapeutics. Having said that today we have real work, I'm told. One of the things I hope to do today is to swear in the new members. And I would urge you to -- as we swear you in,

it will seem a little bit staged, I always take the duty of swearing in new members to the committees very seriously.

It might even look like there is a little more pomp and circumstance associated with it than necessary. But I would urge you all to recognize that it's really not to me that you advise, when you do your work. I'm the vehicle through which your work is transmitted up through the Secretary to the President, more importantly to the people of our nation. And I would wager, without being too rhetorical, the entire world. I mean there aren't -- there isn't a single group of people anywhere else in the world that can claim to have more expertise or more right to deliberate and to advise on this subject than those of you sitting around this table. That is just the fact.

The diversity, the background, the commitment, the passion that you bring to this issue can't be outdone anywhere else. And so, I would urge you to recognize that it's a very solemn responsibility. That your work is not just about bureaucracy. It's about saving lives. Both in advancing the use of blood, and blood components, and cellular technology, and organ transplant, whatever you

discuss but in doing so safely. Availability is important, critically important, that's another part of that saving lives equation. And clearly, a big part of your work as well.

I recommended to the Secretary that he expand the scope of the committee and that's embedded in the charter. I sense that as you talk about ethical, and legal issues, and access, and the availability issues, and safety, of course that you will recognize that although the charter guides you we could never, in the charter, identify all of the key issues that you need to touch on. Science is moving so quickly, so fast. And I would urge you to be guided, in addition to the charter, to be guided by science and evidence. And to have that be the foundation upon which you do your work. I recognize all of you know that's critically important.

I'm actually going to end with this large -- it went a little longer than I had hoped. But I will end by just reminding the audience that the reason we do these things this way, the reason we have these advisory bodies come together and deliberate publicly, is because we set these bodies up to deliberate on things that we think are

important to the public. Are important to the average person on the street. And we do it this way, with all of the laws of the FACA and the like, so that you can see what goes in to the making of the sausage. And so, that you can participate in the making of the sausage. I hate that term, it doesn't sound right does it -- sausage.

(Laughter)

DR. AGWUNOBI: I'm hungry. I'm calling on the audience and others to join in the debate. That microphone isn't set up there as a prop. It's set up there to urge you to voice what you think. To let the panel have a sense of what people who aren't formally on the panel think about the issues that they are discussing. Mr. Chair, thank you.

DR. BRACEY: We can have the new members come to the middle area and we will do the swearing in.

DR. AGWUNOBI: Raise your right hands. I would like you all to follow after me -- repeat after me. I do solemnly swear that I will support and defend the constitution of the United States against all enemies; foreign and domestic. That I will bear true faith and allegiance to the same. That I take this obligation

freely, without any mental reservation, or purpose of evasion. And that I will well and faithfully discharge the duties of the office on which I am about to enter. So, help me God. Congratulations you are all members of the committee.

SPEAKERS: Thank you.

(Applause)

DR. BRACEY: If it's okay with the Assistant Secretary, we are on schedule, and we do have a question and answer session for the Secretary for the members of the committee. So, I open up the flow to the committee members for question to the Secretary. Ms. Birkhofer.

Ms. Birkhofer: I would just like to thank you Dr. Agwunobi and thank Dr. Holmberg and the Chairman for all of the attention you have given.

In your remarks you mentioned the importance of access as a safety issue. Of late there has been an access issue surrounding a plasma derived therapy intravenous immunoglobulin. And I would like to acknowledge and commend my colleague Dr. Bowman from the Centre for Medicare and Medicaid Services for the recent decision to provide brand specific reimbursement for IVIG.

And I know that there are a number of individuals in the community, that I would not presume to speak for, that are seeking a meeting at the highest level within the agency to talk about some next steps that could be taken with regard to assuring patient access to life-saving therapy in the appropriate site of service. So, I would hope that your attention to this would continue. And I thank you sir.

DR. AGWUNOBI: Thank you so much I will just state that I -- actually I'm not sure that there is any other blood derived product or blood itself that has -- in which I have met more often. I think I have met on that subject within the department being briefed at different levels, with colleagues across agencies, with individuals from the outside, on that particular subject more than on any other area that would be under your purview.

We recognize that it is of significant concern to many. And I can assure you that it's taken very seriously. I look forward to that higher level meeting. I have no doubt I will be invited.

(laughter)

SPEAKER: I've got a question and that relates

to in impart our new considerations in terms of transplantation. Transfusion is a -- in many a transplant of sorts but a difference is that it is replaceable. Whereas, for many of the organs or stem cell transplants they are, in essence, irreplaceable. So, I'm interested in your view in terms of comparing the two interactions, one being an important element for life-saving but seemingly fairly replaceable and another more specific.

DR. AGWUNOBI: I had a long conversation with colleagues about the -- one, about availability and about access. The fact that although there are clear issues of commonality, clear opportunities to build the wheel once in the area of the safety, that in the areas of accessibility and availability --access and availability there are, clearly because of the different -- the history, the legacy, the way things have been built over time. There are clearly a lot of differences in the pathways, and in the processes, and the issues, and the concerns, and obviously in the solutions.

I would urge the committee, Mr. Chair to recognize that as we throw this on your table for thought and deliberation, we don't have a proposed end point. I

really -- and I also had this conversation with colleagues across the agencies. As I put this on the table for you to chew on and consider, I don't presume that it will result in a defined outcome.

I don't presume that it will result in a single strategic plan for the safety across all biologics and all organs, and transfusions, and transplants. That would be going well beyond my purview, my area of expertise. I just -- I sense that there is a need, every once in a while, for us to, as a nation, to have conversation. To recognize that things seem to pop up every once in a while.

And my question would be are there patterns? Are there common solutions? Where do they lie? What is the best way to get there from here? This is the beginning of a conversation. It could well be, and I put this on the table, that a conversation ensues and after a while our nation determines that it is better to continue doing things the way we do them now, and that change is not appropriate. I sense, at least on the science side, and the ethics, and the legal, and the realities of the marketplace, for want of a better word, may preclude

change.

But I sense on the science side that there is a consensus that we need to have the discussion. So in answer to your question sir, I'm going to throw it back at you. After you have your discussion and after you think things through and engage the public in this dialog about whether or not there shouldn't be a common approach to certain parts of these things; transplants, transfusion, and everything in between.

Then I will ask you the questions sir, where are the differences, and how we should approach them and recognize them.

DR. BRACEY: Thank you other questions or comments from the committee. Dr. Sandler.

DR. SANDLER: Thank you, Dr. Agwunobi. As you suggested sometimes you can't get ahead of the unanticipated emergency; 9/11, HIV required quick responses in a coordinated way. I wouldn't know, as a physician in a hospital, where to look for the urgent coordinated direction that would be coming from, if I may use the term Blood Czar, I didn't invent it --

DR. AGWUNOBI: That is a wrong term.

DR. SANDLER: Do we look to the FDA and CDC to continue to issue their directives and take that as the national leadership's position. Or is there a higher authority a web page or something that we would look to for the top coordinated leadership.

DR. AGWUNOBI: Thank you Dr. Sandler. Let me just state before I provide my answer that I would urge you to follow any direction that you receive from CDC and FDA. They truly are some of the most wonderful people in terms of their commitment, their professionalism and their scientific background.

They don't issue directives without an awful lot of work. You'd be surprised at how much time is spent churning internally before relatively a small directive spits out the backend here, or the front-end rather, from FDA and CDC.

(Laughter)

SPEAKER: Sometimes it is the back end.

SPEAKER: Strike that.

DR. AGWUNOBI: Backend, front-end. Having said that -- Jay just indicated that it doesn't past the smell test. I am not quite sure what he meant by that.

(Laughter)

DR. AGWUNOBI: Emergencies, that was the subject of your question. The Congress, in its wisdom, and indeed, supported and signed by the President, just provided a new law called the Pandemic and All Hazards Preparedness Act. It was signed into law by the President recently, January.

In that Act it is quite clear that the Department of Health and Human Services know the administration of our federal government, during times of emergency, on issues are that relate to health and public health, has identified a single individual responsible for all aspects of the response. It is the person -- whoever fills this seat and is sworn in by the Senate -- confirmed by the Senate as the Assistant Secretary for Preparedness and Response, fondly referred to as the ASPR in our circles.

Currently that individual is Dr. Rear Admiral Craig Vanderwagen. And Craig is singularly responsible for assuring readiness and response. So, preparedness beforehand and the actual response itself and the learning from each event. Now, as it relates to this community the

ASPR has charged Jerry -- wherever he is -- there he is down there -- Jerry, and CDC, and FDA, and NIH, and all of the branches of our administration to help develop a plan. To help coordinate a plan beforehand.

But on that day, when it hits the fan, he'll be the one that is directing, internally, within the HHS and within the federal government, he'll be the one that is directing the health and public health response to all kinds of emergencies pandemics and all hazards. Now, what that means is that he might direct FDA to issue some regulation to all of you. FDA will get its scientists together work on what the regulation should look like and it will issue.

Or it could be that asks CDC to consider a series of events, to make a recommendation, and to issue that recommendation or that regulation -- now they don't typically issue regulations although they do have some regulatory authority related to quarantining and the like. But they will issue their recommendation or their guideline to the public. So, my point is regardless of where it comes from to you, whether it comes from the Surgeon General, the Centers for Disease Control, from FDA

from or from the Secretary himself, it will have been coordinated across the department internally by the Assistant Secretary for Preparedness and Response. I will just add one note, there is a lot of work going on right now, within the department, across all of these agencies, related to finding ways to assure that we have adequate and safe blood supplies in an emergency.

There are multiple different tracks being pursued including the notion of a national blood reserve. It's in early discussion and I would urge your input on that. I recognize that there will be different points of views. There are pros and cons to every strategy. And before all is said and done, I think, we will end up with a multilayered strategy. One that has multiple pieces to it. There are clearly things going on -- I hate to use the phrase but I will again -- in the marketplace.

The community itself is generating solutions and those solutions, if they are robust and if we can rely on them, I have no doubt they will be built into the federal plan. They will be part of that national plan. There is also talk, in certain regions, small communities are working across -- locally across partner providers, and

blood banks and others to develop other solutions related to donors; the availability of donors in an emergency and how that might be coordinated.

So, there are different strategies that are being pursued. None of them are simple. None of them are the silver bullet that solves our problem once and for all. And I have no doubt we will end up with a multilayered strategy when -- and the truth of the matter is the ASPR on almost all aspects of an emergency, whether it's the use of antiviral, the use of vaccines, the availability of epidemiology or surveillance, the use of antibiotics or blood products. The ASPR almost always is considering a menu of options when trying to coordinate what the best position, in terms of health and public health response, should be.

I will just end by saying the ASPR doesn't make decisions in a vacuum. He, in fact, very rarely is the ASPR making a decision on his or her own. Usually, what's happening is a collaborative group of people are sitting around a table coming up with a consensus position and the ASPR's job is to implement that consensus decision. It's kind of the way it works.

DR. BRACEY: Other questions for the Assistant Secretary. If not, we thank you for attending this morning.

(Applause)

DR. BRACEY: Okay, then moving on we have several committee updates as I mentioned from the recent BPAC meeting. And we also in our next session have an update from Dr. Holmberg on our charter and our previous recommendations. Dr. Holmberg.

DR. HOLMBERG: I don't know if this is on. Okay. Well, thank you. About a year ago we went through and did a very comprehensive review of the activities of the Advisory Committee for Blood Safety and Availability. We at that time recognized some of the things that have been accomplished and some of the things that have not been accomplished.

One of the problems that we have -- you have as a Committee is that many times you have a recommendation that comes forward and goes to the assistant secretary and to the secretary, and you may back at the next meeting and say, well, what’s been done about that. And you have to understand that we are working behind the scenes. Many

things that were even recommended maybe three or four years ago, such as the readiness issues, are continually being worked.

When Dr. Agwunobi mentioned, as far as working with ASPR, there are several people, government officials around the table here that we are actively involved with the ASPR working Committees. And I made a comment the other day that I do have another job other than working for ASPR. So I have two bosses; I have the ASH, and then I also have to provide input to ASPR for readiness and preparedness.

And as I said, there are some government people around the room here and even in the audience who are actively involved with that participation. Saying that, what I'm trying to impress is that even though you may not see an immediate fix such as with IGIV, we are working behind the scenes and we are trying to make a difference. Some of the recommendations are not acted upon. Some of the recommendations, the assistant secretary may take a different view.

And so we take your recommendations and we move those forward to see what the administration would like to

do with those and how do we move forward. I must say though that to reiterate what the assistant secretary said, Dr. Agwunobi said, that anything that is said within this advisory Committee is very valuable, and that the transcripts are preserved. Our websites does have all the transcripts and all the slide presentations so that you can go back and review the history to see what was said.

And as you will hear later on, you will also see how sometimes even though we do not have direct action on a recommendation, it is picked up by others. The recommendation that came out last year, last August, really hovered around the biovigilance and to try to simplify the recommendation, which was a little bit lengthy and the fact that there were some “whereases” and also a definition of biovigilance.

What the Committee charged the department with was that we should put together a PHS task group to look at the GAP analysis of what we’re doing for surveillance; whether this should be mandatory versus non-mandatory, voluntary versus non-voluntary, the scope of test of reporting on database centralization versus sharing, database governance, ownership and accessibility including

sharing that data with other countries, format and standard for data, potential for coordination with non-U.S. safety systems such as other countries, funding design and feasibility of suitable pilot programs.

As I said, this is just a very succinct version of the recommendation. You can read the entire version on the website. But just to tell you the activity that immediately took place on that recommendation was that we did put together a PHS working group last September and Dr. Kuehnert and also Dr. Goldsmith from FDA, Dr. Kuehnert from CEC and Dr. Goldsmith from FDA, are co-chairs of that Committee.

We are continuing to have discussions AABB Task Force and I'm sure that Dr. Strong will mention a little bit more about that maybe in his presentation. Also just to go back and -- January 2006, because I think the last time that I updated the group was January of 2006, that was before the recommendation came out about pandemic influenza, and one of the things that was really emphasized was that blood and plasma needed to be recognized as critical elements for the healthcare infrastructure.

This is well established as Dr. Agwunobi mentioned. And I've had meetings with both Dr. Agwunobi and Dr. Vanderwagen in which it has been very clear, and the policy is that blood is a critical element of the healthcare infrastructure, and it has the recognition within the department. Also for funding for research studies being considered in the pandemic was -- is an ongoing process.

Also with the global surveillance, a lot of that is being done through CDC. I -- very quickly, I think, that you can read these and I do want -- in the interest of time I want to move forward, but you can see that we also have agency activities participating with the AABB Task Force. A draft document has come out from the AABB Task Force.

And the reason why we use the AABB Task Force for many of our activities, I shouldn't say activities, but trying to move forward with some of the recommendations, is that many of the need a government, a public/private partnership. And we are governed by different rules. For instance, you, on the Committee are here because of the FACA rule. That is the Federal

Advisory Committee Act. And to be honest with you, this FACA meeting has to be chartered.

So if we call a group of people together, then that represents an advisory group. And so according to the law, we cannot pull together an advisory group just because we want to pull together an advisory group. It has to be chartered and it has to have a specific scope of activity saying that we do work with AABB Task Force as a central location. And having liaison members from the department interact with the task force so that we -- the task force, the AABB Task Force, has a lot of the interaction and the liaison with the government.

The communication -- the Blood Safety and Availability is working with the communication group, coordination of local and state messaging through the regional health administrators and I have to say that we've had some, I didn't list the specific activities here, but we have some letters to each one of the State health officers saying -- telling them where blood and the priority for blood should be and that the recognition that blood is a critical element of the healthcare infrastructure.

This has gone to each one of the States. One by one, we have 10 regions and I've just made my first presentation to Region 4, which is the Georgia, Florida, North Carolina, South Carolina, Tennessee, Alabama and Kentucky area. And I have met with all the State health officials from that region to express the concern for raising blood, tissues, transplantation to a higher level in their planning and also some of the things that they need to be considering when they're doing their planning cycles. So hopefully that will make a difference.

I'll skip over that because I really just want to highlight. We're going to be hearing some reports, and already you've heard a few activities that have come out from the IGIV issue. The OIG report has been released in April of 2007. The ASPE, that's the Assistant Secretary for Planning and Evaluation Report, came out in May of 2007, and I have provided you the copy of the executive summary of the ASPE Report. It's a one-page summary where ASPE is making comments concerning their contractor's report.

In addition, through the last couple of weeks the CMS has assigned separate codes for the liquid

products, and there are some other areas that we still need to be working on. I still -- in fact, yesterday I had a senator's office call me to try to find access for a particular patient in Alabama. So I continue to get calls on the IGIV issue, but that's an ongoing, and we still have areas that we need to work on there.

I don't want to spend a whole lot of more time on the rest. A lot of it is pretty much a summary of going back to 2001. And so I will just leave it there. For the new Committee members I wanted to give you an overview of what we've done in the last couple of years, and in your handout you can see the activities that we've done since at least 2001. There has been activities even before that, but for purposes of trying to tell you of the most recent, I presented only that time period in the presentation.

Just to also comment because I know that we have some people here in the room that have been long time members of this Committee and also were around when the Committee was founded, and definitely HIV and HCV was an issue, we continue to work through those regulations, both through FDA and through CMS for HCV look back, and that is

an ongoing process. Hopefully one of these days that will be a codified regulation.

At this point that's all I want to say. Are there are any particular questions? If you have any specific questions, especially the new members, on what we've done in the past, don't hesitate to talk to me, and we'll get you the answers to that. Any questions?

DR. BRACEY: Okay, and if there are no questions, we'll move ahead then. And the next presentation will be an update on the FDA's risk communication for plasma-derived Factor VIII and Factor IX and that will be presented by Dr. Weinstein. He's the associate deputy director of the Office of Blood Research and Review and is currently working in areas of standards development, Education, Training and Risk Communication. Dr. Weinstein.

MR. WEINSTEIN: Thank you. Today I'd like to again repeat -- give you an update on FDA's variant CJD risk communication efforts with regard to U.S. plasma-derived Factor VIII and UK plasma-derived Factor XI. I will first give you brief background with regard to this issue.

I'll then discuss how we developed our risk communication materials. I'll give you a review of some of the key points and questions and answer, documents that we prepared, and then I'll tell you about out risk communication strategy. And finally I'll discuss our progress in the risk communication with regard to the Factor XI UK investigational product.

By way of background we learned in 2003 that there was a very high probability that a variant CJD was transmitted by a red cell transfusion. We now know that -- we have evidence of approximately four cases of such transfusion, transmission all occurring in the UK.

This raised our concerns that variant CJD might be transmitted through plasma-derived products including clotting factors and we were very concerned that Factor VIII in particular as used by large numbers of patients in the U.S. might potentially have this as a hazard.

So we do not know what the degree, the magnitude, of this risk might be, and therefore in the Fall of 2004 we began to develop a risk assessment of the potential of variant CJD to learn about the risk of variant CJD transmission from plasma-derived Factor VIII

manufactured from plasma collected in the United States.

Now, we presented our risk assessment concept to the TSE Advisory Committee in February of 2005 and we received comments about this concept, and -- at that meeting as well as the meeting in October of 2005. We prepared a risk assessment and we had it reviewed by three external experts in the Summer of 2006 and the risk assessment itself was presented to the TSE Advisory Committee in December of 2006.

And concurrently, we have prepared a number of risk communication documents. As far as how did we develop these documents, this involved the input from many different sources. These documents -- we received information from our sister agencies including the CDC and the NIH. Of particular note we involved special government employees including patient advocates to help us prepare these risk communication messages.

We, of course, also received inputs from the TSE Advisory Committee members and the communication experts. We asked the GSEs a number of different questions that would help us in the development of these communication materials. We asked them whether or not they felt that

the risk communication materials adequately conveyed the findings of the risk assessment, especially the uncertainties that were involved in developing the risk assessment.

We were concerned whether or not the documents were easily understood. We wanted their comments about the clarity of the documents and we also wanted their input with regard to how information should be transmitted to patients, family members and the public in general. We felt that this input by these external groups, particularly the SGEs, was extremely valuable in clarifying and improving the public health messages.

With regard to the actual message points here, we developed three key points here and I'm going to highlight these. First is the reason why we developed these documents in the first place. In recent years questions have been raised concerning the risk of variant CJD to hemophilia A and von Willebrand disease patients who receive U.S. licensed plasma-derived Factor VIII products.

The second key point is our assessment of this -- - of the risk assessment. Based on risk assessment, the

U.S. Public Health Service including FDA, CDC and NIH believes at the risk of variant CJD to hemophilia A and von Willebrand disease patients who receive U.S. licensed plasma-derived products as most likely to be extremely small although we do not know the risk or certainty.

Variant CJD risk from other plasma-derived products including Factor XI or Factor IX is likely to be as small or smaller. This last statement, of course, is particularly important to patients with hemophilia B, who are likely to be very interested in this issue, as well as the hemophilia A patients.

We then -- the third key point is about -- we are -- interested parties can get more information. Contacting a specialist in hemophilia or von Willebrand disease at a hemophilia treatment center is a good way to learn about new information as it becomes available. We've also cited a number of other information sources in our documents and we'll get to those a bit later.

Now, in addition to the key points, we have attached to the same document, additional information. This includes how or why FDA has conducted a risk assessment. We also include the FDA actions reduce the

potential of variant CJD risk from blood components and plasma derivatives. We talk about the uncertainties that went into the risk assessment model. We suggest to the patients where they might, and other -- where they might get more information. And we have a brief review of the current status of variant CJD risk.

In a separate document we have prepared a number of questions and answers; a very large and extensive list of questions and answers. I'm not going to read all of these, but this gives you a sense of the topics that were covered here. We felt that these are questions that might be of particular concern to patients. Again we receive inputs from healthcare givers and SGEs about these questions and they help to formulate them and to provide suitable answers.

The communications strategy. How are we going to get this information to interested parties? We put this information on an FDA webpage. I'll refer to that in the next slide. We also contacted the Hemophilia Treatment Centers. We actually had a teleconference that included 140 of the Hemophilia Treatment Centers around the country. This was a teleconference that was hosted by

the CDC. We notified them about this risk communication information. We received their input and they have agreed to help disseminate this risk communication material.

At the same teleconference we had patient advocacy organizations represented, and they have also helped to publicize this material in their newsletters and through other media. We have done some outreach to trade and physician organizations, and the -- again, the key points and questions and answers help direct the interested parties to further sources of information.

This is the address of our webpage and it contains the key point document summary information of the actually risk assessment and it also includes links to where interested parties can find guidance documents related to the donor deferral of variant CJD and CJD FDA documents. We have links to other sources of information including the CDC webpage and we have a listing of patient organizations.

So next, some updates on the Factor XI risk communication situation. In this case we recognized that there is a possible health risk to approximately 50 individuals, we actually think the number is probably

lower, who, between 1989 and 2000 received an investigational non-U.S. licensed product, plasma-derived Factor XI that was made from UK donor plasma. And this product was used to treat patients with deficiency of Factor XI.

This -- again, this product was made from plasma from donors in the UK where the actual variant CJD disease has occurred. It's important to note that the product was not made from the plasma of anyone known to have developed a disease and no one who has received this product is known to have become infected by it.

However, even though the product was not made from anyone known to have developed it, it's still possible that a person could be exposed to the disease, who takes this product, if someone who had felt well was carrying the infection at the time that blood was donated.

So FDA used the computer model again to conduct a risk assessment. This model was presented in preliminary form to the Advisory Committee, the TSE Advisory Committee. In February of 2005 we received update information from them, advice from them in October of 2005. And one of their advisory comments here was to

consult again with SGE's including patient advocates to obtain input on the risk assessment and communication materials.

So we have posted this preliminary risk assessment in 2005. We have now revised it and have finalized communication materials with input from the patient advocates and communication experts. We are now contacting each of the IND holders by telephone to answer any questions they might have, to share information with them, and we suggest that they contact patients on an individual basis. We will update our webpage once this one-to-one communication process has been completed, and we will alert the Hemophilia Treatment Centers and patient advocacy organizations about the new webpage posting.

So, in summary we have prepared risk communication materials regarding variant CJD and U.S. plasma-derived Factor VIII as well as investigational UK plasma-derived Factor XI, with input from the TSE Advisory Committee members, PHS, communication experts, and in particular highlight the contribution of the SGEs. These materials as well as links to other sources of information are available on an FDA webpage and we will continue to

update risk communication material as new information becomes available.

DR. BRACEY: Thank you. Questions on this presentation? Yes, sir?

DR. WEINSTEIN: Yes?

DR. KOUIDES: Dr. Weinstein, is there any plans to carry out a risk assessment for FFP for patients with rare hemophilias who rely on that -- for example, Factor XI deficiency?

DR. WEINSTEIN: We have considered that. I should say that we don't have plans immediately at hand to do that, but that is a concern and we are discussing it within the agency.

DR. KOUIDES: I have a question, and may be this really might be better addressed by some of the members of the Committee, but at first I applaud you on your effort to seek input in terms of drafting these information pieces because it's very technically challenging.

But what is -- what exist right now in the field for the patient who reads this material? What I'm specifically getting at is, is there a network for counseling that's available beyond the reading of the

materials?

MR. WEINSTEIN: Members of the Committee, our notion is that the best source for information and for discussion would be through hemophilia specialist or von Willebrand specialist through the hemophilia treatments.

DR. KOUIDES: And I guess what I'm asking is, perhaps you could give me a view about there in the field, do the treating hemophilia docs feel comfortable with their ability to engage and discuss on this matter with their patients?

DR. BRACEY: I think there's been excellent lines of communication with Dr. Weinstein and the hemophilia treatment network and also through the CDC that oversees the national network. So, there have been conference calls to update treators about that. But your point is valid because not all patients with these inherited bleeding disorders are necessarily enrolled or always in contact with the Hemophilia Treatment Center.

There is nationwide, some of these patients are seen by a practitioner who may be licensed in hematology, but is primarily practicing oncology, he may not be as aware of these issues. So I have been privy to those

discussions about further outreach beyond the HDC, but for as much as I'd like to think that all these patients are

DR. KOUIDES: Right.

DR. BRACEY: So, that is a good question. I'm not sure what the solution is.

DR. WEINSTEIN: I also should say that, you know, we had discussions with treators and with the NHF Medical Advisory Committee and so forth ask what has been the response, what has been the degree of concern of patients; have they received many calls. And apparently there have not been -- has not been a great outcry or degree of concern. There have not been a sort of a panic reaction, which is a good thing, I believe. But now, this is the situation.

DR. BRACEY: Next, Pierce?

DR. PIERCE: Mark, I think the risk assessment communication materials have been very good. What I'd like to come back to, are the FDA actions that you referred to in the slides that could prevent transmission given the long incubation time for variant CJD? What is the FDA recommending regarding that?

DR. WEINSTEIN: The present time we have, of

course, our guidance documents that are deferring patients who have lived in Europe and UK for certain period of time. Mostly those are preventive measures that deal primarily with trying to prevent donors from contributing to the pool who have potentially being exposed to the disease. That's a major source of our efforts. Yes.

DR. PIERCE: Is the FDA advocating any sort of other risk reduction methods such as elimination of the agent or the potential agents from plasma?

DR. WEINSTEIN: Well, certainly we encourage -- right, of course, the -- we're encouraging industry to further develop methods of -- explore methods of removal of the agent from plasma derivatives. And, of course, that was a large part of our recent BPAC meetings there about trying to assemble what information is known about removal of the agent looking at various potential assays for the variant CJD, trying to encourage the development of system that might be able to detect the infectious agent. You know, those are all areas that very important to remove the agent.

DR. PIERCE: And what --

DR. BRACEY: Oh, sorry.

DR. PIERCE: Can I continue, please?

DR. BRACEY: Go ahead, yes.

DR. PIERCE: And what's your assessment of the progress that's been made in that area?

DR. WEINSTEIN: It's a very slow process. This whole -- the whole issue of developing good assays and of getting material, for example, to be used as standards is extremely difficult. These are very time-consuming assays for one thing, just the infectious assay material, they're very intensive, as far as the use of animals, and they're very expensive, the progress is slow. But, there is progress and there is interest in pursuing this by industry.

DR. KOUIDES: Just a comment and a question really, and that is that we were charged with Dr. Agwunobi to think to the future. And one of the question I've always had is, are the recombinant products immune from this consideration, and if so then what's the limitation in terms of the broadest application of the recombinant product?

DR. WEINSTEIN: Well, the recombinant products or at least the Factor VIII products are used by about 80

percent or so of the hemophilia community. However, there is a -- at the present time an obligate necessity to use plasma-derived products for patients with von Willebrand disease. We don't have a recombinant von Willebrand Factor; it's a complex of Factor VIII and von Willebrand Factor.

There is also other issues with regard to the utility of plasma-derived Factor VIII products that -- there's a concern about inhibitor formation, there's some discussion here about whether plasma-derived Factor VIII might be better for establishing a new tolerance. There's a whole -- there's a medical --

SPEAKER: So there's a medical issue.

DR. WEINSTEIN: Right. It's not so very clear-cut.

DR. BRACEY: Okay. Dr. Epstein, did you have a question?

DR. EPSTEIN: Well, I just wanted to add a comment regarding Dr. Kouides' question about FFP. I certainly agree with the statement that Dr. Weinstein made, which is that we have considered a formal risk assessment, not just for FFP, but for transfusable

components in general. But just to make a general observation, which is that we focused first on the product at highest risk and the recent to focus on plasma derivatives is because of pooling.

That's if you had one contaminating donation, you've contaminated a pool and that thing goes to many, many patients, whereas in the setting of component transfusion, it would be the risk of encountering a single donor that harbor the infection. So it's -- order of magnitude is less on the face of it.

