Summary:
Advisory Committee on Blood Safety and Availability
Department of Health and Human Services
31st Meeting, May 10-11, 2007

At 9:00 AM, the meeting was called to order by Dr. Jerry Holmberg. As he called the roll, members were provided an opportunity to describe what they bring to the Committee, for the benefit of Dr. Agwunobi, Assistant Secretary for Health, who was to swear them in. Members present (alphabetically) were: Ms Ann Marie Benzinger (President of Alpha-1 Alliance , a patient with alpha-1 anti-trypsin deficiency who has had a single lung transplant and is wait-listed for a second), Ms. Julie Birkofer (industry representative for the Plasma Protein Therapeutics Association – PPTA – with expertise in reimbursement, coalition building and advocacy), Dr. M. Gregg Bloche (member of the Law Faculty at Georgetown, a visiting fellow at the Brookings Institution, who teaches and writes about health policy issues), Dr. William Duffell (absent; a vendor representative from Gambro, which is now being inspected by the FDA), Ms. Anne Marie Finley (a health care consultant in the DC area and a trustee of the Hemophilia Foundation of New Jersey; Previously a congressional investigator on the House Government Oversight and Reform Committee and the author of several reports on blood safety and hepatitis issues. Also has served at the FDA), Dr. Charles E. Haley (absent; Medical Director for Trailblazer, a Medicare contractor), Dr. Peter Kouides (Hematologist from Rochester, NY, and director of the medical center at the Mary M. Gooley Hemophilia Center; also on the National Hemophilia Foundation Medical Advisory Scientific Committee), Dr. Ileana Lopez-Plaza (Medical Director, Transfusion Service, Worcester (MA) Medical Center, responsible for transfusion services and the stem cell processing lab), Mr. David Matyas (Partner with the law firm, Epstein Becker and Green, specializing in health regulatory issues and medical reimbursement; member of the Board of Directors, American Health Lawyers Association), Dr. Glenn Pierce (Past President, National Hemophilia Foundation, member of their Medical and Scientific Advisory Council and director of research at Bayer Healthcare, Berkeley, CA), Dr. Glenn Ramsey (Absent; Northwestern University, Chicago), Dr. Susan D. Roseff-Dickerson (Medical Director, Transfusion Medicine, Virginia Commonwealth University, Richmond; previously 7 years with the American Red Cross), Dr. Gerry Sandler (Director of Transfusion Services, Georgetown University Hospital; previously Chief Medical Officer, American Red Cross Blood Services; representing the American Hospital Association on this Committee), Ms. Linda Thomas (Director of the Marc Thomas Sickle Cell Foundation; her late husband died of sickle cell disease after 28 years; she advocates for patients) and Dr. Darrell J. Triulzi (Medical Director, Centralized Transfusion Service, Institute for Transfusion Medicine, Pittsburgh, representing the AABB on the Committee). Ex Officio Members include Dr. Matthew J. Kuehnert (Assistant Director for Blood Safety, Centers for Disease Control and Prevention; Head of a Working Group for Blood, Organ and Other Tissue Safety; CDC is reorganizing to form the Office of Blood, Organ and Other Tissue Safety; He represents CDC on the Committee) Dr. Jay S. Epstein (Director of the Office of Blood Research and Review, Food and Drug Administration and the FDA Liaison to the Committee; He trained in Infectious Disease, but has been a career scientist and bureaucrat since 1981;

his mission is "to give bureaucrats a good name"), Dr. Harvey Klein (a hematologist by training, Director of Transfusion Medicine at the Clinical Center, National Institutes of Health; he's been involved with transfusion medicine for almost 35 years), Commander Michael Libby (Director, Armed Forces Blood Program; He's a Specialist in Blood Banking and Committee Liaison to DOD), Dr. James S. Bowman (Physician with CMS ["junior bureaucrat"] with prior experience as a transplant surgeon and with Blue Cross and other commercial healthcare payers). Dr Laura St. Martin (FDA) could not attend, but Dr. Ruth Solomon (came later) will represent the Division of Human Tissue for the FDA and Dr. Jim Burdick (Director, Transplantation, HRSA, with oversight of the national systems in organ transplantation and blood stem cell transplantation).

Dr. Arthur Bracey (Medical Director of Transfusion Services, St. Luke's Episcopal Hospital, Houston, and Associate Professor of Pathology, University of Texas; he estimates that in his career he has overseen the transfusion of about a million components to various patients; he has great interest in ensuring safety), Committee Chairman, welcomed new and continuing Committee members, thanked them for their commitment to blood safety and availability and assured them that their deliberations would promote the public health. He reviewed the activities of the Committee for the benefit of new members. The Institute of Medicine report on decision-making in the early stages of the HIV epidemic recommended that the lead responsibility for blood safety be vested in one person in the Department ("Blood Czar," currently Dr. Agwunobi) to coordinate agencies within the Department. The Committee was established to advise the Secretary and is unique in considering not only science, but also policy with regard to ethical and legal issues and economic considerations. At the first Committee Meeting ten years ago, the Assistant Secretary said "The job of this particular committee is to assess consumer and societal factors as they compare the risks and benefits of various actions." The Committee has a diverse membership, encompassing those who need blood therapies, experts in transfusion medicine, legal experts and representatives of industry. With the Charter renewal, the Committee has the additional charge to deal with issues of transplantation safety as well.

Dr. Bracey then introduced the Assistant Secretary for Health, Dr. John O. Agwunobi, who was confirmed as Assistant Secretary for Health in December 2005. He began by thanking Dr. Bracey for his leadership of the Committee and the old and new members for their commitment to the issues at hand. He noted that he was a pediatrician by training, but has spent a large part of his career on health policy at the state and federal levels. This Committee was formed in response to an event, the HIV-AIDS epidemic. Too often policy changes and major interventions are reactive. He expressed the hope that in the future, we would be more proactive than reactive. The risk-benefit equations keep changing and he is proud of the activities of scientists in HHS, CDC, NIH, FDA and other places such as HRSA. The Committee should not focus on the past, but rather look forward, learning from the past about how future events can be prevented. As we proceed with ever more sophisticated therapies, biologics, cellular modalities, genomics and proteomics, the consideration of safety issues with blood should be extended, with an eye toward the commonalities. This includes whole organ transplantation, the use of biologically derived proteins and everything in between. Other experts should be drawn

in as needed. We should predict where cellular therapies might encounter trouble and try to build systems and make plans for prevention strategy. He praised the diversity and expertise embodied in the Group. In proceeding to swear in Committee members, he suggested that the formalities, the pomp and circumstances, might be considered excessive; nevertheless, he believes the work of the Committee to be so important that he believed it necessary. The Committee's work is about saving lives. Upon his recommendation to the Secretary, the Committee's scope was expanded, as found in the new charter, to ethical, legal, patient access, availability and safety issues surrounding therapy with biologics, cells, tissues and organs. He closed by inviting members of the public to join in the discussions, providing their opinions and expertise.

Dr. Bracey invited the new members to come to the fore and Dr. Agwunobi swore them in: "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."

Since the Agenda was a bit ahead of schedule, Dr. Bracey invited questions for the Assistant Secretary from Committee members. Ms. Birkhofer thanked the Committee Chairman, Dr. Holmberg. Dr. Bowman from CMS and others for permitting specific brand reimbursement for plasma-derived intravenous immunoglobulin and asked that action be taken at the highest level to ensure continued availability by patients for this life-saving therapy. Dr. Agwunobi replied that there is no other blood product on which he has met more often. He takes the problem very seriously and suspects that he will be invited to the proposed high level meeting. Another question sought comments about a difference between blood and organs or stem cells for transplants in that the former is replaceable, whereby the latter may not. He replied that access to these therapies had been frequently discussed and would be further addressed. He asked that the Committee come up with strategic plans that address the similarities and the differences in various therapies with organs and tissues, including blood. Dr. Sandler noted that one of the recommendations of the IOM was a "Blood Czar," a single locus for rapid decision-making in the face of unanticipated emergencies, such as the HIV epidemic and 9/11. Is it FDA, CDC or a higher authority; a web page perhaps. Dr. Agwunobi objected to the term, "Blood Czar," but responded that the Pandemic and All Hazards Preparedness Act resulted in the appointment of an Assistant Secretary for Preparedness and Response (ASPR) in DHHS who is responsible for all aspects of the response (currently, Rear Admiral Craig Vanderwagen). ASPR has charged Dr. Holmberg and CDC, FDA, NIH and all branches of the administration to help develop and coordinate a plan in advance of need. He assured the Committee that the availability of an adequate and safe blood supply in an emergency was high on the list. He invited participation in this planning process, noting that robust well thought-out solutions would likely find their way into the federal plans. ASPR doesn't work in a vacuum; multiple inputs are sought and accepted as decisions are formulated.

Dr. Bracey then called upon Dr. Holmberg to provide an update on the Committee Charter and previous recommendations. About one year ago (January 2006), he reviewed Committee recommendations and their results from the beginning. There were some accomplishments and some without concrete effects. The process includes transmission of recommendations to the Assistant Secretary and on to the Secretary. Occasionally, one or the other takes a different view, but, as Dr. Agwunobi said, everything said in the Committee has been valuable. Transcripts and slide presentations are preserved on the Web and available for review.

Even though there may not be concrete evidence of progress, much was, and is, taking place behind the scenes. For example, readiness, discussed by the Committee several times, is being continuously reworked. Dr. Holmberg reports not only to the ASH, but also to ASPR. Last August's meeting dealt mostly with hemovigilance: definitions, mandatory vs. voluntary reporting, data-base governance, ownership and access (including sharing with other countries). As a result, a PHS gap group was formed jointly chaired by Drs. Kuehnert (CDC) and Goldsmith (FDA). They have been hard at work, interacting, among other things, with the AABB task force (which may be discussed by Dr. Strong later in the meeting). As a result of Committee discussions and meetings with Drs. Agwunobi and Vanderwagen (ASPR), blood and plasma are well established as critical infrastructure healthcare elements in case of disasters such as an influenza pandemic. Consideration of funding for research studies is an on-going process. Much work has been accomplished through the AABB task force, partly because a government/private sector partnership is needed and partly because a private organization is not bound by Federal Advisory Committee Act rules (government advisory committees must be chartered and have a specific scope). Federal Agencies can establish liaison with private groups. The Federal Government works through state and local health organizations to get many things done; the multiple meetings required are time-consuming, but necessary.