The second point I would make is a follow-up to Dr. Pierce, which is that we have discussed at our FDA Advisory Committee meeting the criteria that should be applied to the validation of filters to remove prions. Filters could play a role in the fractionation scheme, but there is the question whether it could be applied to removing infectivity from transfusable components. So there has been progress in that direction though I agree with Dr. Weinstein that progress in general in strategies to remove TSE infectivity has been fairly slow, but that's because of scientific limitations.

DR. BRACEY: Ms. Finley, you had a question?

MS. FINLEY: Yes, actually I had two questions. I want to follow up to Dr. Epstein's comment. Do you -- does FDA have a position on leukocyte depletion and its relationship to removing infectivity of TSEs?

DR. WEINSTEIN: Well, this question was discussed again with FDA's Scientific Advisory Committee and the conclusion of the Committee with which we concur is that leukocyte removal in and of itself is insufficient to remove TSE infectivity. And the reason is that about 60 percent of the infectivity is in the plasma anyway.

And so we've not advocated leukocyte reduction as a TSE precautionary measure. However there have been scientific advancements in types of filters that show promise for removing prions and the presumption is that they may also therefore remove infectivity that is yet to be formally shown through removal of infectivity.

MS. FINLEY: A number of other countries, in fact many other countries, developed countries require leuko reduction for purposes of components. Is FDA's position on this the same for pooled products and for components?

DR. WEINSTEIN: I'm not sure what you're saying,

"The same for pool products". We have worked extensively, reviewing scientific information on clearance of prions and TSE infectivity in the fractionation process. Generally speaking that's not accomplished by filtration; it's various partitioning procedures. And as far as the implementation of leukocyte reduction by a number of countries, it's been for a variety of reasons and not strictly because of TSE.

DR. BRACEY: To stay on track we can take on more question and comment.

MS. FINLEY: I just had one quick question for Dr. Weinstein.

DR. BRACEY: Yes.

MS. FINLEY: Laura Manuelidis released a study a couple of months ago implying that the risk for prion diseases was in fact a virus. Is that the kind of information you're including in your risk communication material and what is the threshold for FDA to update that?

DR. WEINSTEIN: I think as -- as we find that there is -- I mean that was at least one point of information that is of interest -- it still I think needs to be verified. Its in the literature, I don't know that

that in itself would be something that we would be putting on the risk commutations website at the present time.

There are of course many articles that appear and evolve here. So, I mean, that would be taken into consideration as we learn more about the disease and how it might affect our products and so forth that that becomes more of the -- a regulatory issue. As far as advancement of science I think this is you know, interesting, potential possibility and so forth.

But it would take -- we have to consider each of these issues as they affect our products.

SPEAKER: Thank you.

DR. BRACEY: Thank you. Let -- quick comment?

SPEAKER: Yeah. Just that FDA's policies have not been based on the prion hypothesis, of course we respect it. But we've always wanted validation studies to include demonstrating removal of infectivity for the reason that we're not sure that the etiology is fully established.

DR. BRACEY: Dr. Sandler?

DR. SANDLER: This is very useful information about the theoretical issues regarding variant CJD. But

there are much more specific problems related to CJD classical. I have three letters from my blood supplier that three specific units of blood were donated by a person now known to have CJD. So, now I have specific units and specific recipients. Where do I find the FDA guidance on how to proceed with that counseling to those persons?

DR. WEINSTEIN: Well, there are programs of follow-up for recipients of components from persons who've later developed CJD. The Red Cross did an extensive study -- as you know, there's a strong body of evidence, which shows the absence of disease transmission in such patients. Nevertheless, it's reasonable for them to be enrolled in follow-up studies as has been ongoing.

DR. BRACEY: Dr. Kouides?

DR. KOUIDES: Just to follow-up on that I think our prion group headed by Larry Schonberger would be able to help with the surveillance aspect of that in terms of the recipients -- the ongoing study with Red Cross and other blood centers a, as Dr. Epstein mentioned.

I also, somewhat related to that I just wanted make a comment about risk in cellular components that we applied and have been, you know, involved in this effort

concerning plasma derived products. But now they were now talking about U.S.-arrived products. We should consider the risk in cellular components although there's not the multiplication of risk that you see from pooling there are individuals who are very frequently transfused with cellular components and this is a known risk.

I mean, we know that variant CJD is transmitted by cellular components. It's theoretical for plasma, although obviously -- theoretically the risk could be much higher because of the pooling. But this is a known risk and something I think we really have to keep in mind both in terms of developing models but also in terms of strengthening surveillance.

DR. BRACEY: Thank you. In the interest of time we'll then move on to our next presentation and that will be an Update on FDA Immune Globulin, (IGIV); and that will be presented by Jennifer Scharpf. She is the Associate Director for Policy and Communication in the Office of Blood Research and Review at the FDA. Thank you.

MS. SCHARPF: Thank you Mr. Chairman, and good morning to the Committee. This morning I'd like to provide the Committee an update on FDA's recent workshop on immune

globulins for primary immune deficiency diseases.

The workshop officially entitled, "Immune Globulins for Primary Immune Deficiency Diseases: Antibody Specificity, Potency and Testing," was held on April 25 and 26 at the National Institutes of Health.

And FDA is grateful to the Immune Deficiency Foundation, the Plasma Protein Therapeutics Association and Dr. Holmberg, and the HHH, Office of the Secretary, Office of Public Health, and Science for their sponsorship of the workshop. And we thank the sponsors not only for their financial support, but also their scientific contributions to the program. And I would also like to recognize my colleague Dr. Dorothy Scott for her role as the organizer and Chair of the workshop.

The goals of the workshop are four-fold. To assess current potency testing of immune globulins, the current potency test required are for antibodies to measles, polio, and diphtheria. And at the workshop, we wish to examine the potential for other potency tests for antibodies against pathogen most commonly associated with infection in primary immune deficiency patients.

Our goals was also to list antibodies needed to

protect primary immune deficient patients from infections, to identify candidate antibody specificities for potency testing of immune globulins for treatment of primary immune deficiency diseases. And on the second day, our goal was to address a purchase to diminishing measles antibody levels in immune globulin products.

On the first day of the workshop our goal was to identify the most clinically relevant antibody specificities for primary immune deficient patients. Epidemiology and surveillance data was reviewed and there was a description of patient registries in Europe and the United States. The registry, supported by the European Society for Immunodeficiency and the United States Immunodeficiency Network have to potential to gather and long-term prospective clinical data on these patients.

We then reviewed data on antibody levels in currently licensed products and both data sets were then taken to address the question posed on this slide: Which antibody specificities would be useful and relevant to measure with respect importance and to ensure lot-to-lot manufacturing consistency?

The first question addressed to Panel of Experts

in workshop audience was: Which pathogens are of greatest concern in immune globulin treated and untreated patients? And to address this question, data on infectious diseases and patients with humoral and cellular immune deficiencies was presented by clinicians.

The workshop participants, identified streptococcus and haemophilus influenzae as the most important bacterial infections for this patient population. Several viral infections were also mentioned as pathogens of concern including Epstein-Barr virus (EBV), CMV, echoviruses, varicella-zoster (VZV), adenovirus, and coxsackie.

Representatives from the FDA Paul Ehrlich Institute and two IGIV manufacturers then presented data on antibody levels in currently licensed products. The presentations revealed that multiple antibody specificities have been studied, and trends in antibody levels over time across products and variations with the plasma source have been observed. And regarding emerging diseases, it is important to note that West Nile (WNV) have been measured in U.S. products although as one would expect seasonal and locational variations are observed.

So, at the end of the first day of workshop, it was proposed that pilot testing of immune globulins for Strep. Pneumoniae and Haemophilus Influenzae should be conducted. And we believe these tests are feasible as Opsonophagocytosis and ELISA assays have been validated for these specificities in serum. And in addition, WHO reference labs already exist, to which samples could be sent for testing.

In the proposed study, manufactures would voluntarily send blinded samples to the reference lab for testing antibody levels to determine the feasibility of testing and the antibody levels and functions and several manufacturers have already expressed their willingness to send samples.

Finally, we would like to measure trough titer levels of antibody to these bacterial pathogens in patients receiving the products, to determine the relationship between in vitro potency and in vivo levels. And we anticipate that by working with manufacturers samples from clinical studies would be available for this type of testing.

On the second day of the workshop, we discussed

the current lot released tests for measles antibodies. Measles antibodies levels is a standard lot released measure of potency in U.S. immune globulins. This is a historically important specificity due to measles epidemics in the United States. Additionally, validated tester available and antibody levels are correlated with protection in normal subjects.

The measles antibody level are currently measured by bioassay, either hemagglutination inhibition or neutralization. Declining antibody levels have been observed in products over the past several years and this is attributed to the decline of titers in the plasma donor population. The regulatory impact of this, declining measles titers is that the products could fail the lot release specification and then a specific lot must be rejected and rejection of lots could lead to an obvious negative on the supply of immune globulin products. We then posed the following questions to the Expert Panel and Audience.

- Is measles infection of current clinical concern for Primary Immune Deficiency patients? How much measles antibody is needed to attenuate or prevent measles in this

population? What is the potential clinical impact of diminishing anti-measles titers in immune globulin products? And what are possible approaches to address the decline of anti-measles antibodies in immune globulins: With respect to clinical efficacy in prevention of measles infection? And with respect to utility as a test for lot-to-lot consistency?

To address these questions, a representative from the CDC presented data on measles outbreaks in the United States. It was discussed that measles outbreaks still occur in the United States. However, they involve a relatively small numbers of patients, and the outbreaks are primarily due to exposures outside of the United States.

– We also learned that travelers are at risk in countries with low rates of measles vaccination and patients with combined B and/or T-cell deficiencies are at the highest risk for progressive measles.

Data at the workshop suggested that measles titers are decreasing in donor plasma, both source and recovered, immune globulin products although the calculated trough levels would still be predicted

protective, and primary immune deficiency patients receiving IGIV and that no neutralization data can be generated from clinical studies to examine this.

And finally we learnt that precise protective level of antibody is not certain in primary immune deficient patients. But there are animal models available to study this question.

This slide illustrates the trend in declining measles antibodies over time and this data was presented by CSL Behring at the workshop -- and shows a decline in levels in one product since 1985 and this trend is apparent regardless of the plasma source used in the manufacture of the product.

So in summery, the possible approaches to address the declining measles antibody levels identified by the discussants at the workshop included one, gathering relevant data, relating product titers to patient trough levels and establishing protective levels; and two, exploring the option that CBER can potentially change the recommendation on antibody potency for measles. However, this change must be scientifically and clinically justifiable.

And in conclusion, the next steps to be taken following the workshops include one, to design and implement testing protocols to assess levels of antibodies in immune globulin to H. Influenzae and Strep. Pneumoniae pathogens -- which are pathogens commonly associated with infection in primary immune deficiency diseases and this study will evaluate the feasibility of using these specificities as potency tests.

Two, implement a study to measure measles antibody trough levels by neutralization assays in patients to better ascertain the relationship between the product dose and trough level and finally CBER will deliberate on solutions to address the diminishing measles antibody titers in immune globulins running of course, scientific, clinical, and supply considerations.

And finally, additional information on the workshop will be posted on the CBER website including the transcript and all of the slide presentations. Thank you.

DR. BRACEY: Thank you. Questions on this presentation? Dr. Pierce?

DR. PIERCE: Can you comment on how many lots have been rejected because they don't fulfill

the criteria?

MS. SCHARPF: We are currently, gathering that data from the manufacturers. We have an inquiry into them at this time.

DR. PIERCE: Do you have any sense for what it is?

MS. SCHARPF: At this time we do not -- although they have obviously expressed concern.

DR. BRACEY: Dr. Kouides?

DR. KOUIDES: Will there be any efforts made to correlate the falling level with surveillance for documented Strep. Pneumonia infection, for example?

MS. SCHARPF: There certainly will be and that is I think why we wanted to include the presentations from the registries at the workshop to try and determine if we can determine that 0-- that information.

DR. BRACEY: Okay, thank you very much.

MS. SCHARPF: Thank you.

DR. BRACEY: Then we will move on to our next presentation, which is -- actually --

(Laughter)

DR. BRACEY: -- well, actually we can take a

break now.

(Laughter)

DR. BRACEY: Sorry, I thought we had one more presentation. Now, its time for a biological break and why don't we reconvene in 15 minutes at 10:02? Thank you.

(Recess)

DR. BRACEY: The next presentation will be a continuation of Committee updates, and it will be an update on the Blood Product Advisory Committee's discussion on -- what's really a hot topic in transfusion with the Chagas Testing and that will be done by Robert Duncan. Dr. Duncan is lead scientist of the review Committee that approved the first blood-screening test for T. cruzi in 2006. Dr. Duncan?

DR. DUNCAN: Good morning. I'm going to just summarize briefly, the discussion and our interpretation -- especially if this goes with the answers here -- all right doesn’t look bad, let’s try "Page Down" here.

So first, I'll give a little background on the disease -- and this is not thorough or complete by any sense. I'm just keying in on the points that are significant from the point of view of blood transfusion

and other means of transmission.

Chaga's Disease is caused by a parasite Trypanosoma cruzi. You can see some individuals there swimming among red blood cells in a blood smear from a patient. And what's important is that after the acute infection, which is often mild and not even noticed, a person will go on to a chronic asymptomatic infection, which they probably keep for life.

In this chronic phase, it's difficult or impossible to treat, but severe symptoms only occur late in about 30 percent of the cases. The disease is endemic to the portions of Mexico, Central, and South America with estimated 16 miiliion to 20 million people still infected. There's progress in lowering the incident cases, but the prevalent cases will have with us for sometime.

Transmission is either by natural bite of an insect that's infected if you rub the feces into the bite wound, you become infected or into the liquid around the eye. It can also be transmitted congenitally by organ transplant; in a blood transfusion or orally, through breast milk, or as recent cases have occurred when people have drunk freshly prepared sugarcane juice, they've

acquired the infection; also possible with lavatory accidents.

The transfusion transmission is a recognized problem in the endemic areas, and most countries where it's endemic, test their blood. What you can't see on the statistic there is that about 12 percent to 20 percent probability of causing an infection if a Chagas positive unit of blood is transmitted or transfused.

In North America, there've been in the last 20 years, 7 documented cases of transfusion transmission, 5 cases of organ, solid organ transplant. And I just call your attention to this fact, because the last four –- the last five transmissions were organ transmissions.

The last transfusion transmission was on 2002, 2003 around in there, so it's clear that there is a trend towards organ transplants transmission. Rarely there is natural transmission from infected insects in the United States were mainly protected by not having contact or housing quality is good keep this clear.

Passed estimate, this is your prevalence, I'm going to give a more recent estimate later, but as the background is shown, it's really the main concern comes

with immigrants who come to this country who're infected early in life and are not aware of it, they become blood donors or tissue or organ donors. So the past history here, in just this past December, FDA approved the first blood donor screening assay as the Ortho T. cruzi ELISA Test System.

It's important to note that there was no supplemental test licensed at that time or currently there's non-available, which means any policy or deferral decisions are made based on repeated reactivity to the screening test. There is no confirmatory statu,s officially. And just this few weeks ago, April 26th, issues were presented to the Blood Products Advisory Committee meeting related to blood donor and cell and tissue donor screening.

And that presentation was in the area of donor management, product management, and areas that needed additional research, such as potential for selective testing as well as testing for other cross-reacting parasites, and also the potential for cell and tissue transmission was discussed.

This is the agenda of that session just to let

you know –- I did a presentation that's very similar to what I'm giving you right now. Dr. Melissa Greenwald also gave a presentation on cell and tissue based products. We had Dr. Susan Stramer of the American Red Cross presenting the experience with screening of the blood supply.

Currently, she has presented results on about 2 million donations tested. We also had a presentation on the public health impact of blood donor screening, Dr. Susan Montgomery from the Centers for Disease Control and Prevention talked about how -- becoming aware of the cases through blood screening will give us a lot more information about epidemiology, and also lead to a need for response in terms of treatment and follow-up of those people that we detect.

We also had a presentation by Mike Busch and Brian Custer on strategies for targeted testing of T. cruzi infection in repeat donors as a possible alternative to universal screening. And there was open hearing and discussion.

I'm going to give you a little bit of update on what we've learned from screening to date beginning January 29th. A fairly large number of centers of the

American Red Cross and Blood Systems Incorporated as well as some other centers have followed. As of April 17th, 1.8 million donors have been screened resulting in the detection of 265 repeatedly reactive donors. And that's 0.015 percent detection rate, which is sort of a consistent with the reactive rate that was seen in the clinical trial, which was a great relief, because one of the concerns without confirmatory test, we would be in bad shape if this was a much higher in number.

So there is a more specific test called the radioimmune precipitation assay for the T. cruzi antibodies, it's not a licensed test, but most of the blood donors who're screened or retested –- their blood retested with that assay, so although we cannot use if for a policy making decision, we can use it to look at –- so how things are going.

Based on that testing at that time 174 of these 265 were non-reactive, 50 were reactive, 41 were still pending. So this 50 reactive is more or less considered true positives, people who actually have the infection. And, you know, they're recommended for follow-up for disease treatment and whatever.

So, the ratio of true positives to false positives is very much in a good range. About 22 percent positive predictive value for the test, were comfortable with that. We can calculate specificity from these numbers and 99.99 percents specificity also falls very nicely on what we saw on the clinical trial.

And this would be our current estimate of prevalence among blood donors, which is considerably less than the earlier estimates. As earlier estimates were probably largely by us by sampling from high prevalence areas, which means places like Los Angeles, South Florida, with a high percentage of immigrants in their blood donor pool have a higher prevalence.

The current screening has been guided by voluntary industry recommendations. The American Associations of Blood Banks issued recommendation for implementation to its member, centers, and that bulletin is available. So what are the issues? First, after testing all donors should we continue your universal screening or should there be selective screening? And it's clear that any strategy for selective testing needs to be validated.

The deferral for a reactive donor most likely will be indefinite, until we have a licensed supplemental test that we could develop a reentry algorithm. They will need to be donor counseling. All repeated reactive donors will be notified about their likely -– the likely medical significances of the infection, and they maybe referred for additional medical diagnostic testing.

The question of cross-reacting diseases, I'm going to develop a little more further on an area of new research. So, there is also issues of product management, all donations from a reactive donor will be probably be quarantined and labeled. Prior collections from the positive donors or reactive donors will be retrieved and quarantined.

And then some recipient tracing will be done, the notification of the centers or hospitals that'd received blood collected from a reactive donor will be notified. So, they can notify recipients of prior donations. The policy for Autologous donations will probably follow, what's already in the regulations just adding Chagas disease to one of the agents that's of concern.

Meaning that an Autologous donation could be transfused, it just has to be labeled appropriately as long as transfused into the donor. So, the response from the advisory Committee suggest that universal screening for T. cruzi for one to two years is appropriate to acquire more data on Epidemiology, test performance, and understanding of the window period, follow-up testing, and reentry of donors before any final guidance be issued.

And this will also allow additional time for other test development. We would prefer to have at least two manufactures on the market before making a binding recommendation. And we would also like to have a licensed supplemental test come forward, so that we'd have a donor reentry algorithm as part of any final guidance.

So, where is additional research needed? I have already mentioned the question of target screening of repeat donors. This means, once everyone has been screened -- a person who had a Chagas negative test comes back to donate, under what conditions would they need to be tested again?

So, we need to come up with the strategy that would target that retesting of repeat donors and that's

the kind of data we hope to be collecting over the next few years. With the strategy that Brian Custer outlined is a certain set of questions that would be on a donor history questionnaire, and they will look at –- and they would ask the questions and then test, and that correlates test results with answers to the questions, and see if any of those questions will guide the strategy to identify the actual infected people.

So, that the general consensus that researched on selected testing should be pursued with the validation of the donor questions and multiple years of selective screening during which time that those evaluation of those strategies can be done. We will continue to work with AABB Chagas Task Force to facilitate effective research strategies in this pursuing period.

So, the other question where we think there is more research needed the possibility of cross-reactive antibodies of -– between T. cruzi and Leishmania. Leishmania is another protozoan parasite that's genetically related to Trypanosoma cruzi. The two parasites are –- have shared an endemic range throughout Central and South American.

And the results from the clinical trail showed that 74 out of a 100 samples of people who had leishmaniasis that lived in a non-T. cruzi endemic area reacted with the T. cruzi screening test. So there is no possibility that they were co-infected with T. cruzi. It's just that their antibodies react to this ELISA.

So that points a potential problem, and it's really, mostly at this point a problem for donor counseling, it would mean if you had a positive test for this T. cruzi test you were negative on a follow-up test like the RIPA, does that mean you're completely disease free or does that mean you're infected with Leishmania?

That's a question for, basically a medical diagnostic question. And this is to be investigated. We have some potential ideas for how that might be done. One of which would be to prospectively follow-up for leishmaniasis all donors who're repeatedly reactive on a licensed T. cruzi screening assays, and follow them for Leishmania serology, risk factors, other medical diagnoses.

The other kind of study that could be done would be to go to repositories samples. The CDC has a

repository of very well characterized. Leishmania infected individuals they were necessarily blood donors. They could be retested with the T. cruzi ELISA and we get a better idea about the real danger of cross-reactivity.

There were some minor cross-reactivity with Plasmodium or Paracoccidioides. That's much lower priority at this point. The response of BPAC was mixed. There were some who express concern that the lack of evidence from T. cruzi blood screening and follow up for Leishmania testing of already over 300 repeatedly reactive donors would indicates there's no pressing need for research. In other words of the 300 repeatedly reactive that have been tested from U.S. blood donors, none of them have showed Leishmania positive.

But there is also concern that more research needs to be done to understand how to counsel repeatedly reactive donors that are non-reactive on a more specific test or other medical follow-up. And really the –- one of the points that the Committee made is that the investigation of cross-reactivity to other agents should be focused in medical diagnosis setting, and we're going to continue to follow that.

And that's my presentation, thank you.

DR. BRACEY: Thank you, Dr. Duncan. Questions from the Committee, perhaps I could ask one question.

The good news is that, it looks like there are a lot of donors that will be positive for this test. The challenge is then, so what does one do with donors who are in fact positive. It seems to me, just speaking from the field that our medical system is not really geared towards the management of these individuals and I'd be interested in your thoughts about that aspect.

And, then I guess, I asked the question, even though you have not approved the RIPA for reentry, in a transfusion service if one could eliminate three out of four cause in worry on the part of donors, wouldn't that be something that would be good to do?

DR. DUNCAN: Expand a little bit, what you mean by eliminating three out of four fields?

DR. BRACEY: Oh, oh yeah. Actually what I –- what -- if we contact -- if we are contacted on the basis of repeat reactive results and let say the transfusion service, and we have to do look-back, you know, that's a sort of a bothersome.

DR. DUNCAN: Right.

DR. BRACEY: And if in fact you can eliminate three out of four individuals from consideration, obviously you don't want to do that for reentry, but just as far as donor counseling patient management, it just seems that the RIPA assay has great potential and it's so expensive that in the field at least -- my sense is that many people are not doing it routinely because of the expense -- maybe in the ARC system, but not others.

DR. DUNCAN: You mean they are not doing the RIPA follow-up?

DR. BRACEY: Yes.

DR. DUNCAN: Or they not doing –- so they're screening with the ELISA, but they are not retesting with RIPA?

DR. BRACEY: In the absence of -- in the absence of guidance to perform additional testing, some are electing not to.

DR. DUNCAN: Right. Well the -- I mean, you are asking a tricky question. For donor counseling, I don't see a problem that the, you know, the recommendation will be for further medical follow-up, after the repeat

reactive tests, and that could include, going to Quest Diagnostics and having a RIPA done.

Where there is a problem is the question of look-back. I can certainly understand the argument that if you could do lookback out of -- for one out of four or one out of five of your repeat reactive donors that would be a lot easier. But I would like to differ to Jay Epstein to speak on why we can't use RIPA for any recommendations about lookback.

SPEAKER: Well, I'm not sure we can. The issue of reentry, as Dr. Bracey said, is separate because that's a blood safety issue allowing the donor back in the pool. And there, you know, it's very difficult, the FDA cannot recommend algorithms with tests that aren't under, you know, the FDA regulatory controls. That said we recognize that laboratory-based test can be available for counseling purposes, and I think what we'll just do is consider your comment whether we could extend that to a decision on the lookback.

In any case when we publish guidance, it would be published as draft, and it would be available for comment. So, you know, I think you've made a valuable

point. The silver lining here though is that this screening test appears to have extremely a good specificity and so we're talking about small numbers.

DR. BRACEY: Right, exactly. Dr. Triulzi.

DR. TRIULZI: Yeah. This is a question toward Jay in FDA. It's been problematic having just a single test license for about half of the centers that use alternative supplier lab testing. And would the FDA consider, in order to facilitate broader testing, allowing centers to do testing under an IND for an alternative manufacturer without requiring consent of the donors and I'll guess to how West Nile Virus testing was implemented.

SPEAKER: Well, in general, IND requires some level of consent. I don't think we entirely waived consent. You know, there were IRB reviews and there was general, you know, blood transfusion consent. And I'm not sure what consent forms were implemented center-by-center. But there were issues of informed consent with West Nile, as well as with, you know, HIV/HCV NAT.

But that said we have not yet issued recommendations that would cause routine use of the license test, and there is room for IND testing even after

we've approved license test. New tests do get developed, and they do become evaluated under IND. So that flexibility does exist today.

SPEAKER: The West Nile -- can I just followup with that, Chairman.

DR. BRACEY: Sure.

SPEAKER: Thank you. The West Nile, most centers handle consent by a donor information sheet as opposed to requiring a specific signed consent. And it's really almost necessary in order to get a throughput in a busy donor drive in order to do that. So it facilitates getting the data needed ultimately for licensure. And I think that it would be interesting using that same methodology for an alternative Chagas test.

SPEAKER: Right, but what I'm trying to clarify is that the acceptability of the form of consent lies with the IRB. IRBs get to decide whether that's an adequate consent or not. And, you know, there were IRB reviews of adequacy of consent for West Nile as well as other new tests.

DR. BRACEY: As we prepare for the charge from the assistant secretary, the information in terms of the

infections with the transplant recipients and transfusion recipients resonates in terms of the issue of commonality and we'll talk about that later. But, for one last question, Dr. Sandler.

DR. SANDLER: I wonder if we could get some information about the demographics of the two-thirds of the people who reacted in the screen test but didn't have a report that was positive. It seems that if those two-thirds or three-quarters of those people were born in a risk area, for example, the screening test is pretty good, but the confirmatory test needs to tuned-up.

On the other hand, if these people from Boston and from Maine who happen to be in California or wherever, where they donated with no risk factors then you've got a different kind of a problem. What does that profile look like on those?

DR. DUNCAN: I don't have those numbers in front of me right now. But what I can tell you is, that is very much like what the strategy for selective testing that's being validated over the next few years will look like. There will be a set of questions attempting to be as objective as possible because when you talk about

questions or ethnicity, you know, you get into some very dangerous territory. But questions about place of birth, travel, congenital transmission is a possibility, so your mother's place of birth. Questions like that will be there. And the opportunity will be there to make that correlation for all repeat reactives how do they break out, and that would be the sort of thing that would guide a question that would be helpful.

Nobody at this point is proposing that the initial blood screening test be determined by a questionnaire. It's been -- there has been research done in the past that shows answers to the questions are often incorrect and have not in the past been a very good guide to separating the reactive donors from the non-reactive donors. But once a person has been tested once and they test negative then this sort of selective screening could be appropriate.

DR. BRACEY: Thank you. One more question. One last question, then we'll move on.

SPEAKER: Thank you very much Dr. Bracey. I'm directing these questions to FDA. How long do you think it's going to be until you have a supplemental test? Can

you tell us if you're currently reviewing a supplemental test or if you think it's going to be a while before you see one? And the second question is, is the whole concept of donor reentry and whether or not we should require test screening using the Ortho and any other approved assay dependent on having a confirmatory test approved?

SPEAKER: Well, first of all, unless Bob you prefer to answer.

DR. DUNCAN: No, go ahead.

SPEAKER: The -- no, we're not going to hold screening hostage to the availability of supplemental testing because it's safety first. And additional testing is counseling and potential lookback and reentry issue, those are secondary considerations. First, you want to protect the transfusion recipient. So we will not hold back from developing recommendations on the implementation of screening.

As to the timeline for development of additional test, as has been stated, medical diagnostic test already exist, and we think that, you know, physicians, medical directors can utilize them for counseling. So that's here now. The really the only issue is FDA approved

supplemental tests, which we would then recognize in any algorithms that we might recommend for donor management. And we don't control that timeline. Why? Because we don't have the authority to command that any manufacturer make any product. So a sponsor has to be interested and willing. Now, without, you know, disclosure let me just say that, you know, there is a willing candidate and I don't control the timeline.

DR. BRACEY: Thank you.

DR. DUNCAN: I wouldn't want to overstep by balance, but the willing candidate made a presentation at BPAC, so it's public information.

DR. BRACEY: All right. Thank you. With that we will move on to the next topic, also a very hot topic if you will and that is an update of the BPAC discussion of transfusion related TRALI. This will be presented by Dr. Leslie Holness. Dr. Holness is currently the medical officer from the division of blood application at CBER.

DR. HOLNESS: Thank you Mr. Chairman. Good morning. This is summary of the topic Transfusion Related Acute Lung Injury or TRALI presented at FDA's Blood Product Advisory Committee on April 27, 2007. FDA sought

at the time to be advised whether available scientific data support the development of FDA policies on methods to reduce the incidence of TRALI. As we'll see, the topic is timely for a number of reasons. Our presenters were Dr. Alan Williams, the director of the Division of Blood Applications are CBER. The Clinical and Laboratory Aspects of TRALI were given by Dr. David Stroncek of the National Institutes of Health, and Current Use of Transfusable Plasma was presented by Dr. Ravi Sarode of the University of Texas Southwestern Medical Center.

A review of the REDS-II Leukocyte Antibody Prevalence Study on HLA and Granulocyte Antibody Prevalence in Blood Donors was given by Steven Kleinman, the University of British Columbia. The American Red Cross Experience with TRALI was presented by Richard Benjamin. And Americas Blood Center's experience with TRALI was presented by Dr. Celso Bianco of Americas Blood Centers.

Sorry, this is cut off a little bit. But thus slide represents the FDA recipient fatality reports for the last three fiscal years attributed to TRALI. First number is the number of reports received for the

particular fiscal year, and the second is percentage of the total recipient reports represented by TRALI reports. The number grew steadily as you can see in fiscal year 2004 it was 30.9 percent of the total fatality reports, and that grew steadily in fiscal year 2005, until in fiscal year 2006 there were 35 reports which represented over 50 percent of the total recipient fatality reports received for that year. So therefore TRALI related fatalities were citing TRALI is the cause of death reported more often than those citing any other cause.

These are components associated with reported fatalities due to TRALI in fiscal year 2006. FFP was implicated more than twice as often as any other component and plasma is also indicated in two other categories. Therefore, transfusable plasma is well represented. TRALI is considered underdiagnosed and underreported. So the incidents spans a broad range from 1 to 1,000, it says 1 to 10,000 units transfused.

Major projects implicated were fresh frozen plasma, platelets and red cell concentrates. TRALI is more likely to be associated with FFP and platelets. Solvent/detergent plasma which is widely used throughout

the world has not been thought to cause TRALI and no causative antibodies have been found in solvent/detergent plasma. So what is TRALI? Basically, it's severe shortness of breath within four to six hours of a transfusion with no signs of fluid overload and with pulmonary infiltrates on chest x-ray. 89 percent of the cases, the first symptoms appear within the first two hours of transfusion. Very few cases allow more than six or less before the first symptoms.

Moving on, more clinical features Dyspnea and hypoxemia, fever, hypotension or hypertension. In the chest x-ray you'll see bilateral infiltrates and a typical gwhite out pattern. All the treatment of TRALI is pretty much supportive. Transfusion should be stopped immediately if the offending component is still being transfused. There is hypoxemia so therefore supplemental oxygen should be given, intubation and mechanical ventilation is necessary in about 70 percent of the cases. For hypotension intravenous fluid should be given and agents to increase blood pressure. Corticosteroid may be used with mixed results.

The symptoms generally resolve within 24 to 48

hours if the -- if provided prompt and rigorous respiratory support. Symptoms may resolve before the diagnosis is made and mortality is 10 to 50 percent. For those who recover rapidly, however, there is usually no long-term effects.

Here are some of the mechanisms of TRALI. 45 to 60 percent of the cases are associated with neutrophil-specific antibodies in the donor. Donor antibodies to HLA Class I or Class II or both in some cases are also implicated, and Allotypic leukocyte antibodies are known to be stimulated by pregnancy and transfusion.

These are prior public discussions of FDA regarding TRALI. TRALI was presented to the Blood Product's Advisory Committee in June 15, 2001. The committee was asked the question, should FDA consider regulatory interventions at this time to identify donors and/or donations with an increased risk of producing TRALI in a recipient?

One panel member answered yes, 13 panel members answered no, and the committee recommended more research. In October of 2001, FDA issued a physician's letter to transfusion -- to the transfusion committee to approve

TRALI recognition.

There has been an increase in fatality reports to FDA since that time. The serious hazards of transfusion or the SHOT program is the hemovigilance arm of the national blood service of the United Kingdom which provides 80 percent of the blood components transfused in the U.K. In their analysis in the U.K. intervention study they noticed that TRALI incidents were five to seven fold higher following the administration of high volume plasma units. The minimize the use of FFP and buffy coat-derived platelets from female donors in October of 2003 and TRALI incidents in the UK subsequently declined dramatically.

April 2004 in Toronto there was a Canadian TRALI consensus conference. The conference introduced standardization of TRALI definitions based on clinical and radiology criteria and recommended that blood collection agencies assess the value and the cost of TRALI interventions.

This slides shows some data from the U.K. SHOT data. The TRALI cases decreased dramatically as you can see from 1999, 2002 to 2005, as well as the probable and possible cases are shown in red and they also decreased

dramatically. In the year 2005, the three cases shown there are buffy coat platelets. There are no cases of TRALI from FFP. However, the UK discards most of its own plasma and imports plasma from the U.S. for patients under 16 and this is for vCJD consideration. This is the American Red Cross study. They objectively assess the 550 system wide suspected TRALI cases including 72 fatalities from the year 2003 to 2005. The results show that plasma transfusion was associated with 63 percent of the probable TRALI fatalities and platelets, pheresis transfusion were associated with 13 percent of the probable TRALI fatalities.

The conclusions were that female donors and high plasma volume components were disproportionately implicated in TRALI, and Limiting plasma from female donors might reduce as many as six recipient deaths annually in the Red Cross System.

In 2006, the AABB convened and TRALI working group and this bulletin 06-07 produced in November of 2006 is the first bulletin from the group. Basically, it illustrates three precautionary strategies. Blood collecting facilities should implement interventions to

minimize the preparation of high plasma volume components from donors known to be leukocyte-alloimunized or an increased risk of leukocyte alloimmunization. Blood transfusion facilities should work toward implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusion. And blood collection and transfusion facilities should monitor the incidence of reported TRALI and TRALI-based mortality using the Canadian Conference Definition.

The voluntary interventions discussed or implemented by the blood collection community. Deferral of donors implicated in previous TRALI cases, which is pretty much what’s happening at the moment. Preferential use of male plasma for transfusion, selected donor questioning or testing for neutrophil-specific antibodies or HLA antibodies. Review of evidence supporting appropriate use of plasma and research, research into the mechanisms of TRALI pathogenesis, prevalence of associated antibodies and other factors, and the role of previous transfusion in white cell alloimmunization of donors.

This is a look at the Reds II Leukocyte Antibody Prevalence which is a five-year a five year study funded

by NIH in 2004 in multiple project areas across the U.S. LAPS-1 determines HLA class I and II prevalence, antibody specificities and correlates them with pregnancy, history of transfusion, and immune status. They compare it with baseline group of individuals who were never pregnant or never transfused. They will determine the prevalence of neutrophil antibodies in those with HLA antibodies and controls. And LAPS-2, which is projected, looks at the Clinical Lookback study of TRALI. The incidence of TRALI in recipients of high plasma volume components from donors with leukocyte antibodies, and that's in the planning stage.

Here are some take home messages for precautionary measures in TRALI. Very significant use of plasma -- significant misuse of plasma, excuse me. There was a NIH plasma conference in 1984 about the risen indication for plasma use. And they -- the conclusion of the conference was there was an overuse of plasma by a factor of 10. Current evidence does not support prophylactic plasma transfusion to correct, mild, or moderate abnormal coagulation tests in patients with no history of excessive bleeding.

Blood banks should practice transfusion medicine rather than function simply as dispensing units. There is a greater need for clinicians and medical students education in transfusion medicine and hemostasis and the clinicians respond well to education. The practice of plasma transfusion to 1.5 times normal clotting time should be revised. Other products should be considered such as Cryoprecipitate, Antifibrinolytic agents, Protamine for heparin-induced bleeding, FFP may make bleeding worse, and prothrombin complex concentrates for reversal of coumadin effect.

This is a slide that shows the BPAC votes after all the discussions from the session. BPAC voted unanimous yes for the use of predominantly male plasma for transfusion. Unanimously no for the non-use of plasma from donors with a history of prior transfusion. Unanimous yes that more data is needed for selective donor screening, for anti-neutrophil or anti-HLA antibodies which could be beneficial but the technology is lacking especially for anti-neutrophil screening and the technology exist for anti-HLA screening but it’s less beneficial because there are fewer cases.

The advisory committee found little or no effect on U.S. plasma supply if predominantly male plasma is used for transfusion. The advisory committee made these additional comments. Females with no history of pregnancy or transfusion should be allowed to donate plasma. Non-specified female plasma could be used in critical shortages, and guidance on appropriate clinical use of plasma should be distributed. The AABB Clinical Transfusion Medicine Committee is working on guidance. And the FDA has two liaison members of that committee. And that the end of my presentation.

DR. BRACEY: Thank you, Dr. Holness. If I may ask one question, and that is influencing practice, I found an interesting bullet with a green, that physicians respond to education because that's been actually the opposite of my experience. And I begin to wonder, you know, one of the things that we're charged with is looking at the development of policies that will promote the best use and safest use of blood.

And, you know, nowadays hospitals pay a great deal of attention to directors from CMS on quality initiative et cetera. And it seems to me that within the

hospital, the transfusion committee although it's being -- there are some resurges, but it's been sort of atrophic, and perhaps that would be an area where through some policies within HHS that the appropriate use of blood might be fostered, not only on simply an educational basis but really a best -- incentives for best practice because again that is a -- we're beginning to see incentives for best practice in a number of areas within hospitals.

DR. HOLNESS: Right. The AABB CTMC is working on that now. Best practice guidance and also the FDA is working also on guidance, and we plan to have more dear colleague letters.

DR. BRACEY: Dr. Holmberg, and then --

DR. HOLMBERG: Has there been a review of the 1984 consensus conference on the use of FFP?

DR. HOLNESS: A review --

DR. HOLMBERG: The reason I ask is that the last time I looked at it, which was probably about a year ago, I didn't see too many things that were different from 1984 to what we're doing now.

DR. HOLNESS: Well, that was the reason I mentioned it, actually. They found that there was an

overuse of plasma at that time and they still have an overuse of plasma, so --

DR. HOLMBERG: And --

Dr. Klein: Jerry, if I could comment on that because I was part of that consensus conference. The problem in 1984 was that there were precious few data, and the overuse of plasma number was pulled out of the air. The problem in 2007 is the absence of data. And any number you're going to pull will come out of the air.

DR. BRACEY: Excellent point. Dr. Sandler.

DR. SANDLER: Dr. Holness, you dropped the hint that if we use solvent/detergent plasma we'd lick the problem, and you didn't have that on any slide as a recommendation that we return to it. There was a licensed product that we used. It was a great product that had disappeared. I'm wondering if you can clarify whether the licensed product was taken off the market voluntarily by the manufacturer and distributor, or was there any body language or other action by the FDA that encourage removing it because of reports of prothrombic activity.

DR. HOLNESS: Well, I'm not prepared at the moment to respond to that, but the product was actually

taken off the market -- I mean, I understood it was for problem other than, you know, TRALI, and that there are other problems with the products, you know, other than TRALI or any of those problems. I'm not sure that answers your questions, but, you know, I was involved in those discussions.

DR. BRACEY: Yeah, I think that is an interesting question because again a number of individuals, well, actually a number of countries continue to use the product without great deal of problems reported. So I think it would be worthy taking a look at it again. Dr. Holmberg.

DR. HOLMBERG: I just want to ask a question concerning the solvent/detergent, and that is, do we know the mechanism of removal of the antibodies whether they're HLA antibodies or the NSA or the allotypic leukocyte antibodies.

DR. HOLNESS: I'm not sure that known. It may be just a dilution effect because it's approved product. I just know that there has been no antibodies found in the product.

DR. BRACEY: Dr. Epstein.

DR. EPSTEIN: I just wanted to answer Dr. Sandler's question. FDA didn't act against the product, but the market did. Now, we made known there was an MNWR I believe and there were publications, and there was, you know, investigation at the hospitals and so forth. We thought the information should be disseminated. But the decisions to discontinue use were market driven.

DR. BRACEY: Dr. Holmberg.

DR. DUNCAN: Yeah, I don't want to take too much time more on this, but I'm very interested in the AABB CTMC working group on the use of the plasma. And I would like to hear, you know, Mr. Chairman maybe later on we could have discussion on whether this is something that you feel that the department needs to have more interaction on and liaison work.

DR. BRACEY: Yeah, I mean, we'll talk about that later. I think that again my perspective is that when we speak from the laboratory side to the clinical side there is a voice. But that voice does not always create action. And I think it would be important for the -- for the department to begin to interact with all folks in the process of developing these guidelines so that we cam make

then work. And become a part of practice.

Speaker: I had -- I didn't go to BPAC so maybe some of this was discussed, but I still really get concerned when I hear the data on how many people have TRALI and die of TRALI. In our hospital, depending on which service you're on, you have TRALI or you don't have TRALI. And despite the fact that there is a true definition that excludes other causes, you know, of respiratory distress during transfusion, like, you know, congestive heart failure we will still get reports from clinicians who believe that the two are happening simultaneously.

Is it TRALI, is it not TRALI. We have a death from TRALI in our hospital, and I believe it's TRALI, we could never prove it, you know, using serology. So, what is getting reported as TRALI, as death from TRALI, changes. I do believe it's underreported, but it may be overreported. When you look at changes in the death rate in the U.K. is there an increased awareness that we're using a product in the UK that reduces the risk of TRALI?

So I'm very concerned there is no definitive test, obviously, and whenever we discuss, you know,

implementing strategies for platelet transfusion we have to think about, is it TRALI, is it not? What is the risk of availability versus safety? So I just wanted to make that point that I'm not convinced. Sometimes when I see some of the data that it really does represent a biological entity versus, again, what people's understanding is of what that entity is?

DR. BRACEY: Well, again I think this is an important point in terms of the need to have a system for biovigilance so that, a, that we track these things, and b, that we refine the definitions of these events. And I think it's notable that the UK has been able to make an intervention, measure and report an outcome. This is something that in the states -- we'll hear more about this later that, you know, we need to do. One last comment from Dr. Sandler and then we'll move on. Question.

DR. SANDLER: The number of transplants of the liver is going up, and up, and up, and fresh frozen plasma is here to stay. And doctor's behavior hasn't changed as Doctor Klein indicated in decades. I'd like the committee to consider the possibility of a strong look at the potential benefits of returning to solvent/detergent

plasma as the standard. I think that solvent/detergent plasma was here. It was really terrific, and I don't believe that there is a critical analysis of the factors that cause the market to withdraw.

DR. BRACEY: Thank you. We will -- we'll address that in our discussion later. If there are no more comments let's move on to the -- oh, Dr. -- Commander Libby.

MR. LIBBY: I have a question. I was not at BPAC either but I know the -- you know, the BPAC votes and comments section, here, you say that there was -- they felt there was little or no effect on U.S. plasma supply, predominantly male plasma is used for transfusion. What's your -- what was the read on the availability of AB plasma because currently we in the DoD pretty much have exceeded our capacity to produce Ab plasma in which case we've had to go to civilian industry to purchase AB plasma, and I kind of -- I'm very much concerned what would happen if we limited lot of our female donors from participating in our donor pools --

DR. HOLNESS: Well, the idea to add back those female donors who have never been pregnant or have no

antibodies, you know, would help that situation. In a critical shortage you could just use non-specified female plasma. I mean, it's not eliminated per se. It's just, you know, predominantly male plasma.

DR. BRACEY: Yeah, I think the keyword is predominant. And I think most people in the field are operating, or planning to use Ab female plasma because of issues of availability. Okay. So we'll move then on to the next presentation which is an update on the BPAC discussion on WNV by Dr. Maria Rios. Dr. Rios is the principal investigator of the laboratory for molecular biology in the Division of Emerging and Transfusion Transmitted Disease of the Office of Blood Research and Review.

DR. RIOS: Good morning, and thank you for the opportunity to talk to you today. I will update you on the issues related to the implementation of West Nile viral testing presented to the Blood Product Advisory Committee on April 27 and that the session began with an update of -- on West Nile Virus epidemic in 2006 by Dr. Farnon from the CDC.

And then we presented the testing issues which

included the approach to confirmatory testing, donor and unit management, and approaches to ID-NAT Trigger. And then the session was closed by Dr. Stramer's presentation representing the West Nile taskforce of the AABB on West Nile Virus the data in support to the current ID-NAT Triggers. CDC presented the ArboNET report of West Nile disease cases in human in the U.S. from 1999 to 2006. And I want to call your attention to the close to 24,000 cases of human disease has been reported to the CDC ArboNET. And close to 10,000 neuroinvasive disease and there has been close to a 1,000 death in these years.

So, since 2002, you can see here from the report, there has been more than 1,000 cases of neuroinvasive disease of West Nile Virus yearly, and a 100, or over a 100 death, all cases of fatality dues to West Nile Virus infection. Since 2003, nucleic acid-amplification test in the mini-pool platform format has been used to screen blood donations to -- for West Nile Virus.

The predictive viremic donors reported to the ArboNET as of April 02 of 2007 we will be -- wasl show also by Dr. Farnon in the blood establishments screen for

West Nile NAT and remove the infectious blood products from circulation, and report the presumptively viremic donors to the local public health department, and then the local public health department is the ones in charge to report to ArboNET CDC. So there is a lack of reporting time. And what CDC has in the internet up to -- in the ArboNET upto April 12 was about 361 cases in 2006 and you can see yearly since the screening, how it increased and then decreased, and the increased again. And we know that these numbers underestimate by looking at other surveillance system such as the biovigilance from the AABB. We know that over 400 cases were confirmed positive for West Nile based in the algorithm that I'm going to show you. And it has been more than 2000 units reactive for West Nile being removed from the blood supply and potentially have prevented between 2 and 6000 transmission of West Nile by blood transfusion.

The status of the current assay -- the current status of assay in December 2005 FDA licensed the first West Nile NAT for volunteer blood donors which was the Procleix Assay West Nile Assay developed by Gen-Probe and marketed by Chiron.

In March 2007, FDA licensed the first fully automated NAT for volunteer blood donor ever, and this was the Procleix West Nile Assay on the TIGRIS system, so we have automation, and there are other West Nile NAT for donor screening currently under IND. With regarding test West Nile has become endemic in the U.S. and it's a reportable disease to the CDC, and it's estimated in the early studies that every 1 in 150, in more recent data with more accurate testing, 1 in 350 infections there is -- every 350 infection there is one neuroinvasive disease. So taking into account the number of reported neuroinvasive disease to the CDC we can estimate there has been 1.5 to 3.5 million infections in the country from 1999 to 2006. There has been consistently, since 2002, over 1,000 neuroinvasive diseases in the West with more than a 100 fatalities a year.

And the human cases are reported to the CDC from January to December showing that there is activity from at least a report from January to December. So FDA is considering whether blood establishment should screen for West Nile by mini-pool NAT year round. In 2003, studies show that after implementation that mini-pool NAT there

were six cases of West Nile by blood transfusion and the studies performed at that time by the blood establishments show that 75% of the reactive units or infected units were identified by mini-pool.

However, 25 were missed by mini-pool because of dilution of factors. And I have to clarify that the mini-pool are in 6 or 16 units pulled as the mini-pool and tested depends on -- depending on the test kit manufacturer. And these led to the decision there should be a conversion from mini-pool to ID-NAT, and this was a voluntarily decision by the blood establishments that should be a conversion from mini-pool test into ID-NAT test during the epidemic period. Based on the fact that the West Nile has low viral load compared to the other viruses, and that 25 percent of the West Nile are not positive specimens could not be detected by mini-pool, but only by ID-NAT.

In 26 of the detected samples by ID-NAT it had antibody which the majority of the antibody positive units required ID-NAT for detection. In 2004, based on these findings, ID-NAT was introduced in areas with high activity in human. And since the selective ID-NAT

introduction there have been three confirmed cases of West Nile transmission by transfusion. So FDA is considering whether blood establishment should implement ID-NAT in areas with high activity.

And I would like just to comment that the implementation of ID-NAT is desirable that this implementation should be a uniform criteria. However, we are currently lacking or have falsity of data to define our universal criteria to implement ID-NAT throughout the establishments. And there is an automation of -- platform automated available and these are in discussion. And there have been some volunteering proposal for introduction of ID-NAT. The current testing algorithm consist of mini-pool of 6 or 16 specimen being tested by either one of the two assays that have been used, and if non-reactive in the unit suitable, then they are released for transfusion.

If the mini-pool is reactive each unit composing the mini-pool is tested individually. And the units that are non-reactive go to the units -- if suitable by transfusion it’s released. If unit are identified as ID-NAT reactive, the unit is discarded the donor deferred for

a 120 days and additional tests are performed for the purpose of donor counseling. These additional tests have been repeat the NAT in ID format, obviously, using either the same assay used for screening or not a NAT assay of equal or greater sensitivity, and also perform antibody in the index donation specimen. I would like to call attention that the Red Cross activity for Flavivirus antibody among all the Flavivirus family of the Japanese encephalitis. The data that the blood establishment collected and analyzed from 2003 to 2005 show that these additional testing has a positive predictive value of 98 percent in the sensitivity of 98 percent. So FDA is considering whether blood establishment should retest ID donations by -- initial reactive donation by ID-NAT using screening assay or the alternate NAT with equal or greater sensitivity and to test the initial donation there are ID-NAT reactive for antibody to West Nile.

There are assays that are specific for Flavivirus but do not discriminate from West Nile Virus, and if that is the case FDA is considering whether blood establishments should perform West Nile specific discriminatory assay to determine West Nile Virus

infectivity.

So regarding additional testing algorithm mini-pool NAT will lead to ID NAT and it’s repeat the same NAT or antibody of the ID-NAT is repeat reactive the unit is considered, the donor is considered positive for West Nile and this is the end of the story. If antibody is positive or present then it’s considered positive for West Nile Virus regardless of not being repeat reactive in the ID-NAT, but if it’s anti-body negative or absent in non-repeat reactive then these units are considered false positive or true negative for West Nile Virus. In the studies that I mentioned to you from 2005 -- 2003 to 2005 followup specimen show that 2 percent of the true negative were in fact true positive because of sero conversion on followup. And moreover about 10 percent of the initial repeat reactive NAT are true positive on antibody in the (inaudible) somewhat the JE set of group vitis. It is not appropriate to consider the individuals through positive for West Nile. And we know that St. Louis encephalitis that belongs to the JE set of group is epidemic in the U.S. So there are sporadic cases. And I would like also to call attention to cross reactivity for these vitis, so

that posses a second level of caution.

Regarding donor counseling, due to the potential false negative results, it is desirable to inform donors with initial reactive result in ID-NAT about the possible infection with West Nile regardless of repeat reactive in ID-NAT or antibody positive because we know that about two percent to now to be true positive in follow-up.

Donors with initial reactive ID-NAT may be counseled and invited for follow-up. ID-NAT antibody takes at least 30 days after the initial reactive donation because there is a gap between affectivity and sero-conversion. Initial reactive ID-NAT donations may not be released for transfusion and donors should be deferred for 120 days. And the FDA is considering maintaining the donor deferral and reentry product retrieval and recipient notification as is stated in the guidance in June 2005 and this is the link for the guidance.

With regard to the ID-NAT triggering, what we call ID-NAT triggering is criteria to that will trigger implementation or conversion from mini-pool NAT to ID-NAT in areas with high activity. AABB has released a bulletin saying that there has to be a minimal criteria that that

should be in the frequency of initial reactive donations and that the action needs to be to implement ID-NAT and that should happen within 24 hours of identification of -- or the minimum criteria is met.

And a criteria to revert back from ID-NAT to mini-pool NAT again following seven days without repeat reactive ID-NAT that it is a repeat reactive or antibody positive. They identified that the missing link between the centers is communication between the facilities, and the communication plan is also listed in these bulletin. And the plan, it is to use existing testing sites that have data to the AABB website, these sites that collect such that are adjacent or have overlap collection, should communicate between themselves because the transmission in 2006 was actually a lack of communication.

There were two transmission of West Nile virus by transfusion and the tools for tracking and planning within and between agents, the site specific maps and location of -- based on donor residential zip code, AABB West Nile NAT-reactive donor website that the centers can enter and update on real time, and use the CDC and USGS maps with AABB virus or with avian in mosquitoes and human

activities to implement those -- this trigger.

It was also mentioned by the -- that the West Nile task force that these criterion needs to be in real time and feasible or otherwise it won't be done. What they are proposing now is two West Nile NAT-reactive donations in the rate of 1:1000 or higher and the no-blood center, which collections are lower than 1000 a week, it should use a weekly collection and combine the adjacent and overlapping facilities to take into account to meet their criteria and look at maps and reports from CDC.

It was also cautioned that the interval between the first and the second reactive unit or test in the mini-pool may be too long and maybe some of the units that still are positive in low viral load, that will be missed by mini-pool NAT. So, there will -- this system won't be perfect. And that the bulletin also referred to a defined area, which the criteria has to be applied and has to be very well defined. In that there are feasible and standard that has been -- method that has been listed and that was in the presentation. It is in these slides presented to the (inaudible), which should include the number of collections.

The committee discussions and comments, this was an information -- informational topics, so no specific questions were asked to the committee. However, there were no objections to the FDA considerations raised by the committee. The committee suggested that the ID-NAT should be used year-round instead of trigger by incidence of frequency of ID-NAT positive in a specific region. But the blood establishment representatives argued that the year-round use of ID-NAT would result in: increase false positive rates and donor deferral, because they are deferred for 120 days; incremental cost and exhaust the laboratory resources.

The importance of early and effective communication to facilitate quick and effective implementation of ID-NAT were exhaustively discussed. The committee stressed that the earlier triggers of ID-NAT is extremely important for the reasons I already mentioned. The committee also alerted that compliance will be challenging without FDA Guidance. And there were also public discussions regarding rate of transmission, donor follow-up and the need for data to evaluate the current criteria for implementation of ID-NAT. And I thank you

for your attention.

DR. BRACEY: Thank you Dr. Rios. This brings to light one area of responsibility of the committee and that is to make sure that if there are safety initiatives that they are appropriately funded in terms of the cost of blood. And we, in the future, will take a look at that because clearly I think that is an issue if we had Chagas testing and others, some sort of an adjustment will need to happen. Questions for Dr. Rios from the committee? Seeing none -- there is a question. Dr. Triulzi. Oh, Dr. Holmberg, I thought it was --

DR. HOLMBERG: I was. I thought he had a question there. Is there a West Nile test that is approved for cadaveric samples?

DR. RIOS: The screening, I'll say, for blood donors is approved for cadaveric specimens. It has been included in the clinical trials and had been approved, both.

DR. BRACEY: I'm sorry. Thank you. Then I will turn the microphone over to Dr. Holmberg who will have a discussion of Conflict of Interest.

DR. HOLMBERG: With our swearing in this

morning, I didn’t have an opportunity to state about the conflict of interest. However, I want to make it very clear that each committee member and definitely each government employee has been reviewed for conflict of interest. If there appears in any of the discussion that there is a potential conflict of interest, we ask the committee members to make that known in a transparent manner to their colleagues and also to the audience.

I ask the same thing for those that may come to the microphone for an open public comment. If there is a potential conflict of interest, I would appreciate you letting the committee know about that potential conflict. Thank you.

DR. BRACEY: Thank you. The -- we now move into the open public comment section. The first comment will be from the Immune Deficiency Foundation and will be made by Marcia Boyle. Marcia Boyle is the president and CEO of the Immune Deficiency Foundation.

MS. BOYLE: Well, Dr. Bracey, thank you very much for giving me this opportunity. I thank the committee for your concern over the last couple of years on IVIG access. I wish I were not here to continue

speaking about it, but I am and I particularly want to recognize Dr. Jerry Holmberg for he has helped our community in trying to get access to this life-saving product.

And we are the Immune Deficiency Foundation for 26 years, has been the voice of the primary immune deficiency patient community. And our diseases, I won't take the time to go over each bullet, but IVIG is the only clinically proven treatment for our disorders and essential to the lives of our patients and to many other patients.

The Immune Deficiency Foundation through the years for the last decade has undertaken credible independent surveys of the experiences of our patients and physicians. And I show this slide just to show the significance of IVIG therapy on our patients with the health status before diagnosis and then the health status after diagnosis in being on IVIG.

Last year, we undertook three independent surveys of -- to access the impact of Medicare reimbursement on access for our patients. And the first survey was a patient survey taken from our database and,

by the way, these surveys, if you read the ASBY (phonetic) study, many of our slides have been quoted, but I'm just going to run through a few of them that probably some of them have been quoted, some of them haven't.

But we took a sample of patients and then we did a Medicare overlay in order to compare both Medicare patient and private pay patient. And so the first slide shows that treatment -- different treatment locations since December 2004. And you can see that Medicare patients certainly have had to change side of treatment much more than the private insurance. Reasons for changed location, again, with Medicare patients, reimbursement is by far the largest reason. It is more convenience for the private insurance.

The site of infusion, where did the patients go, you can see in the Medicare -- the physician's office, a significant drop from 22 percent to 9 percent. They predominantly went to the hospital outpatient and the hospital clinic. Trouble getting IVIG since January 2005, well, our Medicare patients certainly are having more trouble accessing IVIG. And number of times treatments postponed, obviously more times for our Medicare patients.

The reasons for postponement of treatment: IVIG unavailable, certainly more than for our non-Medicare patients, reimbursement obviously almost twice as much for our private pay patient.

Patients experienced increased intervals between treatments, 18 percent for our Medicare patients, 12 percent for the non-Medicare patients. Reduction in dosage 13 percent as opposed to 5 percent. Another question of this as far as treatment of problems, since January 2005, you can see switching brands was almost equal, but treatments postponed was much more for our Medicare patients.

Negative health affects, 26 percent of our Medicare patients have experienced negative health effects as a result of getting or paying for IVIG since January 2005. Types of medical health effects, hospitalizations, more infection, increased antibiotics, new side effects, pneumonia, bronchitis, all impacting our Medicare patients to a much greater extent. We also undertook a survey of hospital pharmacists that was conducted last September through October. You can see current hospital use of IVIG, 71 percent primary immune deficiency. They are on

label in all other conditions.