The IVIG issues have been continuously worked on. The Office of the Inspector General released a report in April 2007 and the Assistant Secretary for Planning and Evaluation (ASPE) released his report in May (executive summaries provided to the Committee). CMS has added separate codes for liquid IVIG. Queries continue to come in, e.g., a recent one from a Senator's office.

Summaries going back to 2001 were flashed on the screen. FDA and CMS continue to work on look-back for patients possibly infected by HCV and it is hoped that a regulation governing this process will come out soon

There were no questions on Dr. Holmberg's presentation.

Dr. Mark Weinstein (Associate Deputy Director, OBRR, currently working on standards development, Education, Training and Risk Communication) updated the Committee on FDA risk assessment and communication for US plasma-derived Factors VIII and IX and investigational UK-plasma-derived Factor XI (of variant Creutzfeld-Jacob Disease – vCJD). In 2003, it was found highly probable that vCJD had been transmitted by red cell

transfusion; there are now 4 such instances known in UK. Planning began for risk assessment and communication strategies in 2004 because of the numbers of patients that have been treated with plasma-derived clotting factor concentrates. The process involved several presentations and discussions at the Transmissible Spongiform Encephalopathy Advisory Committee (TSEAC), consultations with special government employees (SGE) including experts and patient advocates, as well as input from other PHS Agencies (CDC, NIH) and FDA staff. Teleconferences were held involving hemophilia treatment centers and patient advocacy groups. Documents prepared included an estimation of risk (extremely small from US plasma-derived products – Factors VIII and IX) and a listing of sources for additional information. These documents are posted on the FDA Web page (http://www.fda.gov/cber/blood/vjdrisk.htm). The procedure was repeated for UK plasma-derived Factor XI concentrate which was used investigationally for no more than 50 US patients between 1989 and 2000. None of the contributing donors are known to have developed vCJD. A preliminary Web posting was done in 2005. Participating investigators are being polled individually to locate patients with Factor XI deficiency who might have been treated.

The first question to Dr. Weinstein was about the use of plasma by patients for whom no concentrated replacement product was available. Risk assessment for plasma and other blood products has been under discussion, but not definitely addressed at FDA. Dr Epstein later commented that plasma-derived products were first because of pooling, but FDA was considering a broader assessment. Dr. Kouides asked what was available for patients in addition to materials for reading, e.g., counseling. In reply, there is heavy reliance on the Hemophilia Treatment Centers (HTCs). Dr Bracey commented that there was excellent communication between FDA and the HTCs and CDC, who oversees these centers. However, not all patients have a relationship with a HTC; some may be seen by hematologists that are doing primarily oncology and may not be comfortable with hemostasis problems. The Medical Advisory Committee of the National Hemophilia Foundation has discussed the vCJD issue, but there has been no great concern expressed. Dr. Pierce noted the long incubation period of vCJD and asked what FDA was doing for the future. In response, donor selection criteria have been modified to decrease the likelihood that those incubating vCJD would pass it on. They have encouraged industry to explore ways of eliminating or detecting the agent. Progress has been slow and expensive in the use of animals to detect infectivity. Advisory committees have been asked to help establish criteria for measuring success. Dr. Kouides asked if recombinant products had the same potential dangers. Currently, about 80% of patients with hemophilia A use recombinant products. There is an unresolved medical issue about the likelihood of developing inhibitors to Factor VIII with recombinant vs. plasma-derived factors. Ms. Finley asked about leukodepletion to reduce infectivity for vCJD, noting that other countries have instituted universal white cell depletion. She also noted a recent publication by Dr. Laura Manuelides purporting to show that the TSE agent was really a virus. In response, countries have adopted universal leukodepletion for a variety of reasons, not only for possible prevention of vCJD transmission. FDA policies consider but do not require the prion hypothesis as a foundation. The literature is evolving. Dr. Sandler reported that his blood supplier informed him of 3 specific units of blood that came from donors later found to have classic CJD and asked what resources might be

available to facilitate follow up. A Red Cross study of that situation showed no evidence for transmission, but more cases are needed. Dr. Kouides said that Dr Schonberger was involved in surveillance of plasma vs. red cell products and might be helpful.

Ms. Jennifer Scharpf, MPH (OBRR/CBER/FDA) was introduced to summarize for the Committee a workshop (April 25-26), "Immune Globulins for Primary Immune Deficiency Diseases," cosponsored by the Immune Deficiency Foundation (IDF) as well as the Office of the Secretary (Dr. Holmberg) and the Office of Public Health and Science, both of DHHS. There were four goals for the workshop: 1) assess current potency testing for IVIG (antibodies to measles, poliomyelitis and diphtheria); 2) list the antibodies needed to prevent infections in patients with primary immune deficiency syndromes; 3) identify candidate specificities for future potency testing; and 4) address changes in the composition of presently available products (e.g., a progressive decrease in the levels of antibodies to measles. Epidemiological data from US and European registries was reviewed, as well as information about currently licensed products for patients with immune deficiency. Streptococcus and hemophilus influenza were the most important bacterial infections, while viruses of particular concern included Epstein-Barr virus (EBV), CMV, echo viruses, varicella-zoster (VZV), adenovirus and coxackie. Multiple antibodies have been studied in current products with variation over time and from source of the plasma used. Among emerging infectious diseases, West Nile virus antibodies have been measured, showing seasonal and geographic variation. A pilot study of immunoglobulins was proposed to measure antibodies to streptococcus pneumonia, hemophilus influenza, using validated ELISA and opsono-phagocytosis assays currently in existence in WHO reference laboratories. Trough titer levels of antibodies should be measured in patients with primary immune deficiency diseases during treatment. Manufacturers have shown willingness to send blinded samples for these tests.

Measles is particularly important to study because there have been recent outbreaks in the US and antibody levels correlate with the degree of protection. Measles antibody levels have been declining, leading to an increase in lot rejection (measles titer is a lot-release criterion) with a possible adverse effect on supply. The US outbreaks have been focal, however, and usually from exposure outside of the country in places where immunization rates are low. Nevertheless, IVIG measles antibodies are estimated to remain sufficient so that patients are still protected at their trough levels. It was recommended that FDA collect relevant data, such as product titers vs. patient trough levels of measles antibodies to determine protective levels, and determine if the release criteria need to be changed. Similar studies are planned for H. influenza and strep pneumonia.

The transcripts of this meeting and all of the slides will be posted on the CBER web site.

In the discussion, Dr. Pierce asked how many IGIV lots had been rejected. In response, the data are now being gathered from the manufacturers, who are concerned about the problem. Dr. Kouides asked if falling levels were being correlated with surveillance for infection. Response: it is being planned.

After a short break, Robert Duncan, PhD (DETTD, OBRR, FDA) summarized the discussion about Chagas' Disease and blood transfusion at BPAC (April 26, 2007). Trypanosome cruzi infection is endemic in Mexico and Central-South America and transmitted via the bite of a beetle, either directly or more commonly by rubbing insect feces into a wound or into the eye. It can be can be transmitted by blood transfusion (7 cases in the US or Canada in the past 20 years), organ transplantation (5 cases), congenitally and through breast feeding. It can also be transmitted by drinking freshly prepared sugar cane juice. The initial infection is mild or asymptomatic; after a long period of latency (life-long), up to 30% develop severe symptomatic disease. Treatment is unsatisfactory. Countries where it is endemic test donated blood; 12-20% of seropositive units will transmit infection. There are few incident cases in the US; the problem comes from immigrants who were infected in their home country and donate blood after they arrive in the US.

In addition to this background material, BPAC heard about Red Cross and Blood Systems screening activities (Dr Sue Stramer), which began January 29, 2007 (265 of 1.8 million donations or 0.015% were repeatedly reactive; of those 265, 174 were non-reactive in a supplemental radio-immuno-precipitation assay – RIPA – and 50 reactive, with 41 results still pending), from CDC about donor management and epidemiological considerations and from Drs. Busch and Custer (Blood Systems) about long term testing strategies. Voluntary industry recommendations have been published in an AABB Bulletin.

Issues discussed include testing strategy (all, or after the first 1-2 years, selective), donor deferral (probably lifelong), donor counseling, product management (quarantine and discard), possible cross-reacting diseases (leishmaniasis, which is genetically related and shares geography, some plasmodia and paracoccidioides) and management of autologous units. Additional research was recommended to address these issues.

Dr. Bracey opened the discussion with a question: there are likely to be a lot of positive donors; what follow-up should be done re the donor's health? Can the health system handle it? Need one do lookback on donors not confirmed by RIPA, either because the RIPA was negative or because it was not done? Answer: the donor's own health could be handled by a referral to a private physician or clinic. This should happen, whether a confirmatory test was done or not. Dr. Epstein commented that donor reentry was another more difficult problem because it affected recipient safety. Any FDA guidance in these matters will be published in draft form and comment requested. Although these issues are good ones, their effect will be modulated because the test has good specificity and the numbers of donors involved will be small. Dr. Triulzi pointed out that approval of a single test was a problem, especially for those centers that might use a different test platform and supplier. Can other tests be used under an IND? Can informed consent be waived? How was WNV testing handled? Dr Epstein replied that INDs usually need consent which is managed by IRBs. With WNV testing (and NAT for HIV/HCV), consent was obtained by the use of donor information forms and the usual donation consent. Dr. Sandler asked about the demographics of unconfirmed positive screening tests. Can these be used to guide counseling and other donor management issues? In response, Dr. Duncan noted that asking about ethnicity treads on difficult terrain. He

didn't have figures right at hand, but the approach to selective testing takes advantage of these demographics. No one has suggested that initial testing be selective. Another questioner asked how soon an approved supplemental test would likely be available? Dr. Epstein pointed out that the FDA could not control the timeline because they could not mandate that anyone develop such a test. He couldn't disclose the identity of a candidate manufacturer, but Dr. Duncan reported that such a group had made a presentation at BPAC, making their interest public information.

Leslie Holness, MD (OBRR, DBA, CBER, FDA), reported on the BPAC discussion of transfusion-associated acute lung injury (TRALI) at BPAC, April 27, 2007. BPAC was asked if available scientific data supported the development of policies to reduce the incidence of TRALI. Presenters included Alan Williams (CBER – fatality reports to FDA), David Stroncek (NIH Clinical Center – clinical and laboratory aspects), Steve Kleiman (REDS-II studies), Richard Benjamin (Red Cross Experience) and Celso Bianco (ABC experience). Fatalities from TRALI reported to the FDA have been increasing. TRALI was reported as cause of death in 31% of reports in 2004 and more than 50% in 2006 (more than any other single cause). FFP was implicated more than twice as often as any other component. Apheresis platelets and red cell concentrates were also implicated. Solvent-detergent plasma has not been reported to cause TRALI, nor have leukocyte or HLA antibodies been found in that product. Incidence ranges from 1:1,000 to 1:10,000. The major clinical manifestation is severe shortness of breath within 4-6 hours (89% within 2 hours) of transfusion, in the absence of fluid overload. Arterial oxygenation is decreased; intubation and mechanical ventilation with supplemental oxygen is often required. The condition subsides over 12-24 hours, but the fatality rate is 10-50%. Forty-five to 60% of cases are associated with anti-neutrophil antibodies; there is some association with class I or class II anti-HLA antibodies. BPAC discussed TRALI in June 2001 and recommended (13-1) against regulatory intervention. In October 2001, FDA sent out an MD letter aimed at improving diagnosis and reporting. In the United Kingdom, elimination of plasma or apheresis platelets from female donors resulted in a dramatic reduction in the frequency of TRALI. In April 2004, TRALI was discussed and a standardized definition was recommended at a meeting in Toronto. After study, the Red Cross eliminated hi-volume plasma products from female donors, resulting in a decrease in TRALI reports. In 2006, AABB formed a working group to seek ways to reduce TRALI and published a Bulletin in November containing their recommendations. REDS-II began (2004) a 5 year study to determine the frequency of neutrophil and HLA antibodies and the effect of pregnancy, prior transfusion and immune status of donors on the formation of the antibodies. LAPS-2, a lookback study from implicated donors is being planned.

BPAC found there continued to be misuse of plasma transfusions, despite the recommendations of a 1984 NIH Consensus Development Conference. They recommended that blood banks practice transfusion medicine rather than just dispense on order. Education on the proper use should be emphasized, including inappropriate use for minor changes in prothrombin times and the treatment of warfarin overdose with prothrombin complex concentrates. Plasma and apheresis platelet donations should be restricted to males or females who had never been pregnant (this should not create much

of a supply problem; furthermore, any type plasma was permissible in the presence of a severe shortage). There is an AABB Committee, with FDA liaison, working on codifying these guidelines.

Dr. Bracey began the discussion with a comment on the difficulty of changing MD practice with education and wondered if CMS' plans to pay for quality and the use of "Best Practices" could be used to improve transfusion practice. Dr. Holmberg asked if there had been any recent review of the 1984 plasma consensus conference, suggesting that things were not much different now. An unidentified speaker who had been part of that conference reported that a major problem for the panel was the lack of data on use, a situation that still exists today. Dr. Sandler asked about the fate of solvent-detergent plasma and why it has disappeared from the market. Dr. Epstein replied that it was not because of FDA action, but that it was discontinued because of market forces. Dr. Holmberg asked if the absence of antibodies was from removal or dilution. Not answered. Dr. Ramsey commented that in his hospital the reporting of TRALI varied by department: some had few or no cases; others had more. He thought there might be both under- and over-reporting. Dr. Bracey said that was why we needed a system for hemovigilance. CDR Libby noted that the Armed Forces' needs had exceeded their capacity to make AB FFP and they had to seek supplemental supplies from the civilian sector. He anticipated that this situation would worsen if they were restricted to the use of plasma from male donors. Dr. Holness said the Committee developing guidelines anticipated adding back females who had never been transfused or pregnant. Further, the recommendations would likely accept the use of plasma from any source in situations of shortage.

Maria Rios, PhD (DETTD, OBRR, FDA), reported on the Implementation of West Nile Virus (WNV) testing of blood for transfusion, as discussed at BPAC April 27, 2007. The report to BPAC was opened by a survey of the WNV epidemic by Dr. Farnum (CDC), encompassing from 1999 to 2006. There have been more than 24,000 cases reported to CDC, with 10,000 instances of neuro-invasive disease and more than 1,000 deaths. Since 2003, a nucleic acid amplification test (NAT) has been done on all donated blood, using a mini-pool format (MP - 6-16 units represented in each pool). In December 2005, the first NAT (Procleix, developed by Gen-Probe and marketed by Chiron) was licensed by the FDA. In March 2007, a fully automated version (Procleix on a TIGRIS machine) was licensed. The AABB biovigilance WNV program collected weekly (real-time) information on reactive and confirmed positive donations. These data suggest that CDC ArboNet data are under-reported. Extrapolating from AABB data suggests that neuro-invasive disease affects 1:350 infected individuals. At least a few cases occur in every month, although the epidemic follows a waxing-waning course. Data suggest that MP testing detects 75% of those positive when individual donations are tested (ID NAT). Many of the 25% missed with MP testing also have antibodies as well as viremia. Switching from a MP platform to an ID one should be done in response to uniform criteria: the AABB WNV Task Force has suggested 2 reactive units or a frequency of 1:1000 or higher should promptly (within 24 hours) trigger a switch. FDA is considering if ID NAT should be the standard all year round; blood establishments have warned that

this would be expensive, exhaust laboratory resources and increase the number of false positives and donors deferred.

Dr. Bracey commented that with WNV and Chagas agent testing, there may be a need to adjust reimbursements for blood and blood components. Dr. Holmberg asked if WNV NAT had been approved for cadaveric blood testing. Dr. Rios replied that the blood donor screening tests had been so approved.

Dr. Bracey then opened the meeting for Public Comment.

The first public presentation was by Ms. Marcia Boyles (President and CEO, Immune Deficiency Foundation), who began by thanking the Committee and, especially Dr. Holmberg, for helping the immune deficiency community to get improved access to intravenous immune globulin (IVIG). The Immune Deficiency Foundation (IDF) has been the voice of the immune deficiency community for 26 years. IVIG is the only proven therapy for immune deficiency and is essential to patient survival and well-being (19% of patients rated their life as good, very good or excellent in the year before receiving IVIG, while 79% so rated their well-being after such therapy. The IDF has conducted periodic surveys of patients, their physicians and hospital pharmacists over the past 10 years. She presented slides to show that Medicare reimbursement policies have failed to keep pace with actual costs, which has resulted for patients in changes treatment location (hospitals in- and out-patients from home or doctors' offices), frequency of infusions (decreased), dose infused (decreased) and increased difficulty arranging for treatment. Of Medicare patients, 26% reported negative health effects, e.g., increased hospitalizations, use of antibiotics and infections, including pneumonia. Hospital pharmacists reported less availability and a disparity between the prices they paid and the amount reimbursed (for liquid IVIG, price paid was 4% less than reimbursement; for lyophilized products, it was 15% less; 30% paid more than was reimbursed for liquid IVIG and 57% paid more for lyophilized). Members of the American Academy of Asthma, Allergy and Immunology reported similar findings, resulting in an average loss on IVIG products of $1,000/physician. Similar surveys in Europe show many fewer problems. Ms. Boyle asked the Committee to go on record for recognizing the problems and seeking both interim and long term solutions.
Dr. Bloche found the European comparison interesting and asked how the pricing there compared with that in the US. Germany would probably be the best parallel because their financing of health care is most like ours. Ms. Boyle responded that she did not have data and suggested that the PPTA might be a good source. Each country has its own rates. That in Germany is probably higher than the US, while Great Britain and Spain would be lower.

The next presentation was by Nebraska State Senator Abbie Cornett (Alliance for Plasma Therapies). She introduced herself as a former Omaha police officer (retired), a wife and a mother of three who is in the third year of her first term as a state senator. She has common variable immune deficiency, is dependent on IVIG and is representative of how successful that therapy can be when it is given as ordered. She is a founder of the Alliance for Plasma Therapies, a unified voice for patients and providers using plasma

therapeutics. There is a critical need for such an organization which she supported by citing similar statistics to those reported by Ms. Boyle. The Alliance objectives include: to insure fair and adequate reimbursement for IVIG therapy, all brands and all sites; to update IVIG coverage and dosing guidelines for all diseases; to be an IVIG access information resource for patients, providers, US Congress, Federal and State agencies and others; and to advocate before Congress and DHHS for fair access. The Alliance' Board of Directors includes: Roger Kobayashi, MD (practices in Nebraska and consults for the Immune Deficiency Foundation), Jonathan Katz, MD (a neurologist with the Forbes Norris Research Center, California Pacific Medical Center and a board member for the Guillaine-Barre Syndrome, CIDP International Foundation and the California Myasthenia Gravis Foundation), Flemming Nelson (General Manager of Octapharma USA), Patrick M Schmidt (President and CEO of both FFF Enterprises, an IVIG distributor, and NuFACTOR, a home care company providing IVIG services) and Senator Cornett, a patient needing IVIG therapy. She was looking forward to working with the ACBSA on behalf of her constituencies.

Ms. Birkoffer opened the discussion by repeating her acknowledgement of CMS and Dr. Bowman for taking the positive step toward improved access with brand-specific reimbursement. She suggested that Ms. Boyle (IDF) check with the Alliance to seek synergies between the two organizations. This was supported by Dr. Bracey, who asked if Ms. Birkhofer would work with both organizations together; she agreed to do so. Mr. Matyas asked to what Ms. Cornett would attribute her success. Answer: Insurance. He asked if she needed to change her insurance to get the coverage. Answer: No. Her coverage as a retired Omaha police officer provided enough with Medicaid, Medicare and her insurance provider. Nevertheless, when the city changed providers, she had to repeat the approval process and for a while was month-to-month. Mr. Bloche asked about pricing of products: did it correlate with the costs of production or more opportunity driven? Ms. Cornett was unsure, but Ms. Boyle opined that it was not just the manufacturer, but also third party intermediaries (spot market) that were involved.