Change in amount of IVIG dispensed by type of a condition, it is not a surprise that is has increased for the hospitals' primary immune deficiency, other conditions as well. Recent needs met by GPO allocation, you can see that only 28 percent say all, but you can look at this as it is certainly not an overwhelming problem with -- between most and all, but it certainly is a problem.

Turned away patients needing IVIG, at some point 32 percent of the physicians or the hospital pharmacists indicated that, yes, patients were turned away. We don’t know how many, but we know 32 percent say they were. Reasons for turning away patients in the hospitals, it was more product availability, staffing capacity, inadequate insurance. The survey mechanism really doesn’t dig deep into whether product availability at any cost or just at a cost that the hospitals could afford.

Hospitals with patient and treatment committees, priority protocols, only 37 percent had a P&T committee or a "priority protocol." Of the ones that had a priority protocol, 56 percent included primary immune deficiency and you can see some of the other priorities that were

listed. Average price paid for liquid IVIG, as you can see, the main price is below the -- the pay is below the ASP plus 6. It is a greater gap with the average price paid for the lyophilized product.

So the summing up, the average price is 4 percent higher than reimbursement for the liquid, and approximately 30 percent of hospitals pay more for the product, than they are reimbursed, and the average price is 15 percent higher than reimbursement and 57 percent pay more than their reimbursed for the lyophilized products. As far as the adequacy of reimbursement for IVIG by type of coverage, you can see that 62 percent say that Medicare is not adequate. Lower amount, if it is Medicare, was supplement and 71 percent Medicaid.

This was asked of those who said it was adequate, and of those who said it was adequate, still 5 percent or less, 29 percent say they still need 5 percent or less and 6 to 10 percent, 24 percent, and you can read the rest of the chart. Expectation about treating patients in the future who require IVIG, only 24 percent said they definitely will. We certainly would like to see that number higher.

We also conducted a survey with the American Academy of Asthma, Allergy, and Immunology, of their physicians on access and reimbursement, at about the same time in 2006, able to obtain amounts of IVIG to adequately treat PID patients. And, you know, the good news is in most cases they can get the product they want, not in all cases, but it is not a huge difference. Price of IVIG showing the medium, the lyophilized and the liquid that calculated the loss of ASP plus 6 for the average physician is about $1,000 a month. Summing up, the average price is 11 percent higher that reimbursement with 44 percent of physicians paying more for the liquid product when they are reimbursed and the average price is 19 percent higher than reimbursement, but 81 percent of physicians pay more than they are reimbursed. We use the fourth quarter ASP plus 6 numbers in this evaluation.

Effective Medicare reimbursement since 2005, 51 percent of physicians reported having patients changing site of care, 36 percent of physicians have had to reduce frequency of infusion, 26 percent of physicians had to reduce dosage and 36 have had patients who have experienced health problems because of reimbursement. The

effect of Medicare reimbursement on PID patients, as you can see, may several, you know, and one as far as hospitalization, emergency care, outpatient medical visits, increased telephone contact with the staff.

How serious is a risk to the patient's health are current reimbursement standards? 47 -- 56 percent, you know, feel that it certainly is a serious or extreme risk with about 90 percent with moderate included as well. This following question was asked of an earlier survey, survey done early in the year of the (inaudible) membership with the IDF really on treatment practices. This is not about reimbursement, but this question was put in. The same survey was done on the European Society for Immunodeficiency, and you can see as far as extreme risk, serious risk, moderate risk, slight risk that we have a uniquely American problem that Europeans do not see this as a risk and any way that our American U.S. physicians see a risk to patients.

And I also want to say that based on the results of the OIG and the ASPE reports, and the IDF survey data, I'd like to ask the advisory committee to go on record the Medicare reimbursement for IVIG is adversely affecting

patient access and health. I like to suggest that you suggest that CMS make a recommendation to Congress for adjusting the payment of IVIG and CMS keep the pre-administration fee at least until an acceptable solution has been reached. An acceptable solution is not as quoted in the OIG report, 41 percent of physicians unable to purchase IVIG below the Medicare reimbursement rates, and 44 percent of hospitals unable to purchase IVIG below the Medicare reimbursement rates.

That data was taken from the third quarter, after reimbursement had somewhat caught up with price increase earlier in the year. It is also unrealistic to think that prices won't go up again. If 41 percent -- 44 percent are the rosy scenarios, we should recognize that patients have even more serious access problems than the reports demonstrate. Thank you very much.

DR. BRACEY: Thank you. Questions or comments from the committee? Dr. Bloche?

DR. BLOCHE: The -- I felt the European comparison was interesting. Do you know what the pricing is in Europe where perhaps in, maybe Germany would be the most comparable country to ours in terms of its healthcare

financing system?

MS. BOYLE: I really don’t -- I think you'd really have to ask the -- probably the PPTA or the individual manufacturers. I mean, what I hear is that it is kind of across the board in some countries. You know, each country, kind of, has their own rates --

DR. BLOCHE: Does it tend to be lower than pricing here?

MS. BOYLE: Germany, I understand, could be higher. I believe that places like Spain and Great Britain are considerably lower and a number of countries are lower, but I don’t have the data.

DR. BRACEY: There's no comments or questions? If not, thank you for your presentation.

MS. BOYLE: Well, thank you very much for giving me the opportunity.

DR. BRACEY: The next presenter will be, let me get my -- Senator Abbie Cornett. She has represented the people of Nebraska's 45th district since 2005 after previously serving as a police officer in Omaha, and she will give us an update from the Alliance for Plasma Therapies. Thank you.

MS. CORNETT: Good morning, committee members, ladies and gentlemen. I'm grateful for the opportunity to address the advisory committee on blood safety and availability. My name is Abbie Cornett and in my life, I've had the opportunity to serve many roles. I served as an Omaha police officer for ten years, I'm a wife and a mother of three, and I'm the state senator for the 45th legislative district of the state of Nebraska, now in my third year.

I'm also the face of a patient with a common variable immune deficiency. My illness is something that I have kept very private in my life, until today. Today, I'm announcing publicly for the first time, because I want people to see what an IVIG patient looks like, what a success story looks like. I am one of the lucky patients. I receive my IVIG infusions as my doctor prescribes. I'm not as the reimbursement guidelines dictate. Consequently, I am a relatively healthy, hardworking, productive member of society.

Other patients are not so lucky. Their access to IVIG is being hindered. They are not equipped to advocate for themselves and thereby being damaged by the

continuing IVIG crisis, which is the reason for my being here today. I'm pleased to announce the formation of Alliance for Plasma Therapies. Members of the IVIG community have united to form the alliance because patient care has been compromised by lack of access to IVIG, because many providers are no longer treating with IVIG due to reimbursement restrictions and because no other organization exists to provide unified voice for all patients and providers of plasma therapies.

The need for this is critical. Reports recently released by the Department of Health and Human Services along with information from independent surveys confirm a serious decline in patient care. The studies have found, since the implementation of new Medicare reimbursement rules for physicians instituted in January of 2005, 42 percent of Medicare patients receiving IVIG therapy in physician's offices in 2004 had been shifted to other locations by the end of 2005.

In 2006, only about half of hospitals and physicians could purchase IVIG below the Medicare reimbursement rate. An independent survey of hospital pharmacy directors show that 32 percent of hospitals

reported turning away patients for IVIG treatments at some point during 2006. Another independent survey of hospital outpatient clinics and physician providers found that 14.4 percent had already discontinued their IVIG infusion services, and 45.4 percent plan to discontinue those services if reimbursements were not adequate.

Finally, home infusion services generally are not accepting new primary immune deficiency patients with only Medicare coverage because healthcare providers are not able to acquire IVIG at prices at or below Medicare part B reimbursement levels and because they are not reimbursed for infusion services. This data and more reveal the situation in which IVIG access crisis is placing patients and providers. Consequently, the Alliance's initial objectives include: 1) to insure fair and adequate reimbursement for all brands of IVIG in all sites of care, to update IVIG coverage and dosing guidelines for all diseases, to be an IVIG access information resource for patient and provider, communities, Congress, federal and state agencies and others, and to advocate to Congress and the U.S. Department of Health and Human Services for fair access to

IVIG.

The Alliance board of directors include representatives from our board community: Roger Kobayashi, MD, a clinical professor at UCLA who practices immunology in the state of Nebraska and is a national consultant to the Immune Deficiency Foundation; Jonathan Katz, MD, a neurologist who practices at Forbes Norris Research Center at the California Pacific Medical Center and serves on the boards of the Guillain-Barre Syndrome, CIDP International Foundation, the Neuropathy Action Foundation, and the California Myasthenia Gravis Foundation; Flemming Nielsen, general manager of Octapharma USA, a global manufacturer of products derived from human plasma; Patrick M. Schmidt, president and CEO of both FFF Enterprises, an IVIG distributor, and NuFACTOR, a homecare company providing IVIG services, and publisher of IG Living; and me, a patient whose health depends on IVIG therapy.

But I do not want to be one of the few lucky patients. I do not want to be special. I want to be one of the thousands of IVIG patients who are able to live their lives fully because we who are responsible for

serving them have made sure patients can have access to their treatment. They need to stay alive, to stay healthy and to live the life they deserve. This is our vision and as chairwoman of the board of directors for the new Alliance of Plasma Therapies, I will help bring a unified voice to the complex debate on solving IVIG access crisis.

We are looking forward to working with the advisory committee on blood safety and availability with Congress and with the Department of Health and Human Services, with industry, and most important with the patient and providers, who are waiting for a collective leadership to resolve our IVIG crisis. I encourage you to contact our board members for more information about the Alliance for Plasma Therapies and I thank you again for the opportunity to address the committee and for the work you do. Thank you.

DR. BRACEY: Thank you. Questions or comments on this presentation? Ms. Birkhofer?

MS. BIRKHOFER: Thank you Dr. Bracey. Thank you ma'am for coming and for testifying. I also, again, would like to acknowledge the Center for Medicare and Medicaid Services, Dr. Bowman, for, I think, taking an excellent

step in the right direction towards assuring access, the brand specific reimbursement. This is, I think, a little bit of a complex issue that has been before the advisory committee for, as Dr. Holmberg stated in his update several years now.

If I could ask would it be appropriate to have Ms. Boyle restate her recommendation to the committee and to check with this Alliance if Ms. Cornett or if she has any experts that could clarify if this Alliance has come to any recommendations with regard to IVIG access. And let's see if there is some synergies between these consumer groups so that the advisory committee could consider the input from the community.

DR. BRACEY: Well, yeah, I mean, that's an appropriate thing to do. I wouldn't think that we could do it right now. Perhaps if the two could get together and then we could look to see if there is some synthesis that we could look at later in our meeting.

MS. BIRKHOFER: Because I believe I heard Marcia Boyle state that to continue the pre-administration code, which was --

DR. BRACEY: Right.

MS. BIRKHOFER: -- extended in '07 and to also provide for a payment adjustment, and I guess I would really like to have the input from the Alliance on what their recommendations would be so that we could identify some synergies and have some alignment there.

DR. BRACEY: That's -- could you work with those two groups and then come back?

MS. BIRKHOFER: I'd be delighted to.

DR. BRACEY: Thank you. Yes, Mr. Matyas?

MR. MATYAS: Senator Cornett, what do you attribute the ability you have to have access to product versus the majority of people who haven’t?

MS. CORNETT: Insurance.

MR. MATYAS: Private insurance that pays?

MS. CORNETT: Yes.

MR. MATYAS: Did you have to change insurance in order to find someone who would pay?

MS. CORNETT: No. I am retired from the Omaha police department and have coverage until Medicaid and Medicare and my insurance company provides. But when we switched from one provider for the city to the other, I had to go through an extensive approval process and was on

a month-to-month approval basis.

MR. MATYAS: Thanks for that perspective.

DR. BRACEY: Dr. Bloche?

DR. BLOCHE: I'd be -- and this may be something that longer standing members of the committee know much more about. But I'd be interested in understanding more about the pricing strategies of the firms that offer the product, to what extent these prices are locked in by cost versus to what extent it may represent the opportunity to do so much better in the private insurance market that the companies will do better with a lower sales volume even that is lower sales volume because of diminished sales to Medicare. Anybody is familiar with the background, the business strategies behind pricing in the industry, I think that would be really helpful to know about.

DR. BRACEY: That's an excellent comment and from a previous meeting, actually I was coming back to some of the minutes, I had that same question and I don’t have an answer. But I think that is an important question. Yes.

MS. BOYLE: One of the other issues that came up when I first started looking at this problem in 1996 or so

is not just the manufacturers, but also the third party mark -- people who are providing it, which are not the same things. So I would just encourage us to look at both of those issues for the answers.

DR. BRACEY: Okay. If there are no more comments, we have one other presenter. Thank you.

MS. CORNETT: Thank you.

DR. BRACEY: And that is Mr. Corey Dubin. Mr. Corey Dubin represents the Committee of Ten Thousand.

MR. DUBIN: Thank you Mr. Chairman. Members of the committee, Dr. Holmberg, it is always a pleasure to address this committee. Committee of Ten Thousand has a special relationship with this committee. It was our original reach to Senators Graham and Kennedy asking for a Congressional investigation of the AIDS blood epidemic, which led to the IOM report, with recommendation too from the summary led to the establishment of this committee. We've been associated with the committee at every meeting and had people populated on the committee that we nominated for many years.

And it is very important and I think that Dr. Agwunobi set a tone this morning that we are very pleased

to hear. We have said that at times we think the committee has lost its client, the secretary. This morning, we are excited that we think maybe the committee has got its client back and can do some very good work. I would go back to a quote from you, Dr. Bracey that we have up in our office that you made when you sat on this committee before you were the chair. You once said, "Blood is to medicine as oil is to armies."

The committee would agree with you whole heartedly and we would say that everything we've heard today screams out for a national blood policy and this is the committee to establish that policy to inform the secretary who can then inform Congress and something meaningful can occur. We are the only so-called western democracy that does not have a national blood policy. And I think if we are talking about Chagas for instance, we cannot talk about Chagas in a vacuum from immigration patterns.

So we can look at the incidents in Southern California and say, "That's a hot spot." But if we look at some of the UCLA studies on immigration in a larger general sense, we understand that immigrants from Latin

America, Mexico and other countries have spread out all over the United States. So a focus in Southern California won't get us the answers we want. If we talk about immune globulins, and of course, we've always supported IDF's calls for more access, better reimbursement, better care. We were with IDF on the plasma users coalition on the mid-'90s, which was started by a group of us, but again, there is an issue that calls out for a national blood policy, a country setting the record and setting the parameters of what's important.

And I apologize for working from rough notes. We had a car accident on the way in and things got kind of shook up and I'm sorry about that. CJD, for instance, and Dr. Weinstein talking about the risk assessment, obviously we believe that there has been an apparent lack of interest in the hemophilia treatment centers about CJD or variant CJD counseling and education, again areas that could be part of a national blood policy. We could envision a reality where Congress passes a national blood policy. It is reviewed every, say, three to five years, right here in this committee which then makes recommendations for updating it and sending it back up to

be changed.

We strongly want to stand on this. We've been standing on it for many years, and maybe based on what Dr. Agwunobi said today, now it the time to really look at establishing a national blood policy and using this coordinating committee, which obviously the Committee of Ten Thousand feels is a critical committee and one that has so much potential, issues that have not been addressed, hepatitis, hepatitis C, the epidemic out there, the look-back that never happened. The issues are long and I don’t want to go through a totally large list.

It is our hope though that hepatitis C gets addressed in this committee now. We've never really done what we have to do and as with HIV, the hemophilia community is really a shoulder to -- a good piece of the -- the intensity of the HCV epidemic for many years. And it is time for the committee to look at it. But most of all, we were very pleased at Dr. Agwunobi's comments, but we would urge the committee to think in terms of national policy. The people sitting in this table are most equipped to do that. The organizations represented here are most equipped. The stakeholders, we have all the

stakeholders at the take and have a golden opportunity.

So we would urge you to look at that and we would remind you that the Committee of Ten Thousand is here, will be here, and are very pleased to see Ms. Finley seated and at the table as we think she can add a lot of good to this committee. And we thank you, as always, for the opportunity to address you and again apologize for not having our notes in a more formal way.

DR. BRACEY: Thank you. No apologies needed. Questions or comments for Mr. Duvan from the committee? If not, thank you again.

MR. DUBIN: Thank you, Mr. Chairman.

DR. BRACEY: We are ready to adjourn for lunch and we have notes from Dr. Sandler in terms of the possibilities. There are three in the building, I believe three. One is the faculty club, which is a buffet. The second is center grill, which is a cafeteria. The third is the food court, which is fast food. The fourth is the student's grocery store. Is that in the building or outside of the building?

DR. SANDLER: I very much recommend the faculty club, which is an executive dining room. It has got a hot

and cold buffet, Marriott managed. If you go out that door, take the card and come up. There is a cart that goes around. Everything is on the cart that's in the perimeter. At about this point is the faculty club. It is open to the public, hot and cold buffet. If everyone all of a sudden showed up, they are going to be overwhelmed and those of you who are at the end of the line may want to continue to the food court, fast food, pizzas and stuff, or continue to the cafeteria.

The fourth choice, students, you can get a ready-made boogie-mongus, you know, hoggie kind of sandwich. The very, very top floor of this place is one great big plaza. You can sit on the chair in the sun. It is informal, but the faculty club is way to go if you can get yourself in.

DR. BRACEY: Okay. Well, thank you Dr. Sandler. We will reconvene in an hour at quarter to two.

(Recess)

DR. HOLMBERG: As we all try to settle down for this afternoon's session there are several comments that I want to make. First of all, some of you may have lacked the --or seen the -- or I should say realized that there

is a person that is not here today. And that is Captain McMurtry. Captain McMurtry, went on retirement on April 6, and he is currently in Georgia. So, he is no longer with us. Lieutenant Commander Henry is taking a lot on, a lot of his responsibilities on. And Lieutenant Commander Henry had to leave this afternoon but Lieutenant Commander Henry's new title is Deputy Director of Policy and Programs. Also I want to mention that Dr. Laura St. Martin could not be here today, and Dr. Ruth Solomon is here in her place. And she came in after we made the introductions. So, I wanted to make sure that everybody was aware that she was sitting at the table here. Okay, thank you.

DR. BRACEY: With that, we will move into the afternoon session. And this afternoon we are going to have a major focus on systems for accessing transfusion and transplantation safety. First presentation, we are very pleased to have an international representative Dr. Luc Noel, who is a public hospital -- a medical practitioner specialized in hematology and blood transfusion. And he has worked extensively with the World Health Organization. And he will present his view and

their view of the global status of transfusion and transplantation safety. Thank you.

DR. LUC NOEL: Thank you Mr. Chairman. Ladies and gentlemen, I'd like to thank Dr. Holmberg for the invitation to WHO to contribute to this committee. I would like also to express my own personal thanks for benefiting from the experience of this form of searching for progress. I was asked to discuss about the current state of safety in transfusion and transplantation. And that first slide is provided to me by my colleague Dr. Neelam Dingra, who is the coordinator of the Blood Transfusion Safety Unit at WHO. I am myself in the same department of Essential Health Technologies in charge of a unit called Clinical Procedures, which, inter alia, is responsible for cell, tissue and organ transplantation. And we work together.

What is safe blood? Well, you see here the component, donor selection, screening and testing, process, and proper clinical applications. In other words safety, quality, efficacy of the health product of human origin that is what we're -- what is about today, best clinical practices, standards, safeguards against

unexpected adverse events and reaction. And this calls for an involvement of health authorities. This is the first operating paragraph of the resolution adopted by the World Health Assembly in 2004, about human organ and tissue transplantation. Member states are urged to implement effective national oversight of procurement, processing and transplantation of human cells, tissues, and organs, including ensuring accountability for human material for transplantation, and its traceability. This is arch-clear, it is not transplantation, it is not only the matter of the physician, surgeon and the patient. It involves the community through health authorities. Safety involves regulatory authorities and oversight.

What WHO has as tool to assess the global situation? There is the global database on blood safety, a well-established tool. There is the global knowledge base on transplantation that we put up in the last years with four components. The four (inaudible) transplantation is but the first is activity in practices, the second legal and organizational framework, and third threats and responses both from the area of safety and ethics. These tools have limitations. Describing the global situation

is a slow process but a necessary one. Yet, we have shortfall because of incomplete national consolidation. Because of poor hospital records for transfusion in particular. Because of cross boundary exchanges and we know the situation in tissues where this country, I understand, is exporting tissues to more than 30 countries the world over. But a country like Sri Lanka has exported 36,000 corneas over the last decades, in almost -- more than 60 countries.

This is improving because of consistent work. The global database of blood safety of 2004 - 2005 exhibit is not yet analyzed and finalized but will include better precision. And the global knowledge base on transplantation is now being expanded with the help of the government of Spain. And we have set up with the national transplant organization there. A global observatory of donation and transplantation. It is important to provide access to this and the global -- to the public. And the global knowledge base of transplantation at this moment is available on WHO website with its components.

This slide is provided by the world transfusion safety unit and its epitomizes the main issues at global

level. Lack of access to vital transfusion. 81 million donations and you can see in the free categories of countries according to the human development index, how large is the gap between available donation and the population. There is a time (inaudible) factor between organ transplantation and blood donation. These are 2005 estimates of kidney transplant, liver transplant, heart transplant around the world. And one can see related to population the very same distortion, inequity between regions. With obviously, well predictability considering the difficulty to -- of deceased donor donation, Asia but also Africa for economic reasons.

A better look at WHO regions, the six regions you can see separated by color. With histograms where the number of kidney transplanted either from deceased donor in dark blue or living donor in lighter shade, shows the discrepancies between region. The Western Pacific region on the extreme right has the bias of including organs from executed convicts in China. The activity is not only one -- is not the only thing to monitor long-term outcome. And we made a point to put this on the website very early. Long-term outcome reflects the success for the patient,

which is the goal of our activities. And this is -- and since this is from the literature aiming at showing the one-year kidney graft survival, whether the kidney comes from a deceased donor or a live donor. I just wanted to stress the importance of outcome.

When it comes to safety, the basis is testing. And in the area blood with the large number of donation that have to be used, testing is incomplete. And it's distressing to see that 21 percent of -- no, it is not percent. Twenty-one countries still do not succeed in testing 100 percent of the donations for HIV. And this is explained by inconsistent procurement of screening tests and lack of resources whether human, organization, or at country level. In the area of transplantation, we focused on transplant tourism, defined as patient, surgeon, donor, vendor traveling for the sole purpose of exploiting a vulnerable individual to obtain an organ. And this is a source of danger for the recipient. And this is one of the latest paper outlining how the source of organ is associated with risk for the recipient and obviously, as we are all aware of, irrespective of the country where it happens, loss of health and income and stigmatization for

the exploited individual.

This is a very fast survey and I want you to turn this, this is ongoing and essential. We believe this is a key tool for prioritizing, it's a key tool for involving the public, it's a key tool for involving health professionals with whom we cannot progress. And when it comes to vigilance, the involvement of health professionals is vital. The other topic Dr. Holmberg suggested is areas of commonality with blood product or progenitor bone marrow tissue and organ. And we have -- and we have had for a long time slides like this one. Obviously, the order, the area, the surface of overlap can be discussed and justified differently. But the root is the same, the human person and the concern created by this human origin are shared more or less by all these products.

The main issue, the overarching issue, yet remains the ethical one. And there is a need for consistency between products heath products of human origin and consistency around the world. If I come back to my slides the gametes and donation of sperms and oversights -- the fact that there is payment for these is

used as an indicator that organs could be paid for in the same manner. There is place for discussion and thinking there. Among these products the -- obviously, the closeness to the human being is very different with some of them being industrialized in their process. And is in a situation to be called plasma-derived drugs to some extent. But whatever the process the origin and the necessary traceability for -- A known and suspected and expected issue remains to be kept.

Ethics, sale and purchase I will quickly touch. The question of availability of the human body. Simply, the person as a means rather than an end, are questions that have to be discussed at a time where the globe is -- well, the circulation for transplant tourism turns around the globe and everyone, whatever the country, the level of development, and the culture, the background; is involved. This implies that safety of the live donor is also to be put on the forefront. Payment is often a way to buy out any responsibility for the follow-up of the live donor. Invasive procedures vending, donating a right liver lobe obviously, implies more risk and generates questions. And we would like to see data from these individual in

countries where this is a practice. But it also goes for much simpler collection and regular blood donation from anemic donors as seen in low and middle income countries is in itself a concern like the need to follow up carefully GCSF stimulated donors of progenitors or stem cells.

Consent and protection of the vulnerable, equitable allocation. All this properly dealt leads to public trust and public preparedness to give as much as to receive. These products have in common risk and one can map them against categories. This is not pretending to be exhaustive but just to remind that beside transmission of donor's pathogen and disease diseases, besides microbial contamination; a process well known with tissues, besides immunological incompatibility, there may be physiological interaction that are responsible for unsolved -- in unexpected adverse reaction. There may be toxicity risks of process and even those aiming at getting rid of infectious risks. And there maybe, and this is an important question to be settled, altered functional properties of these products. And the question is do we carry out enough preclinical trials to feel confident in

this area, leads to one reply. We need to improve our vigilance of this material.

Obviously, and the past has taught us, how important recurrent serial disaster can occur and the risk of recurrence can be in a gravity indexed as an extra dimension. Therefore, one needs obviously, guidance and safety requirements and this is an (inaudible) memoir for for very basic essential minimally processed human cells and tissues for transplantation that is available on WHO website. But as is described in our guidance to set up select tissue transplantation service it is essential owing to the associated risk to monitor adverse reaction in-patient to allow corrective and preventive action.

This is the latest I found -- the latest information about the risk associated to transplantation that I came by chance to be aware of, and by chance I had the opportunity to inform transplant specialists of the this possibility. It is a LCMV-like virus identified in Australia with the input of US teams. You never know. Hemovigilance is a need, biovigilance is a need. Hemovigilance, which has been recognized as a good practice for somewhat longer time is developing in

countries. This is one of the data of the latest version of the global database on blood safety, the 2004 - 2005 preliminary data that Neelam Dingra, kindly gave to me. And it shows how the hemovigilance is increasingly seen as a necessary component of a transfusion service at national level.

If there are at national level vigilance system, there must be international collaboration, to improve sensitivity denominators, to improve relevancy. Donors are circulating, products are circulating there is no way to stick within the boundaries of one given state. And to improve dissemination, alert, and information that could bear on the safety of services. This has to be a two-way exchange between all types of countries. The outcome of research in wealthy countries will be based on the experience in tropical areas, where of resources are not at all at the same level. It needs to engage all stakeholders, health authorities, regulators, public health agencies. But also, operators, health care staff, scientific and professional societies. It is important to associate everyone each in his role but never leave one of the players beside.

This is important for the circulation of information, for its generation as well. And this need for collaboration extends to other vigilance. Vigilance for devices that are needed to blood banks for example. Devices or ancillary products needed to preserve organs for example. And there is an obvious link with those in charge of infectious disease vigilance starting with my colleague at the alert and response for outbreak in the Infectious Disease Department of WHO. This has been picked up by our consultation process and the -- at WHO for cell and tissue for transplantation. The first we had in Ottawa and vigilance and surveillance were seen as necessary to incorporate at an early stage because of the reason we quoted. And not only adverse events reporting but should include active and comprehensive surveillance. That's the reason we use the term vigilance and surveillance. Vigilance is the attitude, surveillance the method.

It should be the opportunity for valuable collaboration. Point already made. And the need for international exchanges. The second, global consultation on obligatory requirements for human cell and tissue for

transplantation that was few months -- last summer in Geneva. Noted that many countries are in the process of developing systems for vigilance and surveillance. There needs to be a global aspect for vigilance. To ensure a proper and timely reaction. The question went into more concretely what are the tools necessary an inter-communicability between national and regional programs is a requirement. WHO GKG can play a role in this and it was recalled the importance of the EUSTITE project was recognized. I will spend a few minutes about the EUSTITE project. This stems from the European directive the 27 members of the EU have to implement a directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissue and cells.

By the way, the preamble it is stated that as tissue cell therapy is a field in which an intensive worldwide exchange is taking place, it is desirable to have worldwide standards. This has translated in technical directives from the Commission providing, in one of them the second one, providing guidance on adverse

events and reaction reporting, traceability and coding systems. And the European Commission has funded a project off called EUSTITE dealing with inspection, and vigilance, and surveillance involving 12 partners in Europe under the leadership of the National Transplantation Agency of Italy that will run between December 2006, and November 2009. You can see more on its website, which is simply EUSTITE.org. It associates 12 national agency or regulatory authority. In any case, they are competent authorities for inspection either for gametes and embryos. The directive -- addresses includes gametes and embryos with cell and tissues. Or tissues and cells. And this is Italy, Ireland, Austria, Spain, France, Slovakia, Poland, UK, Bulgaria, Denmark, and WHO.

What was the place of WHO there? WHO is the main partner in the development of a model for the reporting and investigating of adverse events and reactions. We started this with forming a vigilance and surveillance medical advisory committee with the European partners. And we made a point from the very beginning one to have observers both from the US with CDC and FDA, and Canada with the Public Health Agency of Canada and Health

Canada. The next meeting in Rome in July 2007, will be enlarged to have a global representation of low and middle-income countries from all regions in order to progress towards guidance simple basic tools that would allow to have a common language, globally, for vigilance and surveillance.

Besides this, before I conclude, there is the issue of coding. Coding in the Geneva Regulatory requirements for human cell and tissue for transplantation was recognized as an indisputable need for globally standardized labeling and coding, coding and description for tissues. The opportunity to work in harmonized way before individual countries or region to develop disparate systems. And WHO could play a role in this.