The final public presentation was by Mr. Corey Dubin, representing the Committee of Ten Thousand (COTT). He began by noting COTT's special relationship to the Advisory Committee. COTT asked Senators Graham and Kennedy for an investigation of the AIDS blood epidemic and the resultant Institute of Medicine (IOM) report made recommendations that brought about the establishment of the Advisory Committee on Blood Safety and Availability (ACBSA). COTT has attended every meeting and successfully recommended potential members. Mr. Dubin also thanked Dr Agwunobi for emphasizing that he, the Assistant Secretary for Health, was the Committee's client, a relationship COTT has worried was lost. Today's discussions screamed for a "National Blood Policy," to be developed in the ACBSA, referred through the Secretary, DHHS, to the Congress for review and enactment. The US is the only western democracy that does not have a "National Blood Policy." Blood issues cannot be considered in a vacuum; for example, Chagas' disease must be addressed with immigration issues. Although Southern California is a hot spot, immigrants from Latin America, Mexico and other countries have spread out through the entire US.

COTT supports the IDF in seeking adequate reimbursement for plasma therapeutics. There are a number of issues that need to be addressed. These include increasing the level of concern at the Hemophilia Treatment Centers about vCJD, HCV in the hemophilia community including lookback which has been incomplete at best. He reemphasized the need for a "National Blood Policy."

There was no discussion.

After a lunch break, Dr. Holmberg noted that Capt. McMurtry had retired April 6 and that LCDR Henry, who is temporarily absent, was the new Deputy Director of Policy and Programs in the ACBSA Office. Committee member, Dr. Laura St. Martin, could not attend this meeting; Dr. Ruth Solomon, also of the FDA, was sitting in for Dr. St. Martin.

Dr. Bracey said the afternoon would focus on systems for assessing transfusion and transplantation safety and introduced the first speaker, Luc P.J. Noel, MD (Department of Essential Health Technologies, WHO; Clinical Procedures - Cell, Tissues and Organ Transplantation). He acknowledged the contribution of Dr. Neelam Dingra (Coordinator of Transfusion Safety, WHO), with whom he works closely. They are concerned about the safety, quality and efficacy of products of human origin, including best practices, standards and safeguards against unexpected adverse events.

He quoted a resolution adopted at The Fifty-seventh World Health Assembly:

"1. URGES Member States:
(1) 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 involves physicians, surgeons, patients, health authorities, regulatory authorities and an oversight process. To help improve blood safety world-wide, WHO has a Global Data base on Blood Safety (GDBS) and several Knowledge Bases on transfusion and transplantation of cells, tissues and organs: GKT 1 (Activity and Practices), GKT 2 (Legal and Organizational Framework) and GKT 3 (Threats and Responses, Safety and Ethical). Limitations on WHO's ability to effect changes include incomplete national consolidation of health authorities, cross boundary exchange and trafficking and poor hospital records of transfusions. There has been some improvement; GDBS for 2004-2006 shows improved tracking of organ donations and transplants (GKT 1 and 2, with the assistance of an initiative by Spain). Much of this information is available on the WHO website.

A major worldwide problem is the geographical disparity between supply and need. For example, 19% of the population accesses 61% of the world blood supply, 81 million donations. There is variation in safety as well. Twenty-one of 152 countries for who WHO have data do not test blood donations for HIV; 28 of 145 don't test for HBV; 68 of 106 fail to test for HCV and 34 of 137 don't test for syphilis. Data have focused on transplant tourism: patients, surgeons, donors, vendor traveling for the sole purpose of

exploiting a vulnerable individual to get an organ. Patients contemplating travel to get an organ transplant should be counseled that the results (3 year graft and patient survival) are significantly worse than for transplants in the home country (Canadian study).

There is considerable commonality between blood products, progenitor cells, organs and tissues: health products of human origin (HPOHO). This includes ethical issues such as a need for consistency between HPOHO and around the world; sale and purchase (availability of the human body, the person as a means rather than an end; safety of the live donor and payment to "buy out" any long-term responsibility for the live donor); consent and protection of the vulnerable; equitable allocation and public trust and preparedness to give as much as to receive. Risks shared by organ transplantation and blood transfusion include: process of donation for the blood and live organ donor; changes in functional properties of the blood/tissue; transmission of infectious disease; bacterial contamination; incompatibility; and physiological interactions. The first Global Consultation on Regulatory Requirements for Human Cells and Tissues for Transplantation was held in Ottawa, December 2004. The second was in Geneva, June 2006. WHO specifications and safety requirements for selected HPOHO can be found on the website (www.who.int/transplantation/cell_tissue/en/). Devices were included.

Determining the risks of disease transmission and taking countermeasures make biovigilance a necessity. For example, an LCMV-like virus was transmitted to 3 organ recipients in Australia, with fatal results. This has been determined by an international collaboration that included the US CDC to be a previously unknown virus. Vigilance is an attitude; surveillance (preferably, active) is the method. From a 2004-2005 survey, about 55% of high income countries had a national surveillance system (35% didn't respond); about 15% of medium income countries had such a system (half didn't answer); 15-20% of low income countries had a surveillance system (75% didn't respond). National systems foster international cooperation, which is essential because of movement around the globe. A good system includes all stakeholders; health and regulatory authorities, public health agencies, operators (health care staff) and scientific and professional societies. No one should be left out.

European Directive 2004/23/EC set standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. The preamble states: *"As tissue and cell therapy is a field in which an intensive worldwide exchange is taking place, it is desirable to have worldwide standard*s." Directive 2006/86/EC deals with adverse events and reaction reporting, traceability and a coding system. The European Union Standards and Training in the Inspection of Tissue Establishments (EUSTITE) project was begun (first meeting March 2007 in Madrid) with 12 partners (Italy, Ireland, Austria, Spain, France, Slovakia, Poland, UK, Bulgaria, Denmark and WHO) and observers from the US (CDC, FDA) and Canada (Public Health Agency of Canada and Health Canada). WHO is the main partner for developing a model for reporting and investigating adverse events and reactions? The project will run from December 2006 – November 2009. The next meeting is planned for Rome, July 2007, and will be enlarged to include representation from low and middle income countries in all regions and will focus on a common language for vigilance and

surveillance. ISBT 128 has been recognized as a potential basis for the common language.

In March 2007, the Second Global Consultation discussed critical issues in human transplantation (the first Consultation had been in Madrid, 2003). The two key issues were quality and safety to minimize real risks and surveillance should be based upon traceability, confidentiality and common codification. Long term assessment should include both recipient and living donors, if used. Guiding Principle 10 is planned for presentation to the WHO Executive Board in January, 2008:

> "Quality of care, safety and efficacy of procedures are mandatory for 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 donors. "

Proposed resolution:

> "To encourage the creation of a global network of collaborating centres on Vigilance and Surveillance for CTO transplantation WHO (should) facilitate the adoption of a common global basis for coding systems for CTO for transplantation"

Dr. Klein opened the discussion by noting that Europe seemed well organized and progressing nicely. Developing countries should play a role, not only for their own safety but also because they may provide markers for future problems in developed countries. Does WHO have any financial incentives to help the less developed countries? In response, Dr. Noel noted that undeveloped countries were invited to the upcoming Rome meeting. WHO will disseminate information as widely as possible because they want all to reach the same level of services. Nonetheless, WHO is a technical organization, not a financial one. What problems have there been in selling the need for surveillance to various countries? WHO has enormous goodwill and the programs are patient-centered and for the benefit of patients. There has not been much difficulty in selling the idea.

Dr. Kuehnert asked if hemovigilance was always government run or if there were any examples of public/private collaboration to serve as a model. Can WHO collaborate with non-governmental organizations? Dr. Noel had no data about government or private management of hemovigilance. Scientific and professional organizations are often key with their global role and level of expertise. They can communicate directly with WHO with minimum red tape.

The next speaker was D. Michael Strong, PhD, MT(ASCP), BCLD(ABB) representing AABB. He began by noting that he was the Chief Operating Officer of the Puget Sound Blood Center. This organization was a blood center and distributor, a transfusion service with cross matching services in the Seattle area, a tissue bank, an histocompatibility laboratory for organ transplant programs in the region. He was speaking on behalf of AABB. There will be a lot of commonality in his and other presentations. AABB's Mission Statement is "To advance the practice and standards of transfusion medicine and cellular and related biological therapies." This encompasses the practice and standard-setting for transfusion medicine, including cellular and related biological materials.

AABB foci are blood components and derivatives, cellular therapy (progenitor cells from marrow, cord blood and peripheral blood), tissue and organs. The priority level for tissue has recently been raised. There is need for a common national strategy for all of these therapies toward the goals of donor and patient safety, availability and efficacy. The risks for each are infectious disease transmission and non-infectious complications. He presented several slides comparing infectious disease markers in first-time blood donors and tissue donors, showing that tissue donors had considerably more such markers. The safety margin is not as disparate because tissue donations are highly processed, lessening the infectious risk. The recipient risks have been lessened by the development of mini-pool nucleic acid tests (NAT) for HIV, HCV and HTLV (now less than 1: Million or so for blood). NAT for HBV has not been widely implemented and risk of transmission remains relatively common (1:34,000 – 1:250,000, and down to 1:1,500,000 with mini-pool NAT, which has not been universally adopted). The marker rates for cord blood and other stem cells are higher than blood, approaching that for tissue donors.

Non-infectious fatalities reported to the FDA include TRALI, bacterial contamination and ABO and non-ABO hemolytic reactions (mismatches). These are likely underreported. The frequencies in other countries vary, but reporting is better because of a single national system. The largest single category, encompassing half or more of the fatal reactions, is giving the wrong blood to the wrong patient ("clerical errors"). The relative significance of this risk is essentially unchanged in the more than forty years of Dr. Strong's experience. The SHOT data from UK suggests that non-infectious fatalities occur in 1:250,000 transfusions. There is insufficient data to establish the figure for the US. An often unrecognized and underreported fatal complication is circulatory overload. It is number 1 in the UK, but does not appear on the FDA's list. Non-infectious risks for tissues are more variable from one organ or tissue to another. Graft failure can be mechanical (non-union/loosening – bone grafts, and incorporation), immune rejection or technical errors (mis-measurement, mis-labeling, mis-processing, broken bags).

In slides 13-28, he focused on the commonalities between blood, cellular therapy products and tissue, starting with donor screening, eligibility and management, collection or recovery, infectious disease testing, processing steps, labeling, traceability transportation and storage, quality surveillance, clinical outcome analysis and adverse reaction surveillance. Some products are very far along, e.g., common blood component labeling using ISBT 128 (stem cells from various sources may also be able to use this system). Tissues are complicated by the large variety being banked. The Joint Commission is setting standards for the management of tissues and organs in the hospital, where currently multiple services and specialties are involved. In all of these, maintaining an adequate supply is key, supported by fair reimbursement. He concluded with a strong recommendation for a common strategic plan using a public/private initiative, focusing on similarities while taking due note of essential differences.

Dr. Bloche opened the discussion by noting that a bill to strengthen FDA's surveillance of drugs was moving through Congress. He asked if that legislation would apply to blood products and if AABB was involved in expanding it to biologics. Dr. Strong replied that AABB was not involved in the pharmaceutical side and they lacked resources to do much

work on Capitol Hill. This Committee and various advisory committees can play a role in addressing deficiencies such as limited biovigilance. Dr. Kuehnert said he would modify the quotation attributed to him that the problems of biovigilance represented a "perfect opportunity" rather than a "perfect storm." CDC has exercised surveillance of adverse effects of all medical interventions, not just biological products and drugs. There are both commonalities and differences. Legislation has focused on FDA. He then asked how Dr. Strong envisaged the public/private partnership working and suggested he provide examples. In response, steering committees have been established by AABB which attempted to include all stakeholders. These groups have focused on what information to collect and how and to whom it should be made accessible. A voluntary system has been proposed, believing that there has been no luck in the past with mandatory systems. AABB's experience has been that they have lost members who have objected to being held accountable. An ongoing question is who pays for the system. There is room for both private and public funds, but will the total be sufficient? Will it be managed by the government or outside the government with federal access and input (preferred)? Dr. Epstein pointed out that there was a successful model in hospital-based infection reporting. Each hospital has an infectious disease epidemiologist to collect and submit data. Should there be an epidemiologist for blood transfusion and tissue/organ transplantation? Dr. Strong replied that a long-range goal was to have transfusion safety officers, modeled after a program in Quebec, but that funding was a problem. AABB proposed a simple beginning with a pilot study in a limited number of hospitals to demonstrate feasibility, collecting and analyzing a data-base. Dr. Klein commended AABB for taking leadership where the government had not in developing a nimble system doing a world-class job with West Nile virus, HIV and Yersinia contamination, for example. He suggested that the Committee help determine how the nimble organization might assist with biovigilance. Dr. Strong noted that he and Matt (Kuehnert) spoke frequently and that CDC was helpful in the face of declining finances. West Nile and Chagas' disease biovigilance has been web-based, facilitating fast reporting and turn-around of data. Dr. Solomon commented that the FDA Center for Devices had a voluntary Medical Device Surveillance Network with 35 hospitals monitoring and reporting adverse events. Tissue transplant surveillance has been added. She asked that Dr. Strong amplify a bit on the significant differences between blood and organs/tissues. He responded with examples, e.g., circulatory overload is not a problem with a tendon transplant. Dr. Solomon suggested differences in risk:benefit ratios, the availability of organs and tissues vs. blood and the need for HLA matching with some transplants. Dr. Strong reemphasized the need to deal with both commonalities and differences.

The next speaker was Celso Bianco, MD, Executive Vice President, America's Blood Centers (ABC), presenting on their behalf. ABC is an association of 77 independently licensed blood centers, 75 in the US and two in Canada. Members collect about 9 million units of blood and supply about half of the blood in the US and all of it in Canada. He stated that blood transfusion is safer now than ever before, but asked is that safety sustainable? The number of units of blood collected in the US has remained about the same since 2001. Platelet collections have increased about 5% during that period. There is little prospect for growth in blood banking and the relationship of income to expenses

is also relatively constant. Blood represents about 1% of hospital budgets, but a larger proportion of laboratory expenditures. He showed a graph (#6) of the price of packed cells and leukopoor red cells in constant dollars; increments represented added tests or procedures. Transfusion medicine leadership is aging but training programs, both at the physician and technical levels are withering, resulting in serious staff shortages. Suppliers to blood banks are consolidating, diminishing competition. Screening assays are supplied by only two manufacturers and both are in financial or regulatory difficulty. Firms are reluctant to develop new tests or products unless there is a guaranteed market. For example, considerable resources have been devoted to artificial oxygen carriers and to pathogen inactivation, neither of which has gone anywhere. Product development depends on a sponsor; FDA has no power to mandate new tests or products. A test used to screen blood donors may not be approved to screen cadaver blood for organ or tissue donors, because a manufacturer has not submitted data and requested approval.

Risks and perceptions of risk are often unconnected, in all aspects of life. This disconnect may lead to considerable expense for very little gain in safety (e.g., nucleic acid testing for West Nile virus). The environment seems to be one seeking zero risk and regulators follow the "precautionary principle," with fear of making a mistake. Accrediting organizations vie to have strict standards and avoid regulation. FDA issues "Guidance" rather than regulations. At a recent ABC meeting, FDA regulatory priorities were listed; Dr. Bianco did not consider many of them to be important priorities for the blood banking industry. At least two parts of FDA regulated blood, tissues and stem cells, while another part of DHHS (HRSA) set standards for organ transplantation. The resulting requirements were not always in harmony.

Dr. Bianco recommended a forum for joint development of common priorities, noting that this Advisory Committee could play a role. There should be a focus on quality processes. Operational and discovery research should be supported. There should be transparency with open meetings and increased expert presentations at BPAC and other advisory committees. He concluded by recommending increased funding for FDA and more support for transfusion medicine and transplantation from NIH.

Dr. Holmberg opened the discussion by asking what the forum would look like. Dr. Bianco described his fantasy in that Dr. Epstein would bring priorities to the Committee and regulators, users and patients would help arrange them in order. Dr. Pierce asked that everyone be mindful of history, lest they repeat it. Where does the evidence for evidence-based regulation come from? It may come from those at the highest risk, which poses a dilemma. Dr. Bianco agreed and suggested that concern about hemophilia patients might be more important than testing for West Nile virus.

Dr. Epstein said that Dr. Bianco was thoughtful and provocative, putting the FDA at the center of the storm. Dr. Epstein wasn't sure that was the right focus. FDA responds to many stakeholders, including industry, patients and other parts of society. We have established no framework for resolving risk/benefit issues. Congress can legislate, but many of the issues are inherently political and Congress tends to steer clear of definitive stances. FDA is left to use the available science to solve problems that are basically

social. He also called attention to a time lag between the development of hot button issues and working through to solutions. Yesterday's cause célèbre may become today's low priority. For example, when FDA approved treponema-based assays for syphilis, the regulatory stance on their use was important. Although syphilis as an issue is of low importance now, the regulatory needs have not disappeared. They do not formally use the precautionary principle in developing guidance and rules, but the 1995 Institute of Medicine report recommended that government agencies, including FDA, be proactive in dealing with a potential threat. He took issue with Dr. Bianco that the approaches used are wrong. Dr. Bianco agreed 99.9%, blaming not FDA but the laws that created FDA, focusing on licensing products, each one of which is an item unrelated to others.

Ms. Finley commented Dr. Bianco's perception of risk would not be shared by many others present, who would put HBV and HCV in a more important category. The IOM report recommended a formula for decision making which was adopted by DHHS in sworn testimony before the Congress. Dr. Epstein gave an excellent summary of appropriate decision-making in the absence of definitive scientific information. Decisions must be made, using precaution where appropriate. She asked how blood centers were dealing with the failure to collect money available from Medicare because of coding and billing problems. In response, most of the work was done by AABB. There is a delay between the provision of information and reassessment of DRG's to reflect increased costs from adding tests or procedures. Hospitals are also strapped and negotiate with blood centers to minimize costs when revenue may not be increased.

After a brief break, Dr. Bracey introduced Richard Benjamin, MD, PhD, Chief Medical Officer, American Red Cross Biomedical Headquarter to present Red Cross concerns about transfusion and safety. They are no longer involved with organ/tissue transplantation. Red Cross blood donor and recipient safety research is mostly internally funded at the Holland Laboratory and at the regional blood centers. There is some participation in the NIH REDS program. Since the publication of a government report (1995) that stated the blood was safer than ever before, a number of new procedures have been implemented (e.g., NAT for HIV, HCV and WNV, cultures of apheresis platelets, donor deferral for possible vCJD) and the process is continuing with the use of plasma from male donors only and the likelihood of screening plasma for leukocyte antibodies in the near future. The focus should be on patient safety, including appropriate use of blood components, delivery of the right product to the right patient at the right time, ready availability and product safety in an absolute sense. The Red Cross has had a hemovigilance program in place since 2003. He reviewed data from 700 adverse event reports in 2006 and placed it in the context of reports to the FDA and other sources. The gross data suggest that physicians are concerned about TRALI, infectious disease (HCV, HBV and HIV) and allergic and hemolytic reactions; confirmed problems are more likely TRALI, TACO (circulatory overload), bacterial contamination and sepsis and emerging infectious disease. FDA data have shown a progressive reduction in ABO hemolytic reactions. Sepsis from bacterial contamination has likely been reduced by 50% since cultures of apheresis platelets were made routine. There have been 105 fatalities reported to the Red Cross in 4 years; about half have been confirmed as blood related after study. With restriction of FFP to male donors and the planned initiation of leukocyte antibody

testing, it is expected to eliminate 60% of the TRALI cases. TACO and antibody negative TRALI are not being addressed as yet. Culturing for bacteria of apheresis platelets has eliminated 186 true positives of about 1 million tested. Most of the contaminated products missed do not cause reactions and are not clinically significant. Babesiosis is geographically limited to the Northeast, where in some areas as many as 1:1,000 units are contaminated. Red Cross has had 8 reports in their system, which is a lot. Dengue fever is found in some US Territories. As many as 1:1,300 donors may be viremic at the time of donation. The list of emerging pathogens is almost limitless so that research in pathogen inactivation should be encouraged. Meanwhile, the focus should be on appropriate use, availability and product safety.