What was acknowledged as a very positive milestone was the commitment to one global coding system for cellular therapy products, that is ISBT 128 by relevant scientific and professional societies at global level. And when we had at the beginning of -- at the end of March this year in Geneva, the second global consultation on critical issues in human transplantation at large. The first one was in Madrid in 2003, November

2003. The title -- the subtitle of this one was, Towards a Common Global Attitude to Transplantation. Two key points came up. First, the quality and safety are key issues of human cell tissue and organ transplantation since risks are real. Surveillance will be put in place based on traceability, maintaining confidentiality, and codification to critical prior steps.

There was a strong recommendation to WHO to lead global traceability by producing an international shared coding system for organ tissue and cell. This meeting, last March, was the culmination of our consultation process on updating WHO guiding principle on transplantation. The date back to '91 they considered the ethics of transplantation; we added a few technical one. I can't help reading the draft from the 10th, which addresses, on the one hand the procedures, on the other hand the product. The quality of care, safety and efficacy of procedures are mandatory for a donor and recipient alike. The long-term outcomes of cell, tissue, and organ donation and transplantation should be assessed for both the donor and the recipient in order to document the benefit and harm for recipients and any harm to living

donor.

The level of safety, efficacy, and quality of human cells, tissue and organ for transplantation has have products of an exceptional nature, has to be maintained and optimized on an ongoing basis. This requires implementation of quality systems including traceability and vigilance with adverse events and reaction reporting. This we shall present, propose to the meeting of the WHO executives board in January 2008, as this is the three points engaging our governing bodies in the world health assembly.

With those guiding principles we hope to be -- to come up with a draft resolution in two of these points will be to the executive board to encourage the creation of a global network of collaborating centers on vigilance and surveillance for cell tissue and organ transplantation. And for WHO to facilitate the adoption of a common global basis for coding system for cell tissue and organ for transplantation. Thank you very much for your attention.

DR. BRACEY: Thank you doctor. We will open up the floor for questions and comments from the committee

members. Dr. Kline.

DR. KLINE: Thank you very much both for coming and presenting this. Clearly, the time is right. It seems as if Europe is organizing very well in terms of surveillance even in terms of coding and some slower countries like the U.S. are thinking about it. But it seems to me that it is extraordinarily important for the developing countries to play a role, not only for their own safety, but also as markers for what we may be seeing in the developed world, part of a whole network. Does WHO have any incentives either financial or otherwise to help assist countries that simply can't do this, nationally, because of resource issues?

DR. LUC NOEL: Well, a number of points. The first one, as you saw, we will involve developing emerging countries in the Rome meeting and will be very careful to disseminate our progress and involve the global community at large. We convinced from the beginning that this being identified by developed countries could in fact lead because the threat is at global level. Because also, we want every (inaudible) we want every country to reach the same level of service. When it comes to financial

support, you know, WHO is not a financial agency but a technical one. But then there may be -- take the coding system, coding system is of course an advantage when you use code bar not to mention radio-frequency and sophisticated non-transcription mechanism, but yet with simple IT and handwritten numbers and check digit it can already be an improvement in traceability. In fact, it's putting -- it’s making sure vigilance, surveillance, traceability are part and parcel of the basis package for any country.

DR. KLEIN: It sounds like you made a strong argument for the vigilance system in terms of identifying new risks that are posed by transplants, and as well as transfusions. In terms of, for example, that case that you presented with the arenavirus virus. How accepting are the transplanters, you know, you have the issue of putting together not only countries but within countries other constituencies, and it seems that at least that's been fairly well received based on the gains to be had. So, could you comment on, you know, how much difficulties you’ve had in terms of trying to explain or to impress people of the need for this sort of a system.

DR. LUC NOEL: I don't know if there is specific difficulty. My feeling would be that there is an enormous goodwill because this benefits the patient and the whole system is oriented to the patient. Not to mention, the live donor of course. And the time is ripe to better organize things, to improve communications. I could translate my response and there is a communication gap. We do not communicate enough, whether to involve the public or to involve healthcare professionals in what is a resource depending on it.

DR. KLEIN: Okay that is good point.

DR. BRACEY: Yes, Dr. Kuehnert.

DR. KUEHNERT: Thanks for the excellent presentation. I just wondered, thinking back to the slide you had on hemovigilance, countries with hemovigilance, and had it divided by the development of the countries. So under highly developed, most countries had a hemovigilance system. There were some that said, no. I am assuming the United States is in that category.

But I'm wondering for those that said, yes, have you looked at those countries to see what sort of systems

they had in terms of them being government-run systems versus systems, which are done -- we've talked a lot about public-private collaboration. Is there any model for that in other countries, or are they all just purely government-run?

DR. NOEL: No, I don't have the data to respond to this.

DR. KUEHNERT: And the other question I had was, you know, as we talk about those sorts of collaborations, what sort of collaborations does WHO have in trying to create global collaborations with non-government organizations that may have global reach?

DR. NOEL: Well, the scientific and professional societies are playing a key role there. The -- because of their global involvement, because of their expertise, because of their ability to communicate differently, let's say, and in a complementary manner to health authorities, this is one of the reason there is an added value in making sure everybody is onboard.

DR. KUEHNERT: I agree, thanks.

DR. BRACEY: Additional questions for Dr. Noel or comments? If not, thank you very much, I enjoyed it.

The next presentation will be by Dr. Michael Strong, and it will take a look at the U.S. status of transfusion and transplantations safety. Dr. Strong is well-known in the world of blood banking. He is the president of the AABB. Currently, he is Chief Operating Officer of the Puget Sound Blood Center, and was instrumental in founding the Northwest Tissue Center out of the Puget Sound Blood Center.

DR. STRONG: Thanks Art. Just from a personal note, excuse me, it's kind of fun to be in this position right now having spent my whole career in transplantation, tissue banking, bone marrow transplantation, cord blood, et cetera, et cetera. So it's kind of all coming together. I think Mat has described it as the perfect storm, we'll see it. And also will say that I do have some strong recommendations to make.

(Laughter)

DR. STRONG: Sorry about that, but everybody does that for me. So I have -- once in a while can use it myself. I do have a conflict of interest, of course, because I come from a blood center that does all of these things. So we're, the Puget Sound Blood Center is not

only a blood center and distributor, but we are a transfusion service, we provide crossmatching services for all the hospitals in Seattle.

We are cord blood bank, we are tissue bank, we do histocompatibility testing for all our organ transplant programs in the region. So we have a bit of action in all of these things. But today I'm speaking on behalf of the AABB.

And just to warn you, I think you're going to find some common themes in the speakers that you hear in the -- today, and this afternoon, and tomorrow, because basically we were all given the same question. And so, we're probably going to be answering it in much the same way. And even Luc, who comes from the other side of the ocean, has already started some of the themes that will be developed here.

AABB's mission includes practice of -- and standards of transfusion medicine, and we've expanded that in recent years to include cellular and related biological therapies. And within this cellular and related biological therapies, we've included tissue. In fact, if you go back to the mission statements of AABB, 10 or 12

years ago, tissue was actually in the mission statement there, it has only more recently gained prominence. And I think we have heard this morning, that often this comes about in response to problems, and we obviously have had a few problems in the last couple of years that needed to be addressed.

(Slide.)

DR. STRONG: This has already been put up as a slide, these are the areas that we're looking at, blood components and derivatives. The cellular therapy products including marrow, cord blood, and peripheral blood progenitor cells, along with tissues and organs. We all do have a common goal, and my theme here just to cut to the chase, is that we agree that there is commonality and a need for a national strategy to deal with this.

Ultimately, we're all dealing with a common goal, a donor and patient safety, and of course availability, which of course, in itself is a safety issue if it's not there. And efficacy is another issue that I think we all have in common. Now, the common risks to address are essentially two in nature. They are infectious risks, which we actually know quite a lot

about, and the noninfectious risk, which at least in the U.S., we don't know a lot about, except from the experience that we've gotten from our colleagues elsewhere.

(Slide.)

DR. STRONG: This is a slide from a paper that we published a couple of years ago, in *The New England Journal* that compared tissue donors and blood donors. And in this case, I have put up the first-time blood donor, because that's probably a fairer comparison, which demonstrates that the risk is quite considerably higher for the tissue donor only in the sense of when we look at the donor coming into the process. Because remember that tissue is highly processed, and risks are reduced on the basis of the processing steps as well.

But in terms of the prevalence of infectious markers, HIV, HBV, HCV, et cetera -- clearly tissue donors, although safer than the general public, when you compare those, do have a higher risk status than first-time blood donors. The same can be said of the -- in terms of risk calculations, we know actually quite a bit because it's been published extensively that the risks for

blood donors are in this range, the highest at this stage being HBV because we have not instituted universal minipool or nucleic acid testing for HBV.

For this, tissue donors, just recently, they have begun testing for HIV and HCV. I would argue that we should be also doing NAT testing for HBV. But here again, the risk assessments are based on prevalence of marker rates in these populations. The same comparison has been done for stem cells. This was data compiled by Dr. Stramer (phonetic) and several of us, including the National Marrow Donor Program, putting together the prevalence rates among different donors in the HPC category, so cord blood, progenitor cells, autologous cells are used for transplantation.

And in this situation, it was a comparison to look at risk assessments using minipool NAT testing. And in fact, the comparisons made between whole blood donors and combined HPCs, there were no significant difference in prevalence rates for the markers with the exception of surface antigen. And I can tell you that the primary contributor to this high rate in the HPCs are the cord blood donors, which had a higher rate statistically.

Rates for autologous blood donors are and have been from the beginning, much higher than the volunteer blood donor. Now in terms of reporting of the noninfectious risks, we've already heard this morning about TRALI and the risk there. These are reports to the FDA that really are recipient fatality reports. And you begin to see here some of the noninfectious risks, such as non-ABO hemolytic reactions, and ABO hemolytic reactions that occur, and the mortality rates. This is likely to be underreported, and it doesn't -- it certainly doesn't cover all of the noninfectious risks that we know about from other reporting systems.

And that gets me to another strong recommendation, which is that we need to have something like this. We don't have it in the U.S. The hemovigilance network has been going on for quite some time. We're about 10 years behind many other countries including France in terms of a global reporting system for risks, both infectious and non-infectious. Now, to be fair, most of these countries are -- have government-sponsored health care systems. These reports are done through government funding, and that's not something that

we've had in this country.

So we have a somewhat broken-up system for reporting in the United States. But it is one of our intentions in AABB to try to establish a hemovigilance, which actually we're calling biovigilance because of the very topic that we're talking about today. We think there is a lot of commonalities between tissues, organs, stem cells, and blood.

Well, in order for us to sort out, what are the noninfectious risks, and what can we learn? We learned this is data from Denmark, and I think it lays out in general what the remaining risks are in one country. They vary somewhat from country to country. The big one here is the incorrect blood component transfused. In other words, that's generally a clerical errors, misidentification of patients, misdrawing -- getting the wrong blood in the tube, et cetera.

I started out in blood banking in 1964, and our biggest error in 1964, was a clerical error, and that hasn't changed, much like transfusion of plasma practices, that hasn't changed either. Now from the SHOT data in UK, they've calculated a risk assessment based on the

reporting system in the UK. And you can see here our mortality at one in 250,000, which is about 10-fold what we know about the risks of transfusion in infectious disease, such as HIV or HCV. Major morbidity and serious hazards are much higher. Unfortunately, we don't have that data in the U.S. because we don't have a system for monitoring, we do not have a vigilance system.

I wanted to point out, however, in terms of mortality that Transfusion Associated Circulatory Overload (TACO) is number one in the UK, that doesn't even show up on the FDA list. And I think it's certainly underreported, and we don't have good ways of monitoring that. Now, I've -- this is information that I've put together actually from personal experience in terms of noninfectious risks for tissues and cellular therapy products. There is a common theme amongst all of these as well, which would be for organs and tissue graft failure, of course, is of concern.

It's different for different kinds of tissue, ranging from mechanical failures, non-unions, or loosening, and with -- particularly with large bone grafts, non-unions is an issue, incorporation of the bone

product and failure of graft. We don't have good surveillance systems for dealing with that. Immune -- rejection is primarily a soft tissue issue, and even more specific than that with heart valves, particularly in the pediatric population where we know rejection takes place.

There are also technical issues that banks have to deal with. For example, mis-measurement, giving the wrong-size graft to the surgeon, mislabeling, for example, a surgeon has ordered the left femur and opens up the package with a patient on the table and it's a right femur, that's a problem. So those issues also occur. In the cellular therapies arena, the same -- some of the same issues are there. Graft failure certainly is important, immune rejection. Here graft-versus-host is something somewhat unique to cellular therapies. But, of course, in blood transfusion, graft-versus-host also can occur.

Technical issues are also an issue for all of these various products in the cellular therapies arena that includes counting errors, processing errors. A big one is a bag breakage because these units are frozen, and if they show up in the transplant ward and they thaw them out, and the bag breaks, you have a problem. Mislabeling

is a common problem. I mentioned tissue, it's also true for cellular therapies and of course there are side effects relative to administration. Luc mentioned the issues of toxicity for tissues. We don't really know much about the side effects of some other treatment measures that are taken for tissue, such as high dose of radiation or solvent/detergent treatment and residuals.

Well, we talk a lot about -- in the blood world, we talk a lot about layers of safety, and these actually are the same areas that Luc has already mentioned. We all have these issues in common. I'm going to talk in comparative terms between these categories. So we start with donor screening and eligibility. That's true for all of us, collection or recovery, infectious disease testing. We generally use the same batteries, there is processing steps, there is labeling steps, traceability has been mentioned, and I'll talk a little bit about that.

We also have to deal with transportation, with storage, temperature monitoring, surveillance of quality. And the area that we're needing to shore up quite considerably is this area of outcomes analysis and adverse event surveillance, which we don't do a very good job of.

Well, let's start with donor screening. Of course, we have FDA regulations, and certain private standards apply with associations such as the AATB and the AABB.

We actually use similar donor history questionnaires, pretty much adopted from the blood industry by all of the agencies that are involved with this. Donor screening and testing for infectious agents is actually quite similar. And of course, in some cases donor counseling doesn't always apply for the tissue donors. We're not talking about counseling the donor in that situation. But in some cases, families are actually informed about infectious risks.

In terms of collection or recovery, there is a informed consent process, there is a certain amount of sterility testing, either microbiological or in terms of bacteria or viruses. For blood and HPCs, we have the common apheresis collection process that's essentially identical. And we -- I'll deal with both allogeneic and autologous collections for organs that would be living, related donors but for bone and tissue and blood, autologous products are also involved.

Now that's not entirely intuitive, but if you

work in a hospital and you're dealing with a bone flap from a head trauma case, and trying to figure out how to deal with that, autologous tissue is a big issue and has resulted in serious problems because of it.

(Slide.)

DR. STRONG: Here is a little chart basically, to compare, and I'm not going to spend much time on this, but again, it's the same battery of tests essentially. There are differences. Some have not been required, for example, HBV NAT is not required on the tissue side.

West Nile is not required, although the blood donors are all being screened now. Most of the tissue donors are being screened. Organ donors is variable across the country, primarily because of access to the laboratories and also timing, getting test results. Chagas' is relatively new and is developing, so we're not sure whether that's going to be required at some stage. In terms of in-process testing, ABO and Rh Types are involved on the tissue side, less so, but certainly with heart valves, ABO and Rh testing is done.

We screen for antibodies in both CT products, and blood products requiring cell counting, amount of QC

is done for red cells and platelets or CE34 analysis for cell products. There is some HLA typing and I can tell you even for tissue that we have done HLA typing for once again, heart valve recipients when there has been a rejection. There is in-process testing, for example, for freeze-dried tissue using residual moisture detection.

And all of us worry about microbial contamination. The one addition for CT products would be cell viability, it would be of course, platelets on the blood side require cell viability as well. In terms of processing, cell separation is a common process for the cellular and blood products, not so with tissue. So there are certainly differences. Cryopreservation is employed in all of these fields. We have to deal with storage, transportation, quarantine of untested, unreleased products, and of course, labeling is a key, and we'll talk about that, because that really relates to traceability.

Now the labeling issue, and Luc has already introduced the concept of ISBT, the blood industry is moving in that direction. AABB has set forth a requirement that implementation take place by 2008. Internationally and nationally, amongst the tissue and

cellular therapies organizations, the discussions are ongoing. I would certainly support a standardized procedure, because at this stage, labeling is not standardized certainly for tissue, and it's needed if we're going to get to traceability.

There is a North American Tissue Technical Advisory Group that's working on investigating ISBT for finished allografts. It's complicated by the huge variety of allografts that are present in the tissue arena. Traceability is probably one of the big issues particularly for blood, and I have put a little data here that was generated by AATB actually. And for tissue, the key is the return of the transplant record. Now, we really only trace to the hospital and in some cases, with the transplant record we can identify who the surgeon was that received tissue.

But you can see the great variability in terms of the return of the transplant records to the tissue banks themselves. I put this one on there of course, because that's us and we like to brag. But you can see that as low as 14 percent of return records, which makes, of course, traceability quite difficult. So

identification traceability is related to how these records are managed.

(Slide.)

DR. STRONG: Transportation, we have the common issue to limit deterioration to maintain proper temperature because these require certain temperature monitoring. We have to have controlled and validated packages, and temperature control and monitoring is a similar issue for all of us. Labeling to ensure appropriate handling has just been discussed. And as Luc mentioned, international shipping is more of an issue for cell products and tissue.

But the concept of going to ISBT for blood relates to the same issue if being able to transport globally.

(Slide.)

DR. STRONG: Storage, I've already mentioned and, you know, one of the points to be made here is that the joint commission now has published standards on management of tissue in hospitals because that's where the deficiency really has been in traceability for tissue. The tissue banks can trace it to the hospital, but once it

gets in the hospital, sometimes it gets lost, because it goes to multiple surgical specialties.

The new joint commission standards require the hospitals begin to get control over this, and because they're asking for control of storage monitoring and record keeping, often within the hospital, it's the blood bank that gets tapped. Now, they are not always totally accepted -- accepting of that. Dr. Klein has already pointed out that he doesn't need that extra work. But in fact, the skill set resides in the blood bank, and AABB has now been working on developing guidelines and tools to assist blood banks in managing tissue within the hospital.

(Slide.)

DR. STRONG: Now the surveillance part really has to do with not only adverse reactions, but product quality. And I can tell you from the tissue perspective that one of the great advantages of having a high return on graft records is it gives us a much better way of monitoring quality and determining when there are problems that occur with the grafts that are distributed. So for the CT products, tissue engraftment is important. And they have begun to set up better systems for monitoring

when engraftment becomes a problem. For tissue, of course, graft function is an issue.

The adverse event reporting has to deal with both donor and patient on the -- in the system. And of course, there are reports that go to the FDA through different mechanisms. What we've been missing in the U.S. has been a hemovigilance system which we, at AABB in concert with several of our government partners in terms of a taskforce it's been established this year, and built within the AABB strategic plan for establishment of a biovigilance system, which actually will be a public-private initiative. And that discussion is ongoing as of this year.

So in terms of adverse events surveillance, again we have some very common issues across these product lines, infectious diseases, mis-transplantation, bacterial contamination, a lot of the noninfectious risks of febrile reactions, graft-versus-host disease, immune reactions, TRALI and TACO has been mentioned already, which may be unique to blood and particularly plasma products. But there are lots of things in common that need to be managed.

Now we can't talk about adverse reactions without also saying that we also need to make sure that we have an adequate supply, that that's a -- really a safety issue in and of itself. And it's already been mentioned that fair reimbursement is also critical to have access to these materials. So in common, I am making a strong recommendation that there ought to be a strategic plan. And it really ought to be a public and private initiative. We all have the patient's safety in mind.

And really focusing on the similarities was the key here taking note of the -- that of course there are significant differences as well. But with the commonalities that exist, we do believe that a common strategic plan is needed.

DR. BRACEY: Thank you Dr. Strong. It seems to me that from your presentation and Dr. Noel's presentation that the absence of such systems really represents an oversight, because one cannot assure quality in the absence of having such systems, and so there's much work that needs to be done. Questions from the committee for Dr. Strong. Dr. Bloche?

DR. BLOCHE: Racing through Congress now, is a

bill that will give the FDA a much bigger role in vigilance with respect to drugs over the long haul, will make a variety of counter surveillance that were voluntary and not much done, obligatory. To what extent does that legislation apply to these products? And to what extent have you been involved, if at all, and you are shaking your head, in trying to shape that legislation to expand it to these products?

MR. STRONG: Well, we haven't been involved on the pharmaceutical side. I think that there is a role to be played here. In terms of associations, we don't have the deep pockets to be up on the Hill doing the lobbying. I think that this committee and other advisory committees can play a role in addressing some of those policy deficiencies, you know, certainly hemo -- biovigilance is a key one for us. We think it's important, we think it's the only way we're going to be able to address particularly these other risks that other countries are addressing well that we haven't been able to address here in this country. So we've talked about legislative initiatives and work on the Hill. I think that's another public-private opportunity.

DR. BRACEY: Thank you. Additional questions or comments? Dr. Kuehnert?

DR. KUEHNERT: Well, I just wanted to maybe modify my quote from perfect storm to perfect opportunity. So maybe if we can do that and not miss it, it will be a good thing down the road. I guess, I wanted to just, maybe suggest some things about the last question. We at CDC have been, you know, looking at not only the so-called biologic products issues, blood, organ, tissue, but also at drugs, vaccines, devices, all are sort of medical interventions that as WHO puts it, that -- they need to be looked at. But there are commonalities, but there are also big differences that need to be kept in mind.

Also, the legislation, it sounds like just looks at what FDA regulates. And of course, when we're just even talking about biologics, you know, that there is some important categories we wouldn't want to leave out. So I don't think we can completely look at that paradigm as a solution. But I wanted to ask Dr. Strong about this public-private partnership and put him on a spot a little bit. I mean, how do you see this actually working? You know, just maybe if you can help the committee understand

with some examples, they might get a better idea of how feasible it is, because no other country that I know of really has that. And we're unique, and there is a lot of reasons why we are unique in the way health care is administered. So how would it work?

DR. STRONG: All right, so how much time do we have? Well, as you know, we have a steering committee that was established by AABB that has all of the stakeholders, we think, at the table to discuss how that might work. We've been working our way through those issues, identifying what it is that we want to capture, and how we would capture it, and how that data could be accessible to all of the agencies who want it, because I think most of the government agencies, who have been at the table, would like to have access to that data.

We've had difficulties in figuring out how to get reporting system. So should it be voluntary or mandatory, you know, of course, as AABB, we think, a voluntary system ought to be the one to go for. We've not had good luck with mandatory system. In fact, at least with AABB what it ends up happening is that we lose membership, because people don't want to be held to

certain standards.

So I do think that there is an opportunity, there is an opportunity for public funds, and private funds. The government has problems dealing with funding from year to year, and changes of priorities by different administrations, and access to resources. But they do have some, the private industry also has access to resources.

Obviously, the big question as to why we haven't been doing this before has been all about how we're going to pay for it, and who is going to pay for it because there is no mandate to -- for it. And nobody wants to put out additional resources when we're all strapped.

So I think that by coming together, sitting at the table and saying, first of all what do we need from this system, what are the goals of this system, and coming up with common and agreed upon goals. Then we move forward for how we develop it, and where it should be. Should it reside inside government, outside government, with government access and input.

Those are all parts of the discussion that we've been going through this year, as you know, because you're

on that steering committee. And we have FDA representation, and we have HHS representation. Everybody is at the table, and I think that's important to start the process.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: Yeah, Mike, thank you also for this very comprehensive overview. Can you comment -- you mentioned the key role of record reporting. And it's been heard from time to time that we have a successful model in hospital-based infectious disease reporting, because we have infectious disease epidemiologists in hospitals. And I just wondered if you could share any thinking from within the task force about the concept of an epidemiologist to report on events related to transfusion and transplantation and whether that it is a kind of simple unifying solution?

DR. STRONG: Well, I think that's the -- that would be maybe the long-range goal. We've talked about transfusion safety officers in hospitals for many years. The question has been how do we pay for it. So I think what we've -- the way we've approached this is that we've got to start at somewhere, and we want to keep it simple

to begin with, to show a feasibility. So we are talking about a pilot study with a limited number of hospitals, with reporting by those who are committed to this kind of thing, usually in the transfusion service, where these reports come.

Now, ultimately, the -- probably the Quebec system is a good model, because they've decided to put the money into putting essentially transfusion service -- transfusion safety officers in every hospital who monitor these kinds of things. And clearly, transfusion and transplantation could be a part of somebody's role. That's how the infectious disease networks work. They've got ID people who monitor these things and the reports come through that system.

That's a much -- I think, bigger job, longer-term job, much more expensive job, when we haven't really even figured out how to set up a database to collect this information, I see that is one that we would like to strive for, but it's going to be much more difficult. Because we -- first of all I have to figure how we're going to pay for the system to begin with.

DR. BRACEY: Dr. Klein?

DR. KLEIN: It does occur to me that although the AABB really has taken the leadership role here, and I think appropriately has taken the leadership role and in many ways government has not. We have a very nimble national system of epidemiologists that has done really world-class work, whether it is West Nile virus, or HIV, or Yersinia contamination of blood components. Perhaps a bit under-funded, but it seems to me that this might be an area where this committee could help to determine how that very nimble organization might assist in biovigilance over the long term.

DR. STRONG: Well, I can tell you that Mat and I have become good friends over the last few years, because -- I think we talk about once a week. Usually it started out with tissue, but it has expanded in that view. And I think it's been a good partnership, because we've -- the blood community has worked with CDC, the tissue community has worked with CDC and that's been an important partnership. But I also know that Mat is a one-man band down at the CDC. And the budgets as you know Harvey have not grown, and in fact they have gone down in the last few years. So it's a challenge for -- for the CDC to manage

this.

Now we've had actually very good comparisons now that AABB has set up a bio -- our first attempt at this was setting up a bio -- biovigilance website for reporting West Nile and now Chagas. And by the way I didn't mention that, but for those of you interested in Chagas you can go to the website at AABB and see where the Chagas reports are coming, and which ones are being confirmed and where they are on the map.

That has been a partnership which I think has been very important and the task force that was generated from the West Nile epidemic included FDA and there has been very valuable discourse between us in the development of that. The reporting system is very interesting, because with the web-based reporting system we get almost instantaneous reporting. With the public health service network, it takes months to get those reports through.

So it has actually been the -- the private part of this that has helped CDC focus on, where epidemics are occurring and where to focus attention through their public health service network. Because that is also a network of 50 states with separate systems reporting, and

they don’t report all the same way. And that’s going to be our challenge, is that we have this disperse and not standardized reporting system.

DR. BRACEY: Dr. Solomon, you had a question?

DR. STRONG: I am going to take up your whole afternoon.

DR. BRACEY: That’s all right.

DR. SOLOMON: I actually have a comment and a question. I would like to mention that the Center for Devices at FDA has a program called MeDSuN, Medical Device Surveillance Network. And it’s a voluntary program where they have individuals in hospitals monitoring and reporting to them adverse reactions and there is a tissue component that has tagged onto that now with about 35 hospitals participating in that. And there -- we have gotten adverse reaction reporting, which is a requirement now for tissues through that mechanism.

And my question is could you expand a little bit on your last bullet of about significant differences as you see them?

DR. STRONG: Well, I think the significant differences deal with the adverse reactions, so for

example, a transfusion associated circulatory overload is really not a problem with a tendon graft, so that's a difference. So there are specific tissues that have different kinds of adverse reactions of -- a femur may have a problem; there may be a problem with non-union or fracture with femurs, loosening of screws, that sort of thing, that's not a problem for blood transfusion.

So there are significant differences, we can't ignore those and there has to be a reporting system to identify those kinds of adverse events as well. But there are also lots of commonalities and what I wanted to focus on today were the commonalities.

DR. SOLOMON: I would just like to mention that when I think of significant differences, some of them that come to mind are the risk, benefit ratios, whereby -- and the availability of organs and tissues. Those are important considerations, particularly for instance, certain cell products require HLA matching. So I think those aspects of it need to be kept in mind.

DR. STRONG: Yeah, and that was my point really, is it there are lots of commonalities and that was the focus, but there are also differences and we do need to

pay attention to those as well.

DR. BRACEY: Okay, I think we'll go ahead and then give Dr. Strong a break. Thank you for your presentation. Our next presenter will be from America's Blood Centers and he is actually a former long-standing member of this committee, Dr. Celso Bianco. Dr. Celso Bianco is the Executive Vice President of the America's Blood Centers, and he will present their perspective on the U.S. approach to safety.

DR. BIANCO: Well, thank you, very much. It's a pleasure to be here. I tried to prepare a presentation that is a touch challenging in a slightly different perspective from the other ones, but I hope you understand it as constructive, even if at times it may sound a bit critical. First, many of you in the community may not know, but America's Blood Centers is an old organization, it is an association, a network of 77 individually licensed blood centers, both in the United States and the two centers in Canada.

Together they collect about 9 million donations a year. And they collect about half of the blood supply, the other half of the blood supply in the U.S. being

collected by the American Red Cross, and all the blood supply in the -- in Canada. And the members are involved in every one of the areas that we are talking about today, expect -- for directly for organ transplants.

The questions that we received from Dr. Holmberg and everybody is trying to look at, are very clear and they focus mostly on what we have been talking about, they are the commonalities among the several products that we -- biological products that we either transfuse or transplant. But one of the questions that I tried to address a little bit is the third bullet -- is it sustainable? How to improve it in the future and is there a need for a master strategy.

When we think about the current state of safety we could say that blood is an -- and these -- many of these, other procedures are safer than they have ever been, this seems to be the common way that we say it. But I -- the concern that I want to express is, can we sustain it? And in order to sustain it, we'll have to address what is happening in terms of financial resources, people, investment in research and development, innovation, standards accreditation, regulation, and ultimately

availability that is without blood, without tissue, without organs, we wouldn't be here. And I don't want to look a little bit in that perspective. For instance about -- with financial resources.

Blood collection and transfusion -- and I'm going to focus on blood, that is our major activity, is a mature industry. It's not like pharmaceuticals that we are having a new product introduced in the market. Every year we have 50 million whole blood collections, and if we look at the AABB and the HHS survey, it's been flat between 2001 and 2004 and my feeling is that it is still about the same.

We have a couple of million aphaeresis platelets, it increased between 2001 and 2004 about five percent. But again, there is little prospect for further growth. Then who are we for the big manufacturers of the products that we use to do our job? When we look at J&J, Abbott, Kyorin, Roche, less than one percent of their revenue comes from the things that we do. The profit markets for projects that we produce is way below those of pharmaceuticals.

And so the interest that those industries have

on what we do is quite limited. Hospitals -- in the same way, less than one percent of the hospital expense is blood. It's five to fifteen percent of the patients on the other hand are transfused. But if we look at blood, the hospitals will try to address with the blood centers the question, because blood being the biggest budget item in the laboratory budget, that in trying to avoid increases in prices they are difficult.

And the blood centers themselves are not-for-profit organizations, low margins, and low reserves. When we look at what happened to the price of blood products, what I have is from 1995, I don't think that is easy for all of you to see it, but the red line is the price of -- the average price of a unit of red blood cell since 1995. And -- okay, that's good, thank you.

The red line is a price of unit of red blood cell since 1995, adjusted for inflation, and the green line is the leukoreduced red cell. And each one of those errors is some event that left to an addition of safety that led to a corresponding increase in the price of the unit of red cells. And so if we add a new HCV Assay, a new West Nile Assay, the prices will correspondingly

increase.

But if we look at this over twenty years, it's a very stable, very -- there is nothing attractive from the point of view of markets to that picture. The same thing in term of margins, we had a very difficult time in the '90s in terms of the way blood centers interacted with hospitals and they priced their products, and so the margins of the blood centers suffered tremendously.

While the hospitals also have very limited margins, that is that you cannot compare with the margins of other industries between four-and-a-half, five percent. Blood centers had a very difficult '90s, started improving in 2000, and reached -- still lower than hospitals where we are now a margin of about between four and five percent.

The fact that these financial resources are not there, affects other areas. There is no new money, there is limited ability to pass on costs, there is limited ability to invest, the current generation of leaders is ageing, if you look at Dr. Strong and myself --

(Laughter)

DR. BIANCO: Small number of training programs

for physicians and PhDs, shortage of technologies, technicians, few training programs, no funding available for biovigilance, as Dr. Strong just mentioned, and limited internal resources to support R&D. The prospects for innovation also are not great. Manufacturers of test equipment and software are few and shrinking. There are two manufacturers of screening assays only. And they are both in trouble, either financially or from the regulatory point of view. Limited competition, higher prices, less innovation.

Companies are -- I'm talking about the ELISA test. They are also two manufactures for the NAT -- for the molecular test, and that's it. When we look at the Untied States and we look at what happens in Europe, we have -- it's incredible, the difference, the number of companies that are entering and working on this field. The number of assays that are available in every aspect of what they do.

Companies are focused here in the Untied States on a short term. They have very limited R&D. Gone is the time when a company would have a hepatitis program, where they would be searching for hepatitis viruses that had not

been discovered as yet. Today a company will develop a test only if they had indirect guarantees from the FDA that may be this test will be mandated one day and Chagas is one of those examples.

And venture capital has disappeared from our field. Look at what happened; they poured a lot of money in oxygen carriers and pathogen inactivation. These went on for many, many years, they didn't get anywhere. So they are very concerned, they are very leery about approaching us in terms of investing into new technologies, into innovations. A lot of it is related to what we deal with risks and our perception of risk and how we set our priorities, and I think that one of the major issues that this committee has to address is how we set priorities in our field.

I just want to remind you over a note -- paper that was published in *Science,* twenty years ago exactly, by Slovik (phonetic). And I think it's one of the most interesting approaches to understanding risk by putting this graph in plotting things in terms of a risk that is known or unknown risk, and in that you put a voluntary or involuntary risk, a risk that is associated with dread or

no dread.

In that paper he puts that certainly, the biggest unknown and most dread risk that you could identify at that time, was three-mile island time, was nuclear reactor accident. It's put auto racing as a voluntary risk, with a little bit less dread. But certainly saccharine was not something that the population would be willing to consider a risk. And a home swimming pool that is one that was at least at that time one of the biggest -- I don't know if it is still today. Biggest causes of accidental death of children were simply ignored in that list of risks.

If we look at what we do I arbitrarily added the things in transfusion that I felt that would fall into each one of the quadrants. Obviously, we talk about Ebola and vCJD, and they are up there. HHV8 since we don't know it, but there was a paper published in *New England Journal of Medicine* few months ago that everybody ignored. It simply didn't fly as a risk. We have a number of risks that are known that like B19, HBV, HCV that we -- but they have no dread, that the population is not scared of them. On the other hand we have HIV that we know a lot about

today, but is still a risk associated with a lot of dread.

Unfortunately, there is a lot of expect -- or an unfortunate affect -- there is an expectation of zero risk by the public and by the recipient advocacy organizations. The accreditation organizations, the regulatory agencies respond to those expectations and this is obviously, and the policy decisions are justified by the precautionary principle, essentially that if we can do something about what is happening, let’s do it, and we will talk -- and touch, but what this perception does with this graph, I think, is very interesting.

Everything is dread, everything is terrible and we become unable to setup priorities, what is the thing that we should address first or last. The environment -- the regulatory environment is another one that certainly affects the development and the future. Certainly, the environment is risk adverse and in over the years from HIV to Vioxx, or peanut butter, or pet food, certainly, there is a focus, particularly in organizations like the FDA on keeping things safe.

And that’s what is expected from the population, from the politicians, from the government and from all of

us in a certain way. In my opinion regulators are, and I don't know if this is true, I'm just giving you my opinion, are terrified of making mistakes. And they are, in many situations, are forced to apply the precautionary principle, that is, take the action before data are available without the balances of risk benefit or cost benefit. And they tend them to take very strict regulatory measures, attempting to prevent all risk is not just most risk, there is no balance.

And so if we talk malaria, or if we talk West Nile virus and we heard today the report, we screen 15 million donations a year. We had three transmissions in three years, 2004, 2005, 2006. And we are focusing all the efforts that we have in preventing a repeat of these three transmissions. Does that make sense from the public health point of view?

Compliance issues also affect safety. We still --- because of the way the law exists in the United States for licensure, the fact that Dr. Epstein actually reminded us today that depend -- that the changes depend on the sponsor, the company that manufactures the test.

The regulatory authorities have no power to tell

the company to do this and that, but still major part of the blood supply in the United States is screened with a second generation assay for HCV. Europeans look at us astonished. They say that we are 10 years behind in this technology, and in a certain way, they are right.

What is also interesting observation is that the regulatory agencies have become more active, and if we look at all the guidances and everything that comes, they have gradually taken over territory. They used to be privileged of the accrediting organizations, the standard setting organizations and today we have many practices set in as guidance for regulations that before were just part of standards.

Obviously, the accrediting organizations, in order to preserve their mission, attempt to preempt regulatory action. Each one has to be more strict than the other one, and then we have a lot of inconsistencies, both between standards, between regulations, or even within different regulations by different portions or parts of the system. For instance, we cannot screen cadaveric donors for some agents, because -- theoretically, because there are no assays available that

have been licensed as for that purpose.

We have discrepancy between requirements for individual donor NATs for blood donors versus that blood donors can be screened on pool NAT, but donors of -- the same donor that donated platelets today donates a stem cell tomorrow for a transplant, that donor has to be screened in a different way. And there are guidances for screening today that are being issued, essentially the accrediting organization in blood, so that is, the AABB is issuing guidance in bacterial detection, West Nile virus, screening for T.cruzi that were before just then by the FDA.

In terms of regulations, and now I come for priorities, not -- I do not want to discuss necessarily the merit of each one of those. But an FDA officer gave a presentation to ABC a couple of months ago, and gave us a list of what they consider priorities, regulatory priorities that they were -- that was our request actually, that they were trying to attend. And I put the list, that is in blue, but I put in red the ones that we really agree that are serious priorities.

Testing for syphilis antibody, in my mind, is

not a priority. Reentry for NAT, for HIV-1 and HCV are guidance, that is, in the works for the past five years. Yes, that's an important priority. Use of NAT for West Nile virus, we are all part of this system. We have been doing it in collaboration with the industry and the manufacturers and the FDA, and certainly guidance was the least important of all those things.

We have as priorities updating the donor assessment for malaria risk. That's where we lose between one and two percent of our donors. We are waiting for abbreviated uniform donor history questionnaire, so not to torture the donors that donate frequently to our system, they have to go to this forty-some odd questions with sub questions every time that they come and donate.

We are worried about our computer systems, which are not being updated at the speed that the field of computing is going. While today, we buy our computer and it comes already with this stuff, most or none of the computer systems that are currently available for blood banking even use windows. And the manufacturers are not interested in coming to review, because they consider the regulatory process burdensome and the market small, the

number of customers too small to spread the costs of managing that.

Let’s go back now that I’m coming to the end of what are the areas of commonality. Yes, there are many areas of commonality, this has been extensively discussed. Maybe, one difference is that one we collect with needles, the other one we need some little bit of surgery to get the material. But even in that sense when we look at the regulatory system in the United States, I -- it’s -- I know that these -- there are historical reasons that led up to that.

But it’s hard for somebody outside to understand that we have an office of blood research and review looking at blood, an office of cellular tissue and gene therapy independently looking at tissue, and stem cells and cord blood, and another HRSA looking at organ transplantation. And it would be hard to find commonalities when we have three different interests.

Is there a need for a master strategy? Definitely, yes. We need a forum for development of common priorities involving regulators, regulated parties, manufacturers, clinicians, product recipients, and we need

also to do it on evidence-based decision-making. I think there is a substantial tremendous role that this committee could play in helping us set these priorities.

All of us have to agree on what these priorities are to be. We have to focus on quality processes, not just products, and we have to fund both operations research, discovery research. We have to be willing to manage risks. We all have to share some risks in search of new technologies, and new levels of safety. Otherwise, we will never try something new. We'll just stick to the old stuff, because we are afraid of trying the new stuff, and this has to apply to blood tissue and organs.

How do we involve the stakeholders is all of us, we need transparency, workshops, open meetings like this one, documents, dockets, increasing participation of experts at BPAC meeting, despite the regulatory issues that these may represent. We need to increase the appropriations for FDA with focus on the evidence-based regulation. They -- all these agencies FDA, CDC are under-funded particularly in our area.

And this is for instance, there is no fee-based system, there is no PDUFA, or MDUFMA for blood and blood

products or for tissue. And increased appropriations for NIH-funded research in transfusion medicine and transplantation. And ultimately, something that I hope we all have in this room is the willingness to change those things and a little bit of sweat. Thank you.

DR. BRACEY: Thank you, Dr. Bianco. Questions from the committee for Dr. Bianco? Dr. Holmberg.

DR. HOLMBERG: Well, thank you, Celso. As always, very thought provoking. I was going to ask you early on, about the prioritizations, especially when you did your perception of risk and then when you got to your presentation, your comment about a forum for establishing the development of common priorities. I really would like to ask you, what would -- what do you think that looks like? How would we do that, what would be your suggestion?

DR. BIANCO: Well, I -- what my suggestion would be on a practical -- I don’t know if it is possible, but I can talk about a fantasy I have.

DR. HOLMBERG: Okay.

DR. BIANCO: The fantasy is that Dr. Epstein would bring to the committee his list of priorities, and

the committee would help him set which one goes first, which one goes next, and which one goes next, so that we could get -- they could get input about not only what the regulators perceive as a priority, but what the users, the community, the patients and the community of blood centers and tissue banks perceives as a priority. I know that from the regulatory, from all -- it's just a fantasy, but that's what I'd like to see.

DR. BRACEY: Comment or question from Dr. Pierce?

DR. PIERCE: Celso, thank you for that presentation. You know they say that those forget about history are doomed to repeat the failures of the past and I think in looking at evidence-based medicine which is extremely important in today's society, one also has to look at the humanistic side of evidence-based medicine.

Where does the evidence come from and who is one the frontlines of supplying that evidence and that's where the, maybe the rubber meets the road, and I think we can't forget about that either. If you try to assess risk, using evidence-based medicine, the evidence comes from those whether they are donors or recipients who are at the

highest risk of having whatever it is you're looking to provide evidence for, and that's the dilemma.

DR. BIANCO: I couldn't agree with you more, Glenn, but that's why I think that we need a mechanism to do that. As you have 20,000 hemophiliacs in this country, being exposed to a poor product with something that could be there, that could simply affect all of them in a matter of days, and you have three cases of West Nile transmission in two years.

You need a mechanism to be able to say, which one of them is going to be my focus today, and which one will be my focus tomorrow, and that's what we don't know how to do today. We haven't learned in face of -- because exactly of this human side, we have a tremendous difficulty, because for us one is too many, and -- but the resources are unlimited, the people are limited and how do we decide which one comes next.

DR. BRACEY: We have two questions and comments, one from Dr. Epstein and then Ms. Finley. Dr. Epstein.

DR. EPSTEIN: Well, you know, obviously, Celso, you've been both thoughtful and provocative, but you've also, sort of put FDA at the sort of, center of the storm,

and I'm not sure that's really the correct focus. I think that, you know, FDA responds to the demands of many, many stakeholders. And the regulated industry is certainly an important stakeholder and they are -- you know, lives on the receiving end of regulation per se, but it's not the only stakeholder. And you know, we're listening to the voice of the patient community, and various other parts of our society.

I think that with regard to the fundamental problem has to do with acceptance of cost and acceptance of risk, and I think that the fundamental problem there is that we don't have a well-articulated or well-established framework in which to resolve the issues of that nature. It's not to say that we can't get at them, you know, Congress can legislate, FDA can regulate, but I think we have difficulty doing so because they are inherently political, but they are not the kinds of issues that the political officials wish to embrace, generally speaking.

There is too much risk to those officials to own those kinds of issues, so it's hard, but I think that FDA is then left attempting, under the mandate of science-based regulation, to solve many, many problems that are

inherently social and I think that that's a core issue which we've not sorted out.

I also would draw attention to the issue of time lags. There is perhaps a misunderstanding when we presented at the ABC SMT meeting, the annual scientific meeting, our list of priorities. We were in essence telling you the work products that are in the pipeline. Now, some of those work products were yesterday's called Celebra. It's just that they're not today's hot issue, but we've made progress on those issues and so they are in the pipeline.

I mean, just to pick syphilis as an example. I know and you know that there has been at least a two decades long debate, do we still need to screen for syphilis, but that's really not what that document is about. What that document is about is dealing with the donor that has a reactive screen when it's a specific treponemal antigen-based screen. It's a very specific technical problem that needs a regulatory solution and the users care.

Well, it's not today's hot issue, but when we first approved treponemal-based assays, it was an outcry,

where is the regulatory posture on the use of these assays. So what you're hearing is that the regulators simply don't forget there issues. You're looking at the accumulation of effort over long periods of time to address issues, each of which, you know, had their day in the sun.

And I think that it -- what's lost here is sort of the time lag effect, and you know, I tell, you know, my colleagues that it's because of a rolling snowball effect in regulation. Now, once we are involved in an issue, the issue grows on us, and it grows on us because it acquires dimensions and you know, you have a draft and you have to finalize and then you have maintenance, you have to update, and so on and so forth. So when we say these are our priorities, we're telling you that we are trying to complete the work on the things that have been put in front of us.

We didn't invent them, they were at many, many times the hue and cry of a stakeholder, including yourselves as stakeholders. And I would particularly draw attention to the hue and cry of approximately a decade ago that we not be casual about recommendations that you know,

and so now we have, you know, regulations for good guidance practice, which create certain time demands and resource demands. And also we are under, you know, a GAO recommendation from 1997, to move all relevant guidance into regulation.

So I think that I'm simply saying all this to illustrate that the situation in which we live is complex. I'm not really disputing your fundamental point, which is that there is a need for a global priority setting. I would specifically dispute one thing though. It's not an FDA policy to adhere to the precautionary principle, that's a misunderstanding of what we're -- what we think we are doing.

We think that we take prudent measures based on available data, balancing, you know, risks and benefits, and we don't feel as if the precautionary principle is ever prescriptive to us. So we don't actually refer to it or cite it, as a basis for policymaking. That's not to say that we are never attempting to be precautionary, and it's not to say that we aren't attempting to be proactive which incidentally were recommendations to us from the 1995 IOM report. But we don't think that we apply the

principle per se.

We think that what we tried to do is take advantage of the available science to do the best we can in whatever issue is emerging. And it's fully cognizant of the fact that we may have to revisit it and change track. So again, whereas I accept your basic premise that there is a need to examine priority setting and that it should be done in a broader context of, you know, costs and risks and benefits. I do take issue with the suggestion of how we go about this and why it's so wrong, because I think that the situation is simply more complex than you portrayed it to be.

DR. BRACEY: In the interests of time --

DR. BIANCO: May I just --

DR. BRACEY: -- rebuttal.

DR. BIANCO: It's not necessarily a rebuttal because I agree with 99.9 percent of what Jay said. Actually, I don't blame FDA Jay. I blame the law that created the FDA.

(Laughter)

DR. BIANCO: You know, you have a law that is focused on products and licensing products, and each

product becomes an item, and these items cannot be compared to the next item, and you cannot say that this one is more important or less important than the other one. You have to follow your deadlines for licensure with all products in the same way regardless.

Yes, you can speed up a few of them, but I think that that's what in part is the cause or the reason why you have to follow that process, all over with everyone of the items, be it critical today or not as critical today. The only thing last that I like to raise, we want to help and I think that this committee can help and if we could help set those priorities in a different way, I think we would and we would all get closer to the world that we want to see.

DR. BRACEY: We have a comment and a question from Ms. Finley, and then we'll take a break. One thing that I think is clear though is a major area that we will have to consider is really looking at benefits. The data for the mere activity of collecting data is really not going to get you anywhere and I always go back to what was the origin of the infection control officer, and it was really sort of a reactive process to bad processes and

hospitals that caused deaths and increase in cost.

And clearly, I think that there must be something within this question that we're grappling that would yield benefits for both patients and economic gain, but we will talk about that later. Question and comment from Ms. Finley.

MS. FINLEY: Thank you Celso for an exciting mid-afternoon antidote to the unusual slump. I had a couple of comments and then a question. I think that you really hit the nail on the head with your perception of transfusion risk. That's your assessment of it, but I think many people in the room would put, particularly HBV and HCV, in other categories, so I think that that's a good illustration of some of the issues that we have here not only historical, but some of the contemporary matters that we're dealing with.

In addition, there was a formula put forth in the IOM report adopted by the department in sworn testimony before the Congress, regarding the appropriateness of decision-making in the absence of definitive scientific information. I think Dr. Epstein did an excellent job of summarizing it, but the department

is behind that, and every member of the committee should understand what that formula is, as you did when you were kind enough to contribute as a member of the committee.

But in the absence of absolute definitive data, we are to make decisions using precaution when it's appropriate, and I think that the failure to do so is the reason we are all sitting here today. I have one other question, that got to the heart of the economic stress being placed on blood centers, and having done some work in that area, and knowing that the AABB did an extensive amount of work in instructing blood centers in how to utilize all the codes and appropriately bill.

Because they were leaving a lot of money on the table unfortunately and there were some revenues owed to them and that they could access. Can you tell us how the ABC and/or the industry as a whole have dealt with that issue and continued to deal with that as we're moving forward.

MR. BIANCO: Well, the big part of that work was made by AABB and we have to recognize that. We all participated in the effort. But certainly -- now, the issue there, Ann Marie, is that there is a delay, there is

the -- the coding is there, the reports are submitted to CMS by the hospitals. But until this is reflected in a change in reimbursement and particularly in the in-hospital DRG, where you have a blend of 300 different things that fall into the same DRG and blood is this little thing, this -- for the hospital, when it negotiates with the blood center, it's hard to translate that into something that really brings more revenue.

The hospitals are as strapped as we are and I think that that's a little bit of the difficulty in the whole system. The only way by which prices have been raised is not because we decided that we have to invest in the future but is because we had to add another test or another procedure. And it would be nice if we could change that paradigm, but I think it will be very hard to do it with the structure that we have today, unless Dr. Bowman has some other answer that would --

(Laughter)

Dr. BRACEY: Okay. With that, we'll take a 30-minute break and we'll --

Dr. HOLMBERG: 15.

Dr. BRACEY: Well, we'll take -- we'll reconvene

at 4:00 o’clock.

SPEAKER: Okay.

(Recess)

- DR. BENJAMIN: –- represent our views on transfusion and transplantation safety; it's a particular pleasure to follow my two senior colleagues who have given you the industry viewpoint. I'm afraid I only view -- I only represent the single blood supplier, and that is the American Red Cross that does collect and distribute over six million units of blood each year in this country to over 2,000 hospitals.

The Red Cross is actively involved in transfusion safety research through internally funded programs at the Holland Lab, and our regions as well as through collaborative programs with the NIH-funded REDS Program, and through analysis of our Internal Donor and Recipient Complications program, that I should remind the committee is the only nationwide but center-based hemovigilance program in the U.S. at this point in time.

Okay. Page down, how do I get to the next page, page down –- seems to be frozen here, frozen in time, I'm afraid, these aren’t working –-

SPEAKER: Get rid of the volume.

SPEAKER: That's why you're having feedback though. The volume on there was the –-

SPEAKER: Okay.

DR. BENJAMIN: My focus today is going to be on transfusion safety, the Red Cross is no longer involved to any great degree in transplantation. I will try and draw on the commonalities of the other cold blood and tissues and organs.

The second –- third question here is a scientific or clinical evidence to support a master strategy for transfusion and transplantation safety. I think that the question is reframed as, “Is there evidence of any unmet need in patient safety?” because that's it, that is I believe going to be the only evidence for need for a master strategy. Just to sum up we do believe in the Red Cross, that this is the case, there is evidence to support a need.

Here we go. Okay. So the blood supply is safer than it has ever been. I think we all agree with that? It was true in 1996, and it's true today. It is interesting that in the last 10 years we have implemented

a large number of safety initiatives, and we continue to do this with the introduction of male plasma and leukocyte antibody testing over the next 18 months.

What this really highlights to us is that the statement is a relative statement, and patients are not really interested in relatively safe blood. They are interested in an absolutely safe transfusion service.

So as we think of a master strategy, clearly we need a vision and a mission for that strategy, and I would posit that we need to jettison this statement. We need to actually have as a vision and a mission, a concept of patient safety that surrounds appropriate use of blood, the right product for the right patient at the right time, ready availability, and finally product safety in a more absolute sense than a relative sense.

So what are the threats to blood now, and how safe is blood now, and that's -- the rest of my talk is going to focus on that part of the discussion. I mentioned that the Red Cross has an active hemovigilance program that we started in early 2003. This program, looking at the data for a year of 2006, we had close on 700 adverse reports –- adverse event reports made. It's

interesting. If you look at the gross reports, and the high probability reports you get a reflection on what were the physicians' concerns and what are the actual threats?

The concerns through the gross data, shows you that TRALI is clearly the most frequently reported adverse event to the Red Cross. Second comes infectious risks such as hepatitis C, hepatitis B, HIV; third is sepsis, bacterial sepsis, and to a low degree hemolysis allergic reactions.

This is kind of the level of what are the physicians' concerns about blood. If we actually look at the high probability cases, the cases where we think that the blood product actually was involved, by far the most common problems are the suspected TRALI, the pulmonary complications of transfusion by a long way.

The infectious risks tend to disappear, because in fact most of the hepatitis and HIV concerns predated testing, and these are old transfusions that we're investigating. The only infectious risk that really actually comes up, and this is interesting, is babesia. We had eight reports, high probability reports of babesiosis transmission last year in the Red Cross system.

That's a lot.

The second-most common problem remains sepsis, and hemolysis, and allergic reactions, in that order. And these as adverse events, mirror the FDA data on fatalities where in fact the FDA reports would suggest there's been a three-and-a-half fold increase over six years in the number of fatalities around TRALI.

Interestingly, the other two most common issues were bacterial sepsis and ABO incompatibility. The bacterial sepsis, in three years up to 2003, and the three years post-implementation of the AABB requirement for methods to reduce contamination or limit contamination, it's interesting, they've seen exactly a 50 percent drop in septic fatalities. They haven't gone away. They have dropped, by about 50 percent.

The other fact that I liked, this is from Adam Wagner's presentation of BPAC, is how in fact the ABO incompatibility issues seem to be going on a very nice downward trend. It's very heartening.

But it does highlight in our mind what are the major current risks as we know them, and they are around TRALI and fluid overload, pulmonary complications. They

remain around bacterial contamination, they are around ABO incompatibility, and patient ID issues, bedside safety, and of course emerging infectious diseases are always on that list.

So I'm just going to spend a little bit of time talking briefly about these four factors. TRALI, the Red Cross has had 105 reported fatalities over the last four years of suspected TRALI fatalities, and we believe about half of them are real. And we worked with the AABB, and with the ABC blood centers over the last year to formulate the recommendations that the AABB went out –- sent out around reducing exposure to other reactive antibodies.

In this paper that just got published all the Red Cross data, analysis of the three years we have identified plasma products as being the principal cause of TRALI fatality in the Red Cross system, and I'm happy to say that according to the AABB recommendation, by November of this year we should have addressed a large proportion of this problem. And hopefully by next year we'll address some portion of the apheresis problem.

So TRALI and TACO really are –- remain the biggest current transfusion risk. The thing to note that

if we are completely successful with implementing male-only plasma and testing for antibodies over the next 18 months, we still would only have addressed maybe 60 percent of the TRALI problem, i.e. the antibody-positive TRALI problem in plasma and platelets.

We haven't addressed antibody negative TRALI, we haven't addressed fluid overload, and we haven't addressed red cells or any other components, and so TRALI and TACO will remain the most important threat to our patients that we are currently aware of.

There is still an urgent need for a better understanding of TRALI and also of TACO, an awareness of TACO, fluid overload, and evidence-based guidelines for transfusion to prevent especially the fluid overload side of this. So this remains a major threat to our patients.

Moving onto bacteria, following the AABB standard, the Red Cross implemented bacterial testing in all of its apheresis platelets, and after testing a million products, we are very proud to have picked up a 186 true positive, true contaminated products and prevented about 292 transfusions of split products to patients. This has been and remains a very successful

program.

What is concerning to us is that there remains reports of septic transfusion reactions, and in fact there are now 26 reports of –- published reports of septic transfusion reactions from apheresis or pooled products that had been tested by bacterial culture within 24 hours or 36 hours of manufacture.

So even with cultural systems there remains a risk, which increases with the age of the product, and in this case of a five -- there have been five reported fatalities, with five-day-old products. So there remains a bacterial risk to platelet products. So from the bacterial side, we remain unhappy with the situation, with whole-blood-derived platelets, where many hospitals continue to screen with insensitive, unlicensed methodologies.

We note that culture systems at the time of manufacturing cannot guarantee patient sterility, and in fact we have estimated now that we in fact may fail to detect 30 to 50 percent of contaminated products, not that most of those would cause sepsis, most of them won’t, but they are contaminated at least at low levels.

And so we do think that there's an urgent need to improve our skin decontamination techniques. It is time to mandate sample first or diversion strategies for whole blood and platelets. I think there is growing consensus in the community that it's time.

We do require -- if we're going to stick with culture systems and manufacture, especially for older products, we do require point of issue retesting of the product, because there's clearly a residual risk. And I will make a plea that we in the U.S. need to look to our northern neighbors, and the recent consensus conference around pathogen inactivation, and seriously consider whether or not we as a country should invest in research necessary to make this a reality in this country, because continuing, adding new tests, we cannot continue to do that.

Briefly ABO incompatibility came up as an issue around hemolysis, and the serious adverse reactions, and this is where the organs and blood do co-mingle in that I find, with many residents and fellows they forget that ABO is a histocompatibility antigen, it's not a red cell antigen.

It's on every blood vessel in the body, and therefore a very important transplantation antigen for organs, and so it's not surprising that while we know that there's a quite a high frequency of error of transfusion and this is data from New York, quite old data now, that suggested a rate of erroneous administration of red cells of one in 14,000 or so in that state of reported error, should I say.

But we're also very aware that errors occur in transplantation as well. In this particular case there was an ABO error around a liver transplant that resulted in a death. Clearly reliable methods to identify and track patients, samples and products are needed to reduce errors in the hospital setting. Bedside safety is a major, major issue that needs to be part of the global view on patient safety.

Finally, let's talk about emerging pathogens, and I'll talk a little bit more about West Nile, because it really has become the paradigm for emerging threats. Remember we have a new generation of physicians coming up that weren't here during the HIV period of time, and know -- really know the West Nile virus as being the emerging

threat of the day. To tell you, the list is endless, for emerging pathogens.

But I want to make point two out, and that's Babesic and Dengue, and in fact Chagas falls in this category as well. What are we doing about infectious diseases that are localized in this country? Okay. We've just implemented Chagas in the Red Cross, but we know that there are certain parts of the country that have much higher incidence and prevalence than other parts.

I mentioned to you that babesia, we have cases of babesia every year, it's localized to the Northeast, and no manufacturer is going to create a test for that infection. We have areas of the country where one in a 1,000 collected units of blood may be infected with babesia.

That's a major issue that I think the national policy can address. We've recently become aware that there are certain territory -- U.S. territories where dengue may be, there may be dengue viremia in something like 1 in 1,300 donors, and again, will the manufacturer step up and invest the money if there are only a 100,000 units of blood being collected there each year.