Ms. Finley opened the discussion by pointing out that she had written the 1995 report attesting to the relative safety of blood transfusion. We can't control external forces, but we can control what we do. What tests would Dr. Benjamin not do, or stop doing? He replied that we really need pathogen inactivation. She asked about the current status. He noted that inactivation had been adopted in Europe for platelets and for plasma. There is a system for plasma, SD plasma that was licensed for use in the US. There is no system for red cells. Red Cross has a small research program at the Holland Laboratory. Dr. Sandler said that the Red Cross had SD plasma and they took it off the market. Why don't they bring it back? Dr. Benjamin said that the Red Cross did not make the SD plasma and it was the manufacturer who took it off the market, not the Red Cross. Dr. Bloche asked for Dr. Benjamin's thoughts about the rationality and management of risks, pointing out that the risks of blood transfusion are lower than most public health risks when subjected to cost-benefit analysis. The response reflected a personal view rather than an official stance of the Red Cross. Blood is basic to health care so that safety should be paramount, somewhat akin to hand-washing. If patients do not have faith in the blood supply they may lose faith in the health care system in general. He prefers to avoid all possible risks rather than use a cost-benefit approach. Dr. Bloche noted that equivalent sums spent on such things as cleaning up environmental toxins in underprivileged areas or other investments in public health. This generated considerable discussion, focusing on one role of the Committee to consider societal issues in making choices on where funds should be spent. The cost-benefit approach is a challenge to the status quo. Although pathogen inactivation is a preferred way to go, it would not obviate the need for surveillance. Another question was about specifics in a hemovigilance system: will it look at outcomes or address specific problems. Dr. Bracey commented that we were in the early stages of planning for a system and it was very difficult to describe it precisely.

Dr. Kouides suggested that guidelines for use should be given greater priority, giving as an example TRALI and the role of plasma. Oral vitamin K is a low tech approach to the treatment of Coumadin coagulopathy with an elevated INR. In his community, 2% of the adults are on Coumadin. It is often a reflex to give FFP for an INR of 1.6. Vitamin K should be tried first. Another speaker commented that of 24 fatal cases of TRALI due to plasma in his region, 12 of them were given plasma for Coumadin reversal. A national body such as AABB or some other forum should definitively state that it is inappropriate to give plasma to reverse Coumadin in a non-bleeding patient. It has been a challenge in

other areas (e.g., chest) to get physicians to follow them. Perhaps if CMS were to reimburse based on "best practice," it would give teeth to guidelines. From the perspective of managing transfusion services for 15 hospitals, Dr. Triulzi confirmed that compliance with guidelines was the problem. When CMS based reimbursement on best practices in the use of ACE inhibitors in congestive heart failure, the compliance rate rose from 30-40% to 60%. Information Technology (IT) is becoming available and ability to correlate ordering with laboratory values, providing concurrent opportunities to improve practice. Another speaker noted that evidence was often lacking to support evidence-based guidelines, but if randomized controlled trials demonstrated that something was harmful, it would be easier to have compliance. Dr. Holmberg asked Dr. Triulzi if his statement of need for a point-of-release test for bacterial contamination of platelets foresaw replacing current culture techniques or would be in addition to them. The answer was no, and since the major risk after culture is day 5 or beyond, point-of-use testing would focus on older platelets. Dr. Holmberg asked also for further discussion of the need for a "mandated funded" hemovigilance program. Dr. Triulzi reported great benefit from their internal hemovigilance program in improving patient safety.

The next speaker was Klaus Nether, MT (ASCP) SV, to discuss Joint Commission (name change from JCAHO) thinking about transfusion and transplantation safety. The focus the end users, healthcare organizations. The Joint Commission (JC) is the nation's oldest and largest accrediting body: 95% of patients admitted to a hospital today will enter a hospital accredited by the JC; they accredit and evaluate over 15,000 healthcare organizations and programs in the United States. The Joint Commission assesses compliance with standards during the on-site accreditation process. There is well documented potential for infections and other adverse events in transfusion and transplantation. The latter is growing in importance with the growth of tissue transplantation. The JC has become aware of a need for better coordination internally between transfusion and transplantation inspections and accreditations. Even though the percentage of adverse events is low, it can add up to an important number of individual patients. The JC has developed Standards for critical access institutions and ambulatory care facilities (including office-based surgery). Blood transfusion standards are comprehensive, while there are gaps in those for transplant. The collection, storage, delivery, intake at the hospital and use by various clinical services is decentralized and complex. JC has spread information about requirements through their web site, including a group of frequently asked questions. Tissue standards and elements of performance used for accreditation purposes tends to be general: require *processes* for intake, storage and distribution of tissue, for tracing to be able to follow in either direction from the source to use in a patient with follow up through the entire course (especially, though not exclusively for sentinel events). JC has a separate office of quality monitoring which review complaints and sentinel events. The sentinel event policy is based on voluntary reporting or on following up adverse event reports. Adverse events should be reported to the supplier (by FDA regulation for blood; by JC policy for tissue). Blood and tissue should have a well coordinated system. Solid organ transplantation are not now addressed. Transfusion is heavily regulated by FDA and CMS (including CLIA). JC requires record retention for 10 years. As for the future, a Standards Improvement Initiative is underway, beginning in early 2007 with a stakeholders meeting for comments

on draft performance measures. They are seeking funding to proceed further. In the summer or early fall of 2007, a task force will be convened to review tissue standards and discuss the potential of including solid organs.

Dr. Bracey opened the discussion by asking what the role of the JC might be in a public/private partnership for biovigilance and safety improvements. Response: The JC expects to convene a group of experts from government, tissue, blood and possibly organ groups to focus on commonalities and blood as a model. A speaker noted that a clinician must recognize an adverse event and decide to report it or not for it to get into the system. He asked what provision the JC had for hospitals to educate physicians to improve their performance. In response, Mr. Nether reiterated the presence of "Frequently Asked Questions" on the JC web site. He agreed that there was underreporting, especially if the outcome was not bad. Dr. Kuehnert agreed and pointed out that the hospital infection control program could be a model. To bridge the gap of clinician reporting will be a challenge. Dr. Holmberg encouraged the JC to move forward with requiring adverse event reporting from clinician to hospital blood bank or laboratory to the blood or tissue center. Many organizations have some stake in safety and adverse event reporting and he hoped that they all could work together to come to a common plan or system.

Dr. Bracey then called for general Committee discussion, focusing on the questions posed by Dr. Holmberg, the first of which was: is there an opportunity to lay out a process for transfusion and transplantation safety in the future? Dr. Klein began by suggesting that there was an enormous opportunity to incorporate the commonalities of tissue/organ transplantation and blood transfusion into a system of surveillance with review and corrective action that we as a nation do not have, contrasting with most of the rest of the developed world. The Red Cross system might serve as a beginning, but this Committee, made up of appropriate people from multiple disciplines, is in a unique position to develop such a system. His personal bias is that this is a public health issue. A public/private partnership would be useful, but this is a government public health responsibility. Ms Finley asked if a better format for the Secretary might be first to lay out the process and then address what elements would be needed. Is Dr. Holmberg asking for a yes/no vote? Or for the development of "points to consider" for the Secretary? There certainly was scientific and historical evidence to support the need for this planning. Historically, there was a National Blood Policy in the 70s, some elements of which led to problems in the 80s. The Policy was never fully embraced, partly because there was no mechanism like this Advisory Committee to implement it. It is important to recognize that at one time there was a national strategy in healthcare policy-making in the US.

Multiple speakers took part in the discussion. It was pointed out that the Committee has already spoken to the need for a system of biovigilance and suggested that a working group be formed to work out the details. Dr. Agwunobi had asked what the real need was, what were the driving forces, is it practical and feasible? Dr, Holmberg said that these recommendations from September 2005 appeared on his slides 9 and 10 and on the handouts provided to the Committee. Dr. Bloche asked how could it be made to happen

and Dr. Matyas raised the questions of the resources needed, how it would be enforced and who would pay for it.

Dr. Epstein suggested that some of the drivers included a desire for coherence in reports across various parts, e.g., organ/tissue transplantation and blood transfusion. The database needed better reporting, acquisition and analysis of information. How can we take advantage of existing data sets? Questions include who owns the data and what is the role of government vs. that of the private sector. Responsibility and accountability must be assigned. It needs to be decided if this is a public health function, as suggested by Dr. Klein. Resources must be provided and incentives determined. Much of the research agenda needed is common to organ/tissue and blood. The current database is not adequate to support many of the standards that are in place. Nevertheless, although harmonization is important, it should not be the goal. For example, ISBT for labeling might be expanded to all materials for tracking, but there is incredible diversion in processing standards. Bacteriological testing of platelets is well established, but methods for determining sterility of tissues are not well worked out and may be ineffective. Dr. Triulzi noted the 8 levels of safety enumerated by the AABB (Dr. Strong's presentation) and suggested that they be applied to other than blood as well. Immediate short term benefit could be gained by fully developed traceability from donor to outcome. There is really no excuse not to have a good traceability system.

Several discussants pointed out that they were still in the middle of the presentations. This discussion might best be deferred until tomorrow after the remaining talks. Dr. Klein pointed out that the May 2006 discussion was high level and tended to lump things rather than split them. One model for discussion may be the FDA Blood Action Plan, which was excellent, but took 10 years to do; this Committee doesn't have that kind of time. He suggested that they select a few parts that would be concrete and doable in the 18 months left of the present Federal Administration. Resource could probably be found for something that was important. Dr. Solomon remarked that available legal authority might restrain Federal action. For tissue, regulatory authority is based upon legislation to prevent the transmission of infectious disease. Current regulations require tracking to the consignee, not to the recipient. There are few regulations on labeling of tissue and they wouldn't allow mandating the use ISBT. Rule-making, if needed will take years. With elections coming, there is unlikely to be a lot of rule-making. Dr. Triulze suggested that the Joint Commission and other accrediting agencies (e.g., AABB, AATB) might pick up the slack.

The meeting adjourned at 6:00 PM, to reconvene in closed session for annual ethics training at 8:30 AM the next day.

At 8:30 AM, May 11, 2007, the meeting was called to order and the roll called. Dr. Holmberg was asked about the policy for substituting attendees for those unable to attend. Representatives of Government Agencies were not designated as individuals, so that substitutions could readily be made. No substitutions were possible for Special Government Employees (SGE).

Dr. Bracey remarked that the previous day had been devoted to blood issues; this day was going to address organ and tissue transplantation before recommendations to the Secretary would be developed.