The list of other infections is endless and HHV8, it's been mentioned, Chikungunya is a wonderful one, I just like saying Chikungunya. But we are very aware that in the southern Indian Ocean, which is close to where I come from, there's a major epidemic going on and there are visitors and travelers from that area of the world, Reunion, Mauritius, Madagascar, coming into this country, who may be carrying this disease.

And the end of our list, I've put –- it is very interesting that many of these emerging pathogens, which might either be emerging as new to the U.S., or emerging to our consciousness as we become aware of them, are first picked up in the transplant community where immuno-compromised patients are highly susceptible to these infections.

And a good case in point here in fact was West Nile, CDC slide –- I remember distinctly the Labor Day weekend, as many of us in the transfusion community do the Labor Day weekend in 2002, and the newspapers reported this, you know, these cases of transplant, West Nile, and we all said, what about transfusion. And for the next two or three months we didn't know what to say, when asked,

shall my grandmother go for her knee operation because we just didn’t know what the risk was.

And as we became aware that in fact this virus was sweeping through the country, we’re very proud of the way in which NAAT testing for West Nile was implemented, because by the next year when this epidemic did sweep through the country, the test was in place.

And although the prior year, let's see, about 400,000 Americans had been infected with West Nile, and in 2000 -- the prior year, 23 confirmed cases of transfusion, transmitted cases were documented, although 200 cases probably occurred, the next year we picked up 700 –- and prevented transfusion of 700 viremic donations, a major success.

We really implemented a test very quickly, but consider the paradigm. We were reactive to this threat. We weren’t proactive. Many patients became infective before this solution became available. The solution is incomplete.

We are aware of breakthrough cases. We are being very nimble about implementing new ways of dealing with those breakthrough cases, but it's still an

incomplete solution.

So then in conclusion, rather than saying that blood is safer than it has ever been, I think we need to level with our patients. And patient safety is why we need a global strategy. We need to basically say blood is low risk, but under constant threat, the risk of coming here today in a taxi was probably higher than the risk of a transfusion. But it's not zero.

We can measure today’s risk, sorry, yesterday’s risk. We can’t actually tell you what today’s risk is, we'll tell you tomorrow what today’s risk is, because we don’t know what arrived at JFK airport yesterday. We believe it to be very small, but it's not zero.

We do need a global view on safety from the patient’s perspective. We have a focus on products of the FDA, we have a focus on process, by industry organizations. We have a focus on bedside safety at JCAHO. How do we put it all together from a recipient’s point of view?

Just to end up, we do need a mandated and funded hemovigilance program to alert us to the issues, to the problems. We do need evidence-based guidelines. There's

a debate going on right now about FFP, and FP24, and it's embarrassing to say to folks that there are no clinical, there's no randomized clinical trials to prove the efficacy of FFP, and there certainly are none comparing FFP and FP24. It's not a good situation.

We need better IT solutions for tracking patients' samples and products in hospitals. We certainly in my view need better pathogen avoidance and pathogen inactivation strategies to get us out of this loop of what test are we going to implement this year.

And finally reiterate the view that as we develop a master strategy, we need a vision and a mission, and the mission I believe, and the vision should be around patient safety, and it should emphasize that they are three components that's appropriate use, the right blood, the right place, the right patient, the right time, ready availability, and product safety, in an absolute sense.

We may not be able to get there, but certainly it should be what we are aiming for, and we should be seen to be aiming for it. Thank you.

Dr. BRACEY: Thank you, Dr. Benjamin. I really enjoyed that. Question from Ms. Finley.

MS. FINLEY: Thank you for taking the time to address us today. I did find many of your comments certainly supportable and interesting in terms of our long-term strategy to deal with these, the obvious stresses on the system.

I did however want to point out that the comment you had about the government reformer board, the blood supply is safer than it has ever been. I wrote that, and I assure you that what we meant is that in the context of the overall report, was that the blood supply in 1995 was safer than it had ever been relative to known risks, and I think that's important because it was safer than it had ever been in the early ‘90s, because we were doing testing, we unfortunately did not do in the ‘80s and the early ‘90s.

And so one of the questions that I have for you is this list of emerging pathogens is just something that unfortunately we're confronted with, and you as a blood banker are confronted with everyday.

We can’t really control the external environment, but we can control what we're transfusing to some extent, unfortunately through testing. Do you have

any thoughts on which of these tests you would not adopt, or stop utilizing, or --

DR. BENJAMIN: I think the point I was trying to make, not too blatantly was that our European colleagues and our Canadian colleagues have recognized that testing is a shortsighted way of going forward.

We need to be investing in proactive pathogen inactivation strategies that will give you some assurance, a certain level of assurance, it may be 90 percent, it may be 99.9 percent, that when the next big virus comes down the road, that you will have proactive protection against it.

MS. FINLEY: Can I ask you where you think we are relative to development of those?

DR. BENJAMIN: I can tell you that it's been actively adopted for platelets and plasma in Europe as we speak. There are systems for plasma that are available, and have previously been licensed in this country --

MS. FINLEY: Are you talking about the SD Plasma?

DR. BENJAMIN: SD Plasma, and the Europeans certainly are using SD Plasma, and they're using certain

other commercial systems. There are at least two systems in development, around platelets, and one marketed in Europe, and the big question is red cells, and there are no systems for red cells, but there's a big area that -- where we should be putting research dollars in to solve the PI problem for red cells.

MS. FINLEY: Are you –- is the Red Cross conducting research in that area?

DR. BENJAMIN: We have a small program in the Holland Lab, just looking at a specific technology.

DR. BRACEY: Dr. Sandler.

DR. SANDLER: Dr. Benjamin, when you weren't here this morning, I pointed out that the Red Cross was distributing the Solvent Detergent Plasma.

It was highly effective for TTP, we loved it for liver transplants, it's probably a very effective solution for the TRALI problem by diluting out the toxic factor whatever it is. Why doesn’t the Red Cross, you're calling for pathogen inactivation, you had this stuff and took it off the market. Why don’t you put it back on?

DR. BENJAMIN: Thank you for that question, Dr. Sandler. The Red Cross was not the manufacturer of that

product, and the manufacturer took it off the market, and so I can’t answer that question. It's not ours to manufacture.

DR. BRACEY: Dr. Bloche, question or comment?

DR. BLOCHE: I'd be interested in your thoughts about the challenge Dr. Bianco posed earlier about rationality and the management of risk. A number of the risks that you put on this meeting are risks that are pretty low compared to what Public Health Authority is thinking, not just about blood, but about the universe of health risks.

A path to ponder, and in terms of that kind of cost-benefit way of thinking, there's at least the suggestion that perhaps these are sad things that occur, that perhaps should be -- I'm not saying I'm endorsing this, but I'm basing this, that it should probably go out to continue to occur at a low level while we make investments in avoiding bad things that are (inaudible) of magnitude or immense. I don’t know whether West Nile was an example of that, or -- the question of course –-

(Off mic)

Dr. BLOCHE: The slow (inaudible) the kind of

influenced the cognitive irrationality of our collective funding --

DR. BENJAMIN: I'm going to give you a personal view because I don’t think the Red Cross has a formal stance on this. The personal view is that blood transfusion is a basic building block of our healthcare system that affects every patient going into a hospital who has a possibility of transfusion, every patient going to surgery, certainly.

To my mind it's as fundamental as hand washing. If your patients don’t have confidence that you wash your hands, or that the blood supply in your hospital is safe, they don’t have confidence in your hospital, they don’t have confidence in the system. It's across the board.

So I do not put it in the same, it's clear, in fact history has taught us that the cost-benefit analysis that is applied to the next widget that comes along is very different to blood. Blood is a fundamental part of our healthcare system; if our patients don’t have confidence at a very high level, in our blood safety, then our healthcare system will –- they won't have confidence in our healthcare system. So I view it at a different

level, and I don’t agree and I don’t agree with a rigid cost-benefit analysis.

DR. BLOCHE: And how is it that –- I didn’t think Dr. Bianco said rigid –- but how is that different, how is the role of blood different, say, from the role of pre-natal care, or the role of cleaning up environmental toxins in underprivileged areas or other potential sources, other potential places where investment can be made for people’s health.

DR. BRACEY: I think you will find that the cost-benefit analysis of some of the environmental, for cleanups are in the same level of low risk as blood currently is, so I'm not sure that I accept your analogy.

DR. BLOCHE: But that's a different argument, that's a different argument. The earlier argument you made is an argument to –-

(OFF MIC)

DR. BLOCHE: –- even when our spending, total spending elsewhere by saving a lot. It should be -- the money should be spent –- somehow.

DR. BRACEY: I think I'm stating the current facts. We are currently spending and investing in things

like HIV, NAT, way -- just proportionate to what we could be doing with the money. So our question to you is, why are we doing that. And I've given you my understanding of why we're doing it, but it's clearly a decision that the community has made, that they're going to invest more money in HIV and NAT, and prevent eight infections or six infections a year, rather than investing in a vaccine that could possibly save thousands.

So I'll turn the question back to you. Why are we doing it? My understanding is that blood is a fundamental part of our healthcare system, that if we don't have confidence in blood, we can't have confidence in the system.

DR. BLOCHE: (OFF MIKE) Let me ask you (inaudible) that assuming that we are not going to continue the current approach, so then why are we doing it, that assumes they're returning for this, the -- rationale for the current approach should therefore apply in the future. I thought what this conversation is about is in part a challenge to current ways of thinking about resource allocation.

DR. BENJAMIN: I would say that the cost-benefit

argument is challenging the status quo, because what we've already done hasn't been done on a strict cost-benefit analysis basis.

DR. BRACEY: Well, I think that's an area that the committee will need to address, moving forward, and that is an analysis of the decisions that we make in the basis for those decisions contrasted to the decision-making process in the rest of medicine.

And this is again something that among our charges in terms of looking at economic as well as societal issues that we need to grapple within, rather than to have the ARC address that. I think that's something that we as a committee will need to address in the future.

SPEAKER: I just wanted to make a quick point and then ask a question. One was about pathogen-inactivation, just to make the point that even if we had that in place there would still be risks that would require a surveillance system to look at.

SPEAKER: Uh-huh.

SPEAKER: And the other –- the question I had for you is that concerning –- we've seen a lot of calls

for a hemovigilance system, but not a lot of details on what it should look like, and what is your feeling on as far as making outcomes, the outcomes be the centerpiece of what you're looking at, because outcomes don't have any (OFF MIC) of what they are.

DR. BRACEY: What are these outcomes, which outcomes are you referring to?

SPEAKER: The outcomes of transfusion. So is that something that you are proposing when you say a "hemovigilance program concerning recipient adverse events to look at outcomes and therefore that looks at, you know, it doesn't buy us towards looking at it, infraction or TRALI or TACO, or under transfusion or over transfusion for that matter.

It just looks at outcomes or are you thinking more on looking at specific causes?

DR. BRACEY: I think we're at a very sort of early days with hemovigilance, and we're looking at very crude parameters at this point. The data we showed you with TRALI and sepsis, I think are the tips of the icebergs; we're not collecting febrile reactions, we're not collecting minor allergic reactions.

Should we get there eventually, it would be nice, but I don’t think that's where we can start. Clearly we need to put a system in place that works. We'll actually get someone to report data, and we will need to narrow the focus initially, and take on the biggest problems first.

DR. BRACEY: Dr. Kouides.

DR. KOUIDES: Dr. Benjamin, regarding TRALI, one time in the discussion we had in the morning session about the relative risks compared to pathogenic transmissions. This is in many ways it should be a greater concern, or there should be further focus, and part of that ties into what you’d mentioned about the need for guidelines and how they should be done.

What would you propose in terms of trying to tie in perhaps this committee, and BPAC and various committees about transfusion guidelines, specifically the TRALI in terms of FFP, for as much as Dr. Klein said early in the problem that there isn't much data to make from recommendations?

There is however emerging data in terms of this management that, oral vitamin K for that matter, very

simple low-tech measure can be correcting elevated INRs before someone needs to give FFP, and too often we see the reverse that patients with Coumadin coagulapathy are given units of FFP, and perhaps it's a day later before they're given, you know, oral vitamin K.

We also know that this is a real issue, just in our community we have two percent of adults on Coumadin. We have their data. So this is a big issue in terms of the need of how would you propose that a guideline be set forth in terms of, you know, risk behavior of physicians of reducing that. Of -- time again, too many units of FFP given, inappropriately. For INRs of 1.6 this reflex, you know, medicine, and for getting to do others measures first.

SPEAKER: It’s interesting about that particular example. I’ll show you a slide showing plasma as being the principal problem with TRALI, and in that slide there were 24 cases of fatal TRALI due to plasma; 12 of those were given for Coumadin reversal, and at least six of those, it was though documented bleeding at the time of Coumadin reversal.

(Slide)

SPEAKER: So it was the only risk factor for TRALI that was statistically significant. Personally, I would be very happy if a national body stood up right now and said whether it is the AABB or some other forum said that this is inappropriate to give plasma to reverse Coumadin in a non-bleeding patient, because I think it's the biggest risk for TRALI out there.

SPEAKER: Yeah, that's actually -- that is indeed a challenging area, and in fact in the Chest guidelines, there are guidelines that are published, but again it is a matter of getting that information out and putting some teeth into it and developing. Perhaps it can do what's done in other areas of medical practice.

In essence, if CMS were to reimburse based on best practice, you know, maybe there is -- so the issue is finding the teeth. Because the guidelines are existent, and it is a matter of making people adhere to those guidelines.

DR. BRACEY: Dr. Triulzi?

DR. TRIULZI: Yeah. You saw the storm, a little bit of a thunder, I was going to mention, but I'll just reiterate that being the director of 15 hospital

transfusion services, I know the guidelines are current. The problem is compliance, and I think guidelines are necessary, but insufficient, and I would say actually a small minority of the problem is having not up-to-date guidelines. It's -- getting physicians to comply is the major issue.

And CMS has done this with things like ACE inhibitor used in congestive heart failure, and compliance rates have run, and most hospitals will begin that process 40 percent, 30 percent compliance rate, and with CMS that puts teeth behind it, and they are up at 60 percent, maybe now, so --

But what I do see which is something to be positive about is the IT controls that are becoming available in the hospital with physician order entry, and the ability to combine laboratory data with the ordering process.

I think it will be feasible in the not too distant future to begin to have some real prospective or concurrent opportunities that I think we in the transfusion service have to press that those systems, that are ordering process be linked and it become a smart

process, and not as was mentioned earlier today that the blood bank is just a pharmacy. And I think the technology is there, and it is incumbent upon us to actually use that to begin to address the compliance part of that equation.

SPEAKER: Can I add to that?

DR. TRIULZI: Sure.

SPEAKER: In my slides, I spoke about evidence based guidelines, and I think the evidence base is the problem. We base our current plasma guidelines on observational studies for the most part. And they don't have teeth when you go to a surgeon and say stop doing this.

However, if we can work up with a randomized control trial and say, "Look, you're doing harm." It's very hard to argue against that guideline. So I do believe that in fact there may be -- appear to be obvious studies, but we should be doing the studies to get randomized control data around plasma especially.

DR. BRACEY: Thank you. One comment from Dr. Holmberg.

DR. HOLMBERG: Actually, I have two questions. First of all, you mentioned that there was a need for a

sensitive point of issue testing in the hospital for platelets. Are you saying in lieu or in addition to the cultures at the blood center?

DR. BENJAMIN: As things stand today, I would -- with the current bacterial testing system the Red Cross is using. If those products were to be used on day 5, 6, and 7, I think it would be a good idea to retest them with a point issue -- point of issue test.

We don't -- I showed you data that the major risk is on point 5. I don't know what the risk is on point 6 -- day 6 and day 7. But we believe we don't have good data on what proportion of platelets are transfused on day 5. So we're unable to work out the actual risk on day 5, but we believe it is much higher than in the earlier day. It may be wise if we had a point of issue test.

DR. HOLMBERG: And one other quick question. Is this the ARC point of view, or your personal point of view, you mentioned about there needed to be a mandated funded hemovigilance program?

DR. BENJAMIN: I see Jack's chair is empty today. I would have to ask. We have seen significant

benefits through having an internal hemovigilance program. We have made interventions around a bacterial testing, but a-year-and-half ago based on the data that I have spoken about, the sepsis data that appears to have reduced the number of true positives and false positives that we are picking up by more than 50 percent. And so that was based on hemovigilance data.

The TRALI data that I showed you, I think, was quite instrumental in helping move the U.S. community towards doing something about TRALI, and that was based on hemovigilance.

We in a blood center can only look at a certain type of data that gets reported to blood centers. I -- it is a strong personal view. I don't think it has been put to the Red Cross as a whole, whether or not this is a policy of the Red Cross. But it's certainly a strong point of view that the data is very useful, and can be used to improve patient safety dramatically.

DR. BRACEY: And in the interest of time, I think we better move on to the next speaker, and in terms of -- it's a nice segue because in terms of organizations that have influence within hospitals, JCAHO is certainly

one of those organizations.

Klaus Nether is the associate project director of the division of standards and survey methods for the Joint Commission, and he will present his perspective and review of activities within JCAHO. Thank you.

MR. NETHER: Thank you, Mr. Chairman. First thing I would like to say is we've changed our name. We're not JCAHO anymore, we're now the Joint Commission.

DR. BRACEY: Okay. I'm sorry.

(Laughter)

MR. NETHER: That's all right. But it's an honor really to be here today to talk to you about the Joint Commission's current thinking on transfusion and transplantation safety.

And the presentation is really going to focus on the end user, the healthcare organizations, and how we the Joint Commission is looking at safety with regards to transfusion and transplantation. So I wanted to give you a little bit of background about the Joint Commission for those of you who are not familiar with the joint commission.

We are the nation's oldest and largest

accrediting body. Ninety-five percent of all hospitals are accredited by the Joint Commission. We also accredit and evaluate over 15,000 healthcare organizations and programs in the United States, which include long-term care settings, ambulatory settings, behavioral health, and laboratory.

And the Joint Commission assesses compliance with the standards during the onsite accreditation process, which I'm going to talk a little bit about later. We all have a common goal, and the common goal is really to continuously improve patient safety and quality of care.

In the past several years, events have occurred that have received national attention and have also raised the questions on a national level with regards to the safety of transplantation. And these were just two examples in terms of transmission of rabies, and also in regards to the BTS what occurred in late 2005 early 2006.

And what I wanted to say is that it just further validates what the joint commission use in terms of transplantation and transfusion safety. And really as the current state is that the potential for infections and

other adverse outcomes in recipients is a significant quality and safety concern. Instances of infections and other adverse outcomes in recipients are well documented.

And one of the things that we have learned in the past with some of the events that have occurred is -- and that there seems to be in terms of adverse event investigation that there is problems within our organizations in terms of coordination and communication.

And this was further validated as we have now looked at our data in terms of noncompliance. And what we have seen with our organizations is that this is a significant problem. Although the percentages are low, with regards to our other standards and other elements of performance, the standards and elements of performance with regards to adverse event investigation is scored frequently.

And finally the number of transfusion and transplantations are increasing. And I like to just take my Joint Commission hat, here off and just talk in terms of data itself. Although the percentages are low in terms of adverse events, if you just multiply that factor by the increased numbers, the number of actual patients having

adverse events could increase. There is a potential (inaudible). So what have we done lately?

We are really starting to look at in terms of both transfusion and transplantation commonalities. Because there are common issues with regards to both those fields, and we feel that with regards to transfusion that we're very comprehensive with our standards, but with regards to transplantation, we felt that we had some gaps.

So in July 2005, the standards became applicable for hospital, including critical access hospital and ambulatory settings, included office-based surgery. And what we had heard from the field and saw from the field was that we started to see a lot of decentralization in terms of who was actually getting tissues within the organization.

So there could be multiple entities. So one of the things that we did in 2005, because prior to that year we had these standards only in the laboratory accreditation program. We felt that it was a huge gap for the joint commission, because now with this decentralization, it was being taken out of laboratories, and we saw a focus that many entities were actually

responsible for receiving tissues.

Also we have seen -- we've got a lot of frequently asked questions from our organization with regards to in terms of adverse event investigation bi-directional traceability, and really not a sense that they have a true understanding of what they are supposed to do.

So in the past couple of years, especially this year, we have put out several frequently asked questions on our website to actually help guide organizations to giving better understanding on how to meet our standards for compliance.

And as I mentioned earlier, I wanted to talk a little bit about the accreditation process. Because this is really how we look at safety in terms of compliance for our healthcare organization, and it really starts with the standards and elements of performance and these are our requirements.

We have general requirements that expand over all services like our national patient safety goals which talk about identification, and we have leadership standards they have talked about planning and resource allocation.

We do also have specific requirements that address blood transfusion services, and donor center, and tissue storage and issuance. And this really leads up to in terms of what all actually should be looked at in terms of survey, and we actually have a tracer methodology where a patient will be followed through the whole course of treatment care and service from the time you enter the organization. And what that really leads then in terms to is whether or not an organization will be accredited.

Outside of that we also have a separate entity, which is our office of quality monitoring, which will actually review complaints that we get from patients and employees with regards to safety. And also they review central events.

We have a central event policy, but it is actually just voluntary in terms of self reporting, but any central event that we become aware of we actually would contact the organization to follow up what actions and steps they have taken to actually handle the central event they have had.

Again, the standards and elements of performance are really the drivers. They are the lot, and they'll

lead up to accreditation decision. And we actually survey our standards with regards to compliance versus noncompliance.

One of the things I did want to highlight here is any element or performance that is noncompliant, actually the organization has to fill out evidence of standards compliance, which is basically an action plan that has taken the organization back into compliance.

MR. NETHER: And we actually review all the evidence of standards compliance for acceptability and that actually will drive up to a final accreditation decision. So when it comes to transfusion and transplantation standards, as I mentioned before, we do have specific requirements. The standards and elements of performance are intended to help ensure that organizations have a well coordinated system for managing blood they transfuse, and tissues that they transplant and implant.

One thing I do want to mention currently, solid organs are not addressed in our standards of requirements. One other things, there are areas of commonality among both. And as I have mentioned earlier, as we're starting to look at transfusion and transplantation, did you see

similar issues, similar problems and similar concerns. But we also see the way to address these are similar processes in similar areas.

The differences though, however, are the specifics in the details that are underneath these areas. Some of this has to do in terms of -- for instance with transfusion services, there are federal regulations with regards to the FDA and CMS, in particular CLEA, that actually have requirements for healthcare organizations. That's not the same case though for tissues. The buck really stops at the door with regards to regulations.

So what are the -- some of the common areas that we see with regards to transplantation and transfusion. Well, one of them is the responsibility for oversight. Especially now with tissues, where there has been this decentralization, we're really looking for the organization to assign this responsibility for oversight.

Second, standardized procedures. We require organizations both for transfusion and for transplantation, to have procedures in place to address both the acquiring and ordering of a tissue or blood, the receiving of the tissue or blood, storing and issuing.

Third is the inspection of blood or tissue. Again, very similar in terms of the process. We look for the -- organizations actually verify that there is no contamination with the blood product or the tissue. The only difference here that we have is that for blood we say there's before storage and before issuance, and with tissue we just say on arrival that they do this inspection.

Four, traceability. From supplier all the way to the recipient and final disposition including documentation. And again this is a big thing for our organizations in terms of -- especially for the adverse investigation that you have this traceability. So it's a very common process for both transfusions and transplantation.

Documentation retention, very common for both. We require for both the transfusion services and for the transplant of tissues for documentation to be retained for at least 10 years. Storage including backup alarms, we require continuous monitoring both the blood products and tissues, including that the organization has functional backup alarms, in case anything goes down. One of the

differences here is, again, with blood we require that there are daily recordings every four hours. With tissues, we actually only say daily recordings once a day.

Acting as a supplier as little -- we require for both transfusions and transplantations. The difference is that we are very general when it comes to the tissue supplying in terms of just following regulations, federal or state. With regards to blood, we go a little bit more into detail in terms of the donor centers, what kind of testing that they have to do, what they have to look for in the selection of donors. We have compatibility testing very similar for both areas that we require, except for tissues we look at histocompatibility as compared to with the blood we look for antibodies screening and cross matching, and finally adverse event reporting.

And we require here that there are procedures in place to investigate adverse events. We expect this to be a bi-directional investigation. Not just knowing from the supplier when they call you that they have identified something as an infection, but also in terms of when the physician or the transplant surgeon or the tissue bank -- excuse me, the blood bank becomes aware that there has

been a blood transfusion reaction, that there is also the bi-directional tracing the other way to go backwards to find out what exactly happened.

We have reporting requirements with regards to reporting for blood where they do direct reporting to the FDA, but this is only fatal transfusions with regards to tissue transplants. We expect any post transplant infection or adverse event to be reported to the tissue supplier, which then in turn reports it to the FDA, because the FDA mandates that.

Identification of and notification to the recipient when an infection is identified, very similar for both transfusion and transplantation, and finally quarantine and sequestering when either a blood product or tissue has been identified as being contaminated.

So in conclusion, the requirements although we have them separate they really address really common areas and common processes. And that’s really because there are similar issues and similar problems, and similar concerns. As we go forward with looking at our transplant and our transfusion standards and elements of performance, we are kind of looking at a master strategy because of these

issues because they are very similar. And also because to resolve these issues there are really common processes and common areas in place.

What are the future plans? Well, currently we have the standards improvement initiative underway. And that's basically we're looking at our current standards and elements of performance really to address clarity in the language, logic, and also in terms of applicability. Early 2007, there was actually stakeholders meeting to explore identification of performance measures for blood management.

And the conclusion out of there where the stakeholders were very supportive of actually moving forward with this initiative. Right now, there is current funding being sought to get this initiative underway. And in late summer and early fall of this year, well, I should be assembling a task force really to review current tissue standards, but also to start to look at inclusion of solid organs.

So with that I would really like to thank the committee for giving me the opportunity to talk today, and if anybody has any questions.

DR. BRACEY: Thank you. Maybe I could lead off with one question. We talked about with the assistant secretary the need for in the U.S. -- in many of the European countries surveillances run by the government. Well, here we need a public-private partnership. How would you envision or -- the role of JCAHO in alignment with government and working towards this sort of a partnership to achieve the end result?

MR. NETHER: Well, that's something in terms of -- as we're getting -- convening now the group together, the expert panel in late summer, early fall. We're going to try to get all experts at the table in terms of government, from the organ side and from the tissue side, really to start to look at in terms of both, like I said, the inclusion of organs, but then also to start to look at our tissues. I know surveillance is a big thing. Currently we have standards that address the collection for -- on the transfusion side of things.

When organization has to actually collect the transfusion reaction they have had to look at blood and blood products, and really go through the whole PI process in terms of analyzing their data, seeing what improvements

they can make. That's an approach I'd like to also take in terms of looking for post transplant infections and adverse events with regards to both tissues and organs, that that process also gets followed.

DR. BRACEY: Other questions from the committee. Dr. Kinder (phonetic).

DR. KINDER: Well, I just wanted to echo the sentiment that really -- that we're trying out where the rubber meets the road, and really that is with the clinician, it's the clinician really that recognizes the adverse event, and makes the decision on whether to report it or not. And that's where we really, I think, have a challenge. And I'm hoping that joint commission can help with that.

Standards always only go so far, I mean, those standards need to be turned into education. I have wondered what processes there are in place to encourage hospitals to educate clinicians about the standards that are in place, and, you know, what they need to do.

MR. NETHER: Yeah, just to address that, and like I said through our FAQs we're starting to really try to guide the organization. Other than that it is really

the accreditation process. There are the -- in compliance or not in compliance, but that has been an issue and a concern in terms of is that bi-directional investigation, because of that self reporting. When the clinician becomes aware that an infection or event has occurred to actually to report that and really do than the investigation the other way back.

A lot what we have heard in terms of -- when there is a post transplant infection is while the doctor treated, the patients are all right. You know, everything is fine and good. So yes that is loss data in terms of I think there is a lot of under reporting.

So yes, our requirements do require in terms of that when there is a post transplant infection or an adverse event that is identified either by the physician or by the organization that that gets reported back to the source facility, and they can at least work with in terms of trying to find out, you know, other recipients that might be affected. At least get the word out, the communication piece out of it.

DR. KUEHNERT: Right, right. So, if it doesn’t get to the blood bank in the case of a -- if doesn’t get

to the transfusion service even, I mean, it is not going to get to the blood center and same for transplant. If the tissue bank never hears about it, and it is likely said loss data. So, I guess, we have a challenge there on how to bridge that gap.

MR. NETHER: Right, and we actually have that same challenge because right now currently for our transfusion services, the only requirement that we have of reporting are really just the fatal transfusions. And that's really just back to the FDA. As compared with the tissues right now it could be a post transplant infection, it could actually be an adverse event. But either one of those has to be reported back to the source facility.

DR. KUEHNERT: Well, again just to make a final comment. I think one can look at the infection control model and see that how we have improved over the last few years and decades in reporting that matter we got, and perhaps that's a path we can take.

MR. NETHER: And we're hoping that you bring that to the table.

DR. BRACEY: Question -- a comment from Dr. Holmberg.

DR. HOLMBERG: Well, I just -- I think you answered my question when you were answering Dr. Kuehnert's, but I would just really encourage the Joint Commission to really move forward with requiring adverse events being reported back to the blood facilities as far as a transfusion adverse event for transfusion. I think that that would really give a lot more impetus.

The other thing is that, I think that there is a lot of turf here, and I would just be, and I would hope that the standard setting organizations and the accreditating organizations sort of have synergy together, and work together on trying to make sure that there is commonality in the standards that they set.

So that that we can have more momentum in this area. And that's what we are really looking for in terms of when we start to bring the expert panels together it's really to get insight from the various groups, and how we can get this accomplished.

Like I said, we don't really call it a master strategy, but in regards to transfusion transplantation since the issues are very similar, as the concerns are very similar, the problems are similar, really, to address

those the processes are also very similar. So we really need to look at that and see can we really kind of join those together.

DR. BRACEY: Additional questions or comments? If not, thank you very much. We're at the phase of immediate discussion. We've heard a great deal today. It seems to me that in terms of one of the large questions, and specifically the questions that were opposed by the executive secretary that begin to have some discussion of those questions, and so the first question is posted and that is, is there an opportunity to lay out a process for transfusion and transplantation safety in the future? What is the committee's thought on that, yea, nay? We're talking about the questions to committee. And so the first question is, is there an opportunity now to lay out a process. Dr. Klein.

DR. KLEIN: Well, I think there's an enormous opportunity at least in one area that we've heard virtually all speakers talk about and that is one of the commonalities with tissues, organs, and blood transfusion is the transmission of disease and, in some instances, very similar adverse events. And yet as a nation, we

don’t (off mic). So even a collecting system like the Red Cross might do so, but as a nation, we don’t. This is the only committee that I know of --

SPEAKER: What? Sorry, didn’t hear you.

SPEAKER: I can’t hear anything. I don’t understand what he just said.

SPEAKER: Use the other mic.

SPEAKER: Use the other mic.

SPEAKER: Try this one.

SPEAKER: Yeah, try a different microphone.

DR. KLEIN: I’d like to use this mic. It seems we’re having a little bit of a problem with the mics. This is the only committee that I know of that’s constituted with the appropriate people to do this. We have representatives of the blood community. We have organ and tissue representatives. We have -- thank you. We have people who are representing the communities. We have people who’ve been transfused. Thank you. And so I think this is a wonderful opportunity to do so.

I’ll give you my bias and that is that this is a public health issue that while it should be a public-private partnership, it’s a governmental public health

responsibility. And I think that we need to have a little bit of discussion about how that might go forward or what this committee might be able to do to improve the safety of blood, organs, and tissues with this kind of a strategy.

DR. BRACEY: Okay. It strikes me that in addition to, as you've mentioned, there being an opportunity, it really seems that there is -- it's a gap. I mean it's something that should be in existence, that others have in existence and we simply haven't addressed it. Comments from other members. So the answer then in terms of the opportunity is that we view this, as a committee, as something that is important in terms of the public health that should be addressed by government.

SPEAKER: Yes.

DR. BRACEY: Ms. Finley.

MS. FINLEY: No, I was just going to say, are these questions really in the most useful format for the secretary? I mean just looking at the first bullet there, would it be easier to say, should the advisory committee attempt to lay out a process for transfusion and transplantation safety for the future as Question 1. And

then Question 2 could be what are the elements that are necessary for that.

DR. BRACEY: Right, the questions are really intended to start the discussion process.

MS. FINLEY: Okay. But I guess I'm clear, Jerry, as to where we're going with this process. Do you want us to vote yes or no? Is this more a discussion and points to consider for the secretary? Or --

DR. HOLMBERG: I think that where we're trying to go with this is that Dr. Bracey is trying to get us to a point where we may be able, before we leave tonight, to start thinking about any recommendations that the committee would like to put forward with some of these things, like the elements of what a master plan would look like.

DR. BRACEY: Okay.

SPEAKER: I'm not trying to give too -- as though not giving credence. But what ABC put forth, I mean they -- there are some answers and I think we can even debate some of those as to, you know, some of the subparts as to -- and then supplement it because we've -- somebody has already started to address those questions

for us. And I think there is consensus that we want to go down this road which is how we got here even today.

DR. BRACEY: Right. Okay, then moving forward, should we move on then to discuss the second question or -- which is the question that addresses the scientific evidence to support the need for a master strategy?

SPEAKER: (Off mic.)

DR. BRACEY: Right. Would you want to -- do you want to repeat your --

MS. FINLEY: What my first two questions were?

DR. BRACEY: You’re right, yes.

MS. FINLEY: Okay, just repeat them? Then what would -- should be the elements for a master strategy. And I -- if I may add one thing to that question, is there scientific and historical evidence to support a need for a master strategy. And I think the historical evidence is important because this country did have a national blood policy in the 70s. Some of the elements of it led to problems in the 80s. And it was something that was never fully embraced by all parties probably because there wasn’t a mechanism like the advisory committee and the (inaudible) to implement those systems. But I think it’s

important to at least acknowledge that the concept of a national strategy did at one time exist in healthcare policymaking in the United States.

DR. BRACEY: Okay, then Dr. Epstein.

DR. EPSTEIN: Well, I just want to comment. Whereas I agree with Ms. Finley that we potentially could be discussing a national blood program, there's -- we have to be careful what the scope of this discussion really is. Are we talking about a master plan for surveillance or are we talking about something larger than surveillance? And that's not clear to me.

DR. BRACEY: Right.

MS. FINLEY: Okay, it's not clear to me either --

DR. BRACEY: Well --

MS. FINLEY: -- and I would agree with your concerns.

DR. BRACEY: Yeah, and as I see it, the -- what we're currently discussing is whether or not we feel that there should be a program of biovigilance, surveillance, whether that program should include both transfusion as well as tissue as well as transplantation. And knowing

that and assessing that, then the question would be, you know, what are the areas that exist and that are common between these therapies, and where will we gain the most traction in terms of having a surveillance system.

SPEAKER: I just wonder, Jerry, whether you have the prior recommendations of the advisory committee, because the committee already spoke about the need to establish biovigilance, already spoke about the elements of a biovigilance system, and called for the creation of a task group to try to, you know, work out the material details.

So I guess I am puzzled where we are in this question compared to where we were on this question. And I think that the missing element here is that when this draft committee recommendation was brought to Dr. Agwunobi, he was basically asking for the underpinnings. He was saying, “Well, you know, is there a need? Is there a driver? Is it practical and feasible?”

And that’s why we have this set of questions. And I think what he wants to know from the committee is, is there a vision of a thing that he could embrace and try to champion through the resources of HHS. So I think he

is looking for some clarity, but I'm not sure we're really back to question 1. I think this committee answered question 1 at a prior meeting. Maybe Jerry can help clarify that.

DR. HOLMBERG: Yes, this committee did address the issue of biovigilance, and specifically hemovigilance, but we did define the biovigilance, what biovigilance was. The committee also made a recommendation that there be a PHS task group to look at gap analysis, mandatory versus non-mandatory. And you can read right down the line there.

Where we are going with this now is that with the increase in responsibility or the scope of the charter, do we expand this? -- although our definition of biovigilance was for all biological products in the transfusion and the transplantation. And I think that that is sort of a difficult comment to make. I think that we should look at tissues and blood as being a transplant also. I think that that might simplify things.

But what I'm trying to say is that with the expansion of the charter for transfusion and transplantation safety, where do we go with this? How do

we formulate a biovigilance program? And this is a little bit more meat to it than what the initial recommendation came, unless you want to reiterate some of these things that we already talked about for, you know, the PHS task group looking at.

Has there been more commonalities coming out? And there may be more commonalities coming out tomorrow that we need to address. I think at this point in time, we were sort of maybe tunnel vision, and did not have all the input from the tissue and organ groups.

SPEAKER: Well, you know, one of the big differences in our previous discussion is that the charter hadn't been changed as of yet. And you're right. It seems to me that the fact that the charter was changed and broadened, says that we've been given the green light to proceed. And so then the issue becomes what is it then that we feel is the important undertaking?

In other words, what is -- what can we grasp -- what can we effectively achieve given the resources within the department?

DR. HOLMBERG: Well, I think it goes back to what Ms. Finley mentioned about the elements of a master

plan, and I think that biovigilance may be only one aspect of that, that plan. Maybe there is other aspects such as the commonalities that were brought out this -- today as far as traceability, storage, donor eligibility, different areas there. Those are -- that's more than just biovigilance.

MS. FINLEY: Okay, but the question didn't -- I'm sorry. It wasn't recognized. It didn't say --

DR. BRACEY: Okay, Ms. Finley, go ahead.

MS. FINLEY: -- biovigilance. So again, without -- I think we should be clear about what exactly we're voting on here, or what we're discussing. And I have to add --

DR. BRACEY: Right.

MS. FINLEY: -- I am a little fuzzy, and I bet I'm not the only person.

DR. BRACEY: But -- yeah, right now we're not voting. This is a point of discussion.

MS. FINLEY: Are we discussing just biovigilance? Because if all you want us to do is address biovigilance, I'd rather address one thing, you know, thoroughly, rather than --

DR. BRACEY: Right. We are at the point of addressing biovigilance, and the idea is that is there a basis for having a biovigilance system.

MS. FINLEY: Okay. But that's not a master strategy for all of these issues across biologics. You want a master biovigilance strategy.

DR. BRACEY: That's what we're talking about.

MS. FINLEY: Okay. All right, great. Can I ask one additional question? The PHS working group -- we've heard from a lot of the outside players, but I haven't heard the response from the Feds about what it is they think should be in a master strategy. So at some point when we get to considering the elements, could we hear what Dr. Epstein, Dr. Kuehnert, Dr. Klein, you know, everyone has to say about that?

DR. BRACEY: Sure.

MS. FINLEY: Thank you.

DR. BRACEY: Dr. Bloche.

DR. BLOCHE: A clarifying question about what might get done with this. What are the possibilities and limits for HHS' role with respect to finding a vigilance strategy? Your question -- as we've heard, as we've been

reminded, a huge difference between us and other industrialized countries is that, we don't have a centralized system with the possibility of HHS simply implementing the strategy and then everybody else follows it.

There is leverage in the form of conditions for participation in the Medicare and Medicaid programs. There is leverage that takes the form of an example being set, which then others might or might not follow, but it's very soft, it's kind of, you know, soft power to borrow a phrase from another contact. Given that, what's the official understanding of the possibilities and limits of the HHS role into finding a strategy?

DR. BRACEY: Any inside information on that, Dr. Holmberg?

DR. HOLMBERG: When this question was raised in discussions by Dr. Agwunobi, I think that he was looking for -- trying to establish a roadmap for where we go when this administration is done, okay, that he has X amount of time before a new administration comes in, whatever administration that is, and how do we shape the future for increasing or improving the safety of transfusion and

transplantation safety.

I think what we're looking for is -- first of all, what are the commonalities? And we've identified one big issue is the commonality of adverse transfusion diseases, transplantation diseases which would -- could also go into adverse events and biovigilance. But what are the common areas that we can be a little bit more consistent across the department in, and where are the areas that we need to tackle for the future? Is that -- does that clarify?

DR. BLOCHE: But what's the leverage in theory that --

DR. HOLMBERG: The leverage?

DR. BLOCHE: -- all this to be implemented, or is it the idea of just setting forth additions so that when President Obama comes aboard he can implement it?

(Laughter.)

DR. HOLMBERG: I think that with anything that recommendation that goes forward from here, I think that we also have to bear in mind that there may be need for legislative support on this. So, you know, there are -- that's always a possibility. There is also some other

avenues within the agency that we could have, whether it be a regulatory requirement through one of the agencies, whether it's HRSA, FDA, or even CMS.

I think that there is a lot of capability there to improve the safety. And there are some mechanisms -- I'm not saying that there is one specific mechanism, and I don't think that I have the answer for one specific mechanism. But I think that what we're asking you all to do is to put -- to think about and discuss what are some of the mechanisms that could be in place to help.

DR. BLOCHE: That is really -- that's very helpful, because it makes it clear this is not limited by existing authority, this is a big picture of endeavor.

SPEAKER: Big picture? Well, but that's the last question which is why you, Jerry, just jumped at the last question which is what resources are needed, and it may be legislation in order to get appropriations on the lot. But that's why I thought you laid it out very well in going through it, which is do we agree there should be a master strategy?

If so, what generally -- again and we can talk through what should be within that strategy. I think your

notion of what are the commonalities I think you should -- we should also develop not only a list on the last one to put what would be on, but not only what are the commonalities, but what's different --

SPEAKER: Exactly.

SPEAKER: Right.

SPEAKER: -- between them so that we see that, and then -- I mean I think you laid out what the steps are to be able to then at the end come up with a recommendation that can be voted on. These I think are the -- these are the whereas clauses so to speak as we've done in resolutions before supporting it to then come up with a resolution saying we would support the notion of --

DR. BRACEY: Dr. Roseff for the comment.

DR. ROSEFF: What are the specifics? Would it be helpful for us to look at what we've done in the past? I mean there are going to be some similarities in that bio- hemovigilance discussion we had, and then from that we can see what's different to frame the other part of the discussion.

DR. HOLMBERG: You should have all received a handout of my complete presentation, although I didn't go

through that. It may be difficult to read because when I was copying it, I wasn't able to get the letters reversed for the black and white. But I think that if you'll go to this handout, it will lay out some of the recommendations that were made specifically for biovigilance in 2006.

But there is other elements such as when we started talking about an overall strategic plan in September of 2005, I think we very clearly laid out some of those elements that Ms. Finley may be wanting to address. And I think that what we need to do is to see whether there are commonalities with the tissues and the organs and the cellular products.

I think one of the things that I thought was missing in Dr. Strong's presentation was that with the identification of the testing and the requirements, we just went from blood and tissue, and we missed the organ part of it, which I realize that in many places we just found out from the Joint Commission, they don't touch the organs either.

And so I think that that's one definite gap that we see especially with the organs. But we also have to recognize that there is a difference with organs too. And

so we have to understand, okay, if we're going this far with tissues and organs, how far can we go with organs, okay? But I think maybe for tonight's reading might be great. Good to look at this.

DR. BRACEY: And I guess that one of the questions that was raised is in terms of the discussions that have been within the department. Dr. Kuehnert, you are on that taskforce that's been addressing biovigilance and its look. From your perspective, how much do we need to revisit the master plan if you will, or do we need simply to flush out the details of the commonalities that we are seeking?

DR. KUEHNERT: Well, my opinion is I think the ladder -- I mean, I think looking at the gaps is the most important thing. I think the discussions previously have been quite good. And I think it really flushed out a lot although, you know, we don't have answers on how we're going to capture emerging infectious diseases necessarily.

And we agree that it's going to take basically an informatics challenge to be able to capture those rather than some direct method. And then, you know, divining, you know, donor issues and recipient issues. I

mean I think, you know, all that was sort of done in looking at the surveillance issues, and then similarly with some of the other issues related to preparedness and coordination research, et cetera.

DR. BRACEY: Right.

DR. KUEHNERT: So I think the issue is, for instance, if we want to look at differences and commonalities if we're looking at risk realizing that what we've heard today is that there is a relative risk of transmission in organs and tissues is probably above that of blood. On the other hand, there are reduced -- there are less -- there is less intervention as far as, you know, the donor screening that's done for various reasons.

And so there are -- there is a risk gap, that's the essential thing. And then there are some issues to consider, which we'll hear more about tomorrow, concerning how tissues are processed, and that there is a differential risk there. So -- I mean there is a bunch of different things to consider, that frankly I think after the presentations tomorrow, we'll maybe make things more clear in trying to determine where the specific gaps are in considering solid organs and tissues compared with

blood.

DR. BRACEY: Okay. Dr. Holmberg, do you --

DR. HOLMBERG: Yeah, let me just quickly direct you to page 5, September 2005. And what I tried to do is to simplify the overall recommendation. But the recommendation was for a strategic plan and a structured process for policy and decision making. I think that we've heard that several times today.

Integration of blood systems into the public health infrastructure, surveillance of adverse events related to blood donations and transfusions, risk communication, air prevention in blood collection centers, transfusion services, and clinical transfusion settings, donor recruitment and retention, donor recruitment -- I'm sorry, clinical practice standards for transfusion, strategic research agendas, disaster planning, stable and sustainable reimbursement, and funding for promising new technologies.

DR. BRACEY: So again, getting back to what Dr. Epstein's point was, is that, you know, much of the high-level discussion has already taken place. And as I see it, the idea is to try to come away from this meeting with

something that’s embraceable by the assistant secretary that addresses gaps that we’ve identified. And we haven’t really heard all of the presentations.

But perhaps -- so perhaps rather than get bogged down into issues of redeveloping blood policy right now, we’ll deal with the strategic plan recommendations and the recommendations that we submitted for biovigilance before, look at details that are -- in essence, try to figure out something that’s doable for the department over the course of the next day or so.

Does -- I mean, does that sound reasonable, or do you think that we really do need to -- and I’d be interested in the perspective of the committee that we actually do need to revisit the higher level discussion. Dr. Lopez.

DR. LOPEZ-PLAZA: I’m just a newcomer in here, but as -- well, I hear all the presentations. Yes, we need some kind of surveillance; we need to know more, you know, look at everything that is happening. I think that there is already things in place in the community that we can at least look at them and see what we can use for them, like the tracing methodology, how the drug industry

do their surveillance.

The successful programs that the European and Canadian health system has -- was established as you know as a role model, and see how we can adapt it to our system. The only thing that is very important I think that at least to see how things work maybe basing on commonalities.

As you know what is in common of all those different tissues transplant/transfusion, why things are in common, why don't we trace that? See what's happening with that, and then go from there. The other point I wanted to make is that I've seen that the blood industry in here, the blood centers, just because of regulations they are a lot better equipped to see things from beginning to end.

I think that the factor in here that would be more problematic would be the clinical aspect of it, because we have forgotten that there is the user, there is the physician there, that it's going to be slightly multiple things, and it's not only going to be the organ that get transplanted or the blood that got transfused.

You're talking about maybe tissues, you're

talking about transplant, you’re talking about blood in that -- in the same patient, you’re talking about medications in the same patient. So looking at that outcome, adverse events, they might not be only related to the one problem that we're looking. It's going to be a combination of things. So I think that we have some things that we can look at.

DR. BRACEY: Okay.

DR. LOPEZ-PLAZA: And then from there, try to develop something.

DR. BRACEY: Yeah, again, I think that -- again, from my perspective, the need is there. It's pretty clear. And I think it's already been discussed, perhaps by Dr. Bloche that we are the teeth. How are you actually going to make this happen? And then tying into Mr. Matyas' position, what are the resources. So how can you enforce it, how are you going to pay for it? To me again, and perhaps I'm thinking at a lower level, but I think the need is clear and it's not that -- what am I trying to say, it's not at that highest level. We've already addressed the highest level, and so I see this as fleshing out the details.

DR. BRACEY: Dr. Epstein?

DR. EPSTEIN: Well, I guess at this point my thoughts are a little scattered on this because I'm not exactly sure what we have embraced. But just a few comments. I think that some of the drivers focus on infectious disease events, that there is a strong sense that we'd like to have more coherence in the reporting of infectious disease transmissions across these various types of transfusion/transplantation. The second general theme that I think I've been hearing is about databases. It's the idea that we need better reporting data, better acquisition and better analytic tools.

And I think that the commonality, as it were, is the informatics that Matt just mentioned, that the advancement that's needed is informatics. It's how to take advantage of existing data sets, how to do build, you know, new data sets, how to build, you know, new data sets, how to mine them for triggers and how to extract significance, or mine them for central observations and extract significance.

We haven't talked too much about the issue of who owns it, you know, who has access to that information

and what does anybody expect to be done with it. And I think the ownership issue is delicate and lies at the core of the debate about the government role and the private sector role because I think that that debate has to do with two things. It has to do with responsibility and accountability. And I think we heard Dr. Klein say, well, this should be a public health function.

But on the other hand, I think that the tension that underlies that issue is that the private sector may not be so happy with dissemination of specific information, possibly because of competitiveness issues or other things, you know, confidentiality issues et cetera. I think we haven't even begun to touch that area. And then one last point is the ultimate point of all this ought to be risk communication. In other words, you find things, you analyze them, you discover causes and then you have to do something about it, but that's never going to happen if you don't communicate.

And so we haven't talked about, you know, the mechanisms, the procedures, you know, and what are the resources and the incentives. And I just want to -- so that's my sort of set of tasks. I think that's what we

have to sort out.

DR. BRACEY: And I agree. I think there is one other task or area to focus upon. And that is -- and it's -- but how (off mic) -- we heard about failures of, you know, tissue in various ways. The infectious piece is clear. That's something that we've got experience with, but reporting outcomes of the intervention, I think, would be important. JCAHO and its standards for example requires that -- in the transfusion world the reality is that most hospitals really don't do it. But if there is some way that we could sort engender or foster greater outcome reporting, though outcomes are somewhat nebulous. Dr. Triulzi.

DR. EPSTEIN: I had two more points and --

DR. BRACEY: Okay, Dr. Epstein, want to finish your points?

DR. EPSTEIN: No, I can remember them.

DR. TRIULZI: If you look at Mike Strong's presentation, which is under the second yellow tab on page 8, he has the eight common layers of safety. And that's the logical progression that we're familiar with with blood but they do apply to -- as you go up, from blood

cell, tissue, organ, and you see that Adverse Event Surveillance is the bullet of 12 of them. And what I'm afraid is as important as that is that we don't get overly bogged down because the resources and complexity for that piece are probably the greatest.

And I think they call can be addressed for all the tissues and we probably could be missing some low-lying fruit that would have immediate and short-term impact. Like traceability to me immediately stands out that there is no excuse and there is really no major expenses to know that tissues have traceability. And we just found that out the hard way. And so what I would say is the overwhelming answer to the Secretary is yes, there is common layers, and there is, I think, opportunities to address these in relatively efficient manners and quickly across everything from blood to organs. At the time while we are trying to work out the Adverse Event Surveillance because the resources and complexity -- if we wait to do that, we will have missed opportunities for the others, enabling -- another one to me that stands out immediately is a low-lying fruit issue that can be done across all those tissues and organs.

And there's others in here, you know, we could go down to do that. But I don't want adverse -- the adverse event, and I am the first proponent for biovigilance though, to make us lose sight of opportunities in the entire process that starts with a donor qualification.

DR. BRACEY: Dr. Epstein.

DR. EPSTEIN: Yeah, thank you, I apologize. The two additional points I wanted to make are these. I think our research agenda needs to be looked at in a common framework across, you know, blood cells, tissues and organs. And the reason is because we have a shared problem about a lack of evidence base for the standards that we have. And I think that it would be an opportunity for, you know, efficiency leverage if we began to look at it in that light. That's one point.

And then I wanted to remark about commonalities. I think what's been said many, many times here is that the framework for approaching safety in these different areas of products is quite in common and I think that that is very coherent with Dr. Triulzi's prior remarks. But I think that we need to be careful here that harmonization

is not necessarily the goal. And this, you know, harks back to what Mike Strong was saying is that yes, there are commonalities in the framework, but the details can be quite, quite different.

So for example, you know, labeling -- well, maybe the commonalities are so strong that it's just a question of some additional ISBT codification and we just continue to use, you know, our ISBT framework. But on the other hand if you talk about process standards, you very quickly get into incredible divergence. So for example a simple thing like bacterial culture, we know how to do it on a platelet and we haven't begun to know how to do it on a vast array of tissues. So I think we just have to be careful not to confuse a framework of commonalities with a sort of sub rosa agenda of pushing harmonization where it may not work.

DR. BRACEY: Dr. Kouides and then Dr. --

DR. KOUIDES: You know, I think that, you know, one of the problems here is that we are in the middle of the presentations right now. And one of those issues that's just been touched on, which is that surveillance in a way is the top of the pyramid. You really need a whole

bunch of things under it in order to do it. So we're trying to figure out how to make a typical pyramid, you know, sort of stay in midair. And as we'll hear tomorrow, I mean, with the discussion that -- transplantation/transmission -- what you need first is traceability. And then you build from there.

So I agree with the low-hanging fruit comment. I think that we have to start with some very basic things that are non-present in all the products that we're talking about. And I think only at the end of the presentations are we going to be able to realize, okay, we need to fill those in first and then have a uniform -- only then do we have a uniform approach where appropriate to these array of products.

DR. BRACEY: Other comments? Dr. Burdick, you are in the line of tissue and transplantation. Your thoughts on this discussion and where we are headed.

DR. BURDICK: In -- sort of in general I agree with all that's been said. I think that there has been more done -- more discussed and actually more thought given to this than has been represented thus far. And I think particularly when -- from the argument tissue point

of view, when you hear from Dr. Fishman tomorrow that will help to provide some background. I think there are commonalities and there are differences and there are a lot of different activities underway. The differences with organs and with blood stem cells are obvious and need to drive appropriate activities that are different for let's say, blood and blood products. But those are details that I think can be worked out and many of the surveillance and testing and so forth problems are pretty much in common and therefore we all benefit from having those things together. So it's a mixture. And I -- that's about all I think I have to say right now.

DR. BRACEY: Dr. Pierce, you had a comment.

DR. PIERCE: Yeah, I think I would echo what our last two speakers said. We are in the middle of the presentations and one of the things that I'm struggling with is I don't really understand the flow from donor to recipient for each of these individual organs. I do know it's different, very different. Whether it's a tissue or an organ and I don't really know what the regulations are at this point for governing each of those individual tissues. We are going to learn something more about that

tomorrow.

But I also tend to be -- I think I'm hearing a lot more about biovigilance and there is a lot more to this than that. These are all limiting resources. There aren't enough organs or tissues to go around and it's not just a matter of biovigilance, making sure that they have a certain bacterial load or have that level of safety, but it's how they are implemented and used. What's the quality that goes into transplanting a given organ or a tissue and what's the outcome. And really, we haven't heard anything about that. I don't think that we can really have a discussion just on biovigilance without knowing what the outcomes are for the majority of patients who receive these tissues. We hear anecdotally a lot about the need for a repeat transplant and that sort of thing. Well, to me that seems to be where the money is. That's the problem.

DR. BRACEY: Comments from the other side? Ms. Thomas?

MS. THOMAS: Thank you. I would like to say that I do feel that we have made great strides under Dr. Kuehnert, everyone else that talked about the

biovigilance. However, I think for me personally, it will be more beneficial to hear what will transpire on tomorrow. I also appreciate Dr. Holmberg and I do agree that everything was laid out what I thought was clear and then after the debate -- but that will be my only suggestion, is I would really like to hear what will transpire tomorrow.

DR. BRACEY: Well, yeah, part of the idea is not just to have discussion because there is a line there that says "Discussion."

(Laughter)

DR. BRACEY: But when you begin to have your discussion, you can work through some of the issues. In other words, by beginning the discussion, you get over the humps. And I think one of the things that's clear is if we as a committee all go back and focus on our previous set of recommendations, look at them, think about them, see if there are any particular gaps -- and then when we start to have -- when we hear the presentations tomorrow we can again begin to look at some substantive issues that hopefully we'll be able to make as recommendations. Dr. Klein.

DR. KLEIN: I just wanted to make a comment that this committee is walking what I consider a fairly fine line. Many of the people here today weren't here in May and when we did have a very high-level discussion, laid out a strategic plan. And if you try to embrace all of that -- I suppose it depends on whether you are a lumper or a splitter, you'll get nothing but a very high-level plan. And I would just point to the FDA's blood action plan, which I think is terrific but took 10 years to do. And I don’t have that much time, frankly.

(Laughter)

DR. KLEIN: On the other hand, if we look very, very low and pick out a few lumps I think we could probably get them done. We're going to miss I think probably -- potentially a historic opportunity, if we can believe the Assistant Secretary, and I do. There is an opportunity here in the next 18 months or so to do something very big. So I would encourage the committee as they listen to the presentations and deliberations tomorrow to pick out something relatively big, concrete, and doable. And regardless of what the resource is, I think there are ways of getting those resources. But I

think not flying too near the sun or to -- immedial tutismo ibis (phonetic) I think is the way Virgil put it.

DR. BRACEY: Thank you for those comments. Oh, yes, Dr. Solomon (phonetic).

DR. SOLOMON: Okay. What you think are low-lying fruit may not be low-lying fruit when it comes to the Feds. For instance, we are restricted by our legal authority. For instance for tissues the legal authority just focuses on infectious disease transmission. So if there would be an adverse reaction in another venue, we -- that wouldn't come under FDA. And therefore we have -- the regs are what they are. We have tracking to the consignee, but not the recipient, and we have very few regs on labeling, we can't mandate ISBT for instance.

So what -- any recommendations that you make may require rulemaking and rulemaking takes years and -- with an election coming up, believe me, there is not going to be a lot of rulemaking. So I think that the -- you can make recommendations, but whether they are going to be enforceable recommendations is -- you know, may not happen.

DR. BRACEY: Dr. Triulzi.

DR. TRIULZI: Yeah, I'll respond very quickly which is that's where we need to take advantage of. For instance, JCAHO may pick up where FDA has to drop off at the door. JCAHO picks up from the door on. As to accrediting agencies, whether it's ABB for blood banks or ATB for tissue banks. And so if the strategic plan is there of what's expected, then those organizations know where they need to pick up where FDA leaves off. So I wouldn't say that that should excuse us from recognizing the need to have recommendations for the whole process.

DR. BRACEY: Okay.

DR. SOLOMON: True, but those -- the professional organizations have standards that are voluntary. So you would be dependent on the goodwill of people to do --

DR. BRACEY: Trust me, that goodwill is -- that goodwill has a great influence within the world of the hospitals. Yeah, it goes a long way. I think we have sort of laid out pretty much what we need to do and that is we're really thinking about being concrete and trying to take advantage of an opportunity that exists. And so with that I would -- one more comment from the Secretary.

DR. HOLMBERG: For the new committee members I laid at your desk an appointment affidavit; if you would sign that, so that I can get Dr. Agwunobi to sign the statement also. And also remember that we will meet tomorrow at 8:30 in the morning for our annual ethics meeting. The Feds are not required to be here, so when we -- we go through our own annual ethics training on an annual basis.

DR. BRACEY: With that, I'd entertain a motion for adjourned. Okay, and seconded?

SPEAKER: Second.

DR. BRACEY: We stand adjourned. All right.

(Whereupon, at 6:00 p.m., the meeting was recessed, to be reconvened on Friday, May 11, 2007, at 8:30 a.m.)

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