He then introduced Scott A. Brubaker, CTBS, representing the American Association of Tissue Banks (AATB). The AATB was founded in 1976 as a professional non-profit, tax-exempt, scientific and educational organization with a mission to promote tissue transplant safety with sufficient availability to meet patient needs. It serves as a liaison between their member banks and multiple organizations and hospitals. Authoritative standards were first promulgated in 1984 and voluntary accreditation beginning in 1986. Technician certification exams have been offered since 1987, with more than 3,000 Certified Tissue Bank Specialists (CTBS) worldwide. There are now 99 accredited tissue banks in the US and Canada that recover tissue from about 25,000 donors and distribute about 2 million grafts. They are also involved with reproductive banks (about 12 listed) and with living donors, autologous and allogeneic. For tissue banking, there are Joint Commission Standards, some state laws (e.g., NY, Florida and California) and Federal Regulations (including GMPs; much of the regulation is under classification as "devices"), but AATB Standards are more extensive and detailed, and sometimes supplemented with "Guidance" and "Bulletins." A surveillance and reporting plan is being developed.

Donor histories follow a uniform standard (similar to that for blood donors), but are usually from records or relatives and have their limitations. It sometimes is difficult to get a satisfactory blood sample for testing. About 11% of organ donors are also tissue donors; organ donor acceptance criteria are not strictly defined by OPTN/UNOS and use CDC recommendations from 1994. Laboratories testing organ donors do not need to be certified and there is no requirement to assess hemodilution (from IVs). The tests need to be approved by the FDA for use in transplant donors, but the degree of compliance is unknown. Tissue banks may be at a disadvantage when using material from organ donors. HIV and HCV NAT have been required for two years. On the other hand, tissue is processed, sometimes highly so. For example, bone is cleaned and washed and may be acid-treated, subject to sonification, lyophilized and irradiated. Some bone may only be cryo-preserved. Skin may be cryo-preserved, lyophilized or used fresh. All grafts are sent from the tissue bank with a response card to record use and allow tracking. Compliance with completing and returning these forms is less than 100%. He provided several examples of disease transmission from organs and tissues. Highly processed bone did not transmit, while fresh-frozen bone, ligaments or joints did. Solid organs from infected donors had a high probability of transmitting the infection. Some of the examples had near 100% traceability from and to the donor and recipients. Some bone chips and powder are used in dentistry, sometime in a dentist's office. Traceability of bone chips or powder may be difficult.

Another problem identified by Dr. Brubaker was the wide responsibilities for regulating tissue banking. Most of the advisory committees (e.g., BPAC, ACOD, ACBSA) have minimal or no representation from tissue banking. There are commonalities in donor screening, for example, in reproductive, ocular, organ, cell and blood donations. The

processing, of course, may be considerably different. Nevertheless, safety, especially for tissue transplantation, is high.

Dr. Bracey opened the discussion, asking what percentage of tissue banks are accredited by AARB? Dr. Brubaker replied that he wasn't sure; he had submitted a Freedom of Information request to FDA, but had not yet received a reply. From a manual search, there were 865 "processors," 15 of which listed bone and 13 were accredited. He estimates that 95% of the tissue *distributed* in the US came from accredited banks. Ms. Finley asked about the statement on slide 11 that there was 85% compliance with FDA requirements. That was clarified by Dr. Solomon that it was in the "estimated industry burden" in the preamble of the Good Tissue Practices final rule: a bank following AATB standards was already in compliance with 85%, so that the additional burden of the rule was minimal. Ms. Finley then asked if all tissue banks met AATB standards? Or if only those who were members did so? A requirement of membership was following the standards. Compliance was not known, although FDA ORA would have those data. AATB does not keep tabs on non-members. He confirmed Ms. Finley's comment that registering with the FDA and listing procedures were regulatory requirements; following AATB standards was optional. Dr. Kuehnert noted that tissue banking had no "home" advisory committee. He asked about the completeness of follow through on the examples of tracing tissue after a report of disease transmission. In response, rabies had been transmitted only by organs, where tracking was complete, but not by tissue where there were some gaps in traceability. In other cases, tracking was initially 74% complete, increased to 98% after thorough investigation. How long did the tracking take? About 30 days. It is hoped that the bank involved will discuss their performance and problems at the next AATB annual meeting.

The next speaker was David Ball, PhD, representing the American Society for Reproductive Medicine (ASRM) and the Society of Assisted Reproductive Technologies SART). Although he is an embryologist working primarily in the laboratory, he also has contact with patients. They deal primarily with materials produced by couples for "autologous" use. ASRM is a voluntary organization, but a huge majority of those who work with ART are members. SART members work primarily with in vitro fertilization; 98% of IVF clinics are SART members. Donations include sperm, eggs and embryos. Most sperm donation is handled by commercial organizations; SART members deal mostly with infertile couples that are sexually intimate. There are 120,000-139,000 "cycles" (never really defined) per year in the US, 10% of which or 10,000-12,000 actual fertilizations per year. Eggs are handled primarily by ART programs, although some commercial agencies are involved. None of these do testing of donors. Embryos are handled only by ART programs, although there are a few non-profit "adoption" agencies that find "homes" for some embryos produced by couples who no longer have a need for them. Their useful shelf life is measured in decades, perhaps centuries. Embryos may be stored by facilities that do perform donor eligibility screening. Current oversight is limited and ART has been an unregulated industry. The Wyden bill in the early 90s mandated that "cycles" be reported to CDC for outcome monitoring. Laboratories are regulated through CLIA and often inspected by CAP and the Joint Commission. Since

May 25, 2005, these activities have been inspected by FDA and subject to GTPs. As of January 2007, 30% of ART programs had been inspected by FDA.

ASRM and SART have several concerns. There seems to be no recourse from a false positive test result, no re-entry protocol. Egg donors are rare and often related to the infertile couple. There can be very few donation cycles per donor. Hence, donor loss can be a problem. The costs for IVF treatments must be borne by the couple; insurance rarely covers. There are no good data on embryos as disease vectors, although such transmission is believed to be rare. Sperm disease transmission is also low. They are dealing with sexually intimate couples, so that added risks must be small. There are ethical considerations surrounding the fate of embryos no longer needed or wanted by the generating couple. Eight years ago, a study suggested that there were 500,000 embryos frozen in liquid nitrogen with a "shelf life" of at least decades. There are undoubtedly more now. Most (80-90%) were generated for "autologous" use by couples who by now have completed their families.

Next was Michael J. Joyce, MD (Cleveland Clinic), a member of AATB, who spoke on behalf of the American Academy of Orthopaedic Surgeons (AAOS). Bone allografts are safe and may improve function, allow the reconstruction of limbs and enhance quality of life. There has been considerable progress with the development of Federal Regulations and Guidelines and standards from the AATB and the Joint Commission. Dr. Brubaker has discussed some of the problems, although most have involved non-accredited tissue banks.

Advisory Statement
Use of Musculoskeletal Tissue Allografts Dec 2006

The American Academy of Orthopaedic Surgeons (AAOS) believes that for appropriate patients musculoskeletal allografts represent a therapeutic alternative. These tissues should be acquired from facilities that demonstrate compliance, use well-accepted banking methodology and follow Food and Drug Administration (FDA) Good Tissue Practices. The AAOS urges all tissue banks to follow rigorous national guidelines and standards[1, 2] and recommends the use of tissue from banks that are accredited by the American Association of Tissue Banks (AATB).

FDA has required that tissue banks register and list what they do since May 2005. A non-binding Guideline (effectively a mandate) published in February 2007 asked that all tissues collected after August 28, 2007 be tested for HIV and HCV by NAT. It should be noted that musculo-skeletal tissues are stored for an average of 2 years before use and they may be held in inventory for as long as 5 years. Inventory testing was not addressed in the Guideline. Tissue is usually ordered by the hospital and an individual orthopedic surgeon may not have control over the source. Aside from knowing and trusting the source, sticking to tissue from accredited banks is a safety measure. He estimates that the return rate for cards sent with tissue, as mentioned by Dr. Brubaker, was only 70-75%. This may improve as a result of Joint Commission standards, since most hospitals feel the need to be approved by the JC. He is not aware of any major hospital being cited by JC for failure to return the cards. Tissue management is decentralized in most hospitals: cardiovascular tissues and human heart valves are handled by cardiothoracic surgery;

orthopedic and plastic surgical use by their respective services. Blood banks may not wish to become involved. At the Cleveland Clinic, they can get NAT testing done for organs and tissues with a 5 hour turnaround time. This is not true for all Organ Procurement Organizations (OPO). Unless a NAT result is available "up front," it may create more problems than it solves. An upcoming speaker, Ted Eastland, is expected to address the need for centralization within a hospital.

In the discussion, Dr. Holmberg asked if the immediately preoperative checklist ("time out") could include the completion of the return card for the tissue bank. Dr. Joyce thought this was a good idea, but cautioned that physician behavior could not easily be changed. Another question was about a possible role for a tissue committee, analogous to a transfusion medicine committee. The response was that some places do have such a committee in place. Dr. Solomon pointed out that FDA Guidance focused on helping comply with regulations. FDA was considering a public discussion about some of the issues mentioned, e.g., defining sterility, standardizing processing methods and terminology. If this is scheduled, a notice will appear in the Federal Register giving time, place and topics. One speaker cautioned that transmission of an infectious agent by blood did not automatically mean transmission by tissue. Ms. Thomas asked about the frequency of disease transmission. The response was that exact figures were not available and that more data were needed.

The next speaker was Jay A. Fishman, MD, Transplant and Immunocompromised Host Program, Transplant Center, Massachusetts General Hospital, Boston, representing the United Network for Organ Sharing (UNOS). He was trained in infectious disease and, although heavily involved with organ transplantation, he doesn't really speak for UNOS. There are key differences between organs and other transplants, including blood, although blood is perhaps most closely parallel. Organs are made up of vascularized viable tissue which makes them a superb vehicle for virus transmission. There is only a short time for screening because organs must be transmitted within 4-24 hours of harvest. Screening technology is limited; tests developed for mass screening of donated blood may not be approved for single donor format using cadaver blood. Organ transplantation is regulated by HRSA, not by FDA. Organ recipients are all immunocompromised, at the least by therapy to prevent rejection. A recent example is the transmission of a new virus (found to be LCMV-like) to 3 recipients of organs from a single donor with a fatal outcome in each. The virus was not detectable in the donor blood or tissues, even after specific primers had been developed. False positive test results can be a problem. NAT assays are highly sensitive and as such capable of being falsely positive. Unnecessary loss of donors can be a problem: In the US each year, there are about 8,000 donors providing about 28,000 grafts, a long waiting list for organs, from which 7,000 die each year waiting for a donated organ. Things have changes since 1997 when viruses were "where they were supposed to be: Japanese encephalitis in Japan; St Louis encephalitis in St Louis and West Nile Virus in the West Nile." New tests may not be the answer: they take time to develop and validate and they must fit into the short time available between harvest and transplant. The only absolute infectious disease exclusion at present is HIV. UNOS is setting up a Transplant Transmission Sentinel Network to which an existing Disease Transmission Advisory Group will report. Needs include resources to

investigate potential problems, reference laboratories readily available, anticipatory action to discover emerging pathogens and mandated reporting. UNOS is considering archiving specimens for follow-up studies when needed; Canada is currently piloting such a project.

Dr. Kuehnert began the discussion by clarifying that organ transplants were regulated by HRSA, not by some amorphous part of DHHS. Different deferral criteria are used for prospective organ donors. There are no absolute reasons for deferral. Rather, informed consent is obtained from the transplant team and the potential recipient for donors who have risk factors for transmitting an infectious disease. They may even harvest organs from donors known to have an infectious disease. The social history forms differ from one OPO to another. The history is often obtained from stressed out relatives or friends who may not know details about the potential donor's behavior. Hearts and livers are often used for recipients with an urgent need who may die within a few hours or days. For kidney recipients, dialysis is available to tide a patient over until a suitable organ is available. Organs are often shared with other transplant units who might have patients with a more urgent need. Dr. Holmberg asked if there were different numbering systems for organ identification in the TTSN. Dr. Fishman replied that the numbers were different for different grafts, but that each donor had a unique number to which the others were tied. Dr. Holmberg asked about donor testing. In response: blood donor screening tests were used, although they might not have been approved for use with cadaver or neo-mort blood. Dr. Solomon said that all currently licensed tests are approved for organs donor testing. Dr. Fishman replied that the manufacturers' information for WNV NAT tests did not reflect that approval. Dr. McCurdy reported that one of the two original contracts (from NHLBI) to develop NAT tests specified for use on organ and tissue donors, with the expectation that they could be done in the regular hospital laboratory at any time (24/7) by technical staff that had little or no specific training for NAT testing. The contractor's (Gen-Probe) original concept was for a single tube procedure. Dr. McCurdy did not know the final outcome of this concept, although approval of a test for organ donors was obtained. Dr. Fishman questioned if the labs would be available all 24 hours. The response was that laboratories in hospitals with a transplant unit would be staffed for many tests 24/7.

The first speaker in the Open Public Hearing was Ellen Heck, MT, MA, Director of the Transplant Services Center, University of Texas Southwestern Medical Center, speaking on behalf of the Eye Bank Association of America (EBAA). Eye banking (mostly cornea) has many similarities to other types of organ/tissue banking and transplantation, but there are important differences, as well. EBAA was founded in 1961 and now represents 98% of the eye banks in the US and some others world-wide. The first standards were promulgated in 1981 and are kept current with board review at least twice a year. Testing for HIV began for eye donors in 1986 (the first among tissue transplants to require testing), followed by the addition of tests for HBV and HCV. There have been only 2 disease transmissions reported since 1987. She remarked on a recent transmission of rabies in Texas (she is from Texas). The donor was disoriented, febrile and was considered perhaps to have encephalitis; he was declined by the eye bank on these grounds (recovery of eye tissue is safer for the staff than is retrieval of other organs or

tissues), even though the policy often is to retrieve the eyes first, deferring the decision to use until more information is available. Of 35,000-40,000 eye tissue transplants annually, primary graft failure occurs in only about 0.2%. Chagas disease may be a problem in Latin America, but less so in the US. There have been no reports of transmission of Chagas' disease by cornea transplants. Cornea transplant recipients are not immunosuppressed, as is the case with other transplants. Irradiation and other approaches to sterilization are not an option with corneas. The question if WNV can be transmitted by corneas is unanswered at present. The fact that corneas are avascular may be saving. The EBAA applauds the attempt by the FDA to divide tissues into white cell rich and white cell poor, treating them differently.

The next speaker in the Open Public Discussion was Barbie Whitaker, PhD, Director of the Center for Data and Special Programs, AABB, and participant in the Interorganizational Task Force for Hemovigilance, which includes both government and private representation. The elements of a national biovigilance system are: reporting should be voluntary; it should be non-punitive, confidential and web-based. A pilot system to start should focus on 5 serious untoward results of transfusion and 4 important events, but should allow and encourage other reaction reports. The ISBT Working Party's definitions of adverse events could be used as long as it didn't contradict US terminology in common use. The MERS-TM system for defining and classifying events should be used (described during the August 2006 ACBSA Meeting). It is useful to learn from the experience of other countries, but one should realize that the US does not have a unified national healthcare system, like other countries. The government doesn't pay for data collection and analysis. We have a public/private healthcare delivery model which relates to a public/private model for hemovigilance. Examples include the TTSN, a partnership between CDC and UNOS and the data are outside the government; the Stem Cell therapeutic outcome data base that is funded by the CW Bill Young Cellular Transplant Program through HRSA, but maintained by the CIBMTR. The system would collect information for evidence-based medicine and decision-making and must be flexible. A regulatory requirement that questions and software be approved by the OMB would make it difficult to be nimble enough to respond to new threats. Another suggested model is the National Healthcare Safety Network from CDC for the collection of information about nosocomial infections in hospitals. These infections have an effect on length of stay in hospitals, which in turn affects the finances of hospitals and third party payers. This provides more incentive for establishing an infections control officer than is present for the parallel transfusion safety officer (as is seen in Canada). She cautioned against collecting data for its own sake as too costly, but urges the development of real time analysis to provide prompt useful feedback to support changes where needed.

Corey Dubin (Committee of Ten Thousand) began his comments with a case report. A patient with hemophilia had joint replacement surgery that involved the use of cadaver bone. Two months after surgery he was told that the graft was infected with HIV. It is upsetting that the patient was not informed for two months and that there apparently was no adverse event reporting system to help prevent future problems of this nature. This type of orthopedic surgery is common for hemophiliac patients and others are getting

liver transplants for hepatitis C. There are only three places where an HIV positive patient with hemophilia can get a liver transplant for end-stage hepatitis C. He and COTT don't understand why adverse event reporting isn't mandatory. He strongly recommended that reporting be made mandatory.

After the lunch break, Dr. Cunene (phonetic) commented about the likelihood of near misses in addition to the adverse events discussed. He asked Ms. Hech about the shipment of corneas outside of the US, e.g., to Algeria, and their effect on tracking. She responded by noting that within the US, corneas are usually shipped with a particular patient in mind. After harvest, they are offered in the US for up to 4-5 days, and then offered overseas if not taken. Overseas tracking is less easy, but fairly well established. On the other hand, scleral tissue may be stored for a period before use. The number of sclera samples is limited, however, a maximum of 8 pieces per donor, simplifying the problems of tracking. Eye Banks get good compliance, better than with orthopedic, plastic or burn surgeons for whom tissue is taken out of storage for use. About 7,000 - 8,000 corneas are exported outside the US annually or about 15-20% of the total. Dr. Solomon commented that eye recovery can be done by one person in one of several places (e.g., OR, hospital room, funeral home, pathology department), much less complex than with other tissue retrievals. Dr. Holmberg remarked that there must be different criteria for accepting eye donations vs. organs and tissues. Ms Hech noted that Eye transplant activities are regulated by the FDA, which facilitates standardized procedures. Dr. Black asked where overseas corneas were sent. What are the allocation principles? Answer: Too many countries, too numerous to list. Allocation within and outside the US is based on semi-formal networks. Money is not an object, although cost-recovery is sought. There are no formal protocols, nor is anything about allocation available on the web. Eye banks take as their mission to restore sight, and all else is secondary.

After the Open Public Comment period, the next speaker was D. Ted Eastland, MD, Medical Director, Transfusion Services, Therapeutic Apheresis and Stem Cell Collection, University of Minnesota Medical Center, Minneapolis, whose topic was Managing Tissues in Hospitals. His experience encompasses 11 years as a transfusion service director, 16 years as a regional blood center director and 11 years as a regional tissue services medical director. There are many similarities and a few differences between blood services and tissue services. In particular, donor exclusion criteria and testing are similar, but the processing are different and the differences have an effect on disease transmission. Most tissue need not be viable and processing may involve physical cleansing and other techniques to remove extraneous tissue (e.g., fat), treatment with peroxide and gamma irradiation. Missing in most hospitals' approach to tissue banking and use are follow-up of adverse reactions, recalls and look-back to other recipients of transplants from an implicated donor. Traceability to and from donors and recipients is often less than 100%. More studies are needed, both prospective and retrospective, about the prevalence of infected tissue. For example, it has been estimated that 18-20% of non-sterilized tissues are contaminated with bacteria, despite care in harvesting and handling the tissues. There is movement of bacteria from the gut and from the skin after death, but the rate and quantities involved are not known. Around 1990, the potential problems with tissue transplants were recognized and the Red Cross, AABB, AATB and Joint

Commission developed standards for tissue banking and use in hospitals. The JC had teeth in that most hospitals both needed and wanted accreditation. JC 2005 standards pertained to operating rooms, surgical centers and hospitals. In hospitals, various non-standardized services ordered the tissues and traceability was attempted via the patient billing system. The chain of command for reporting adverse events was unclear. Recognizing this, the AABB convened a Tissue Committee, with representatives from the Joint Commission, FDA, Eye Bank of America, AATB, Armed Forces, American Association of Orthopedic Surgeons and CDC. A 2005 survey showed great heterogeneity in the management of tissues. In only about 50% did the blood bank play any role; many hospital blood banks were not interested. The role of the tissue bank medical director was often minimal and unclear. Nevertheless, available information suggests that tissue transplantation is relatively safe. The Tissue Committee, however, recommended that tissue management be patterned after the management of blood for transfusion.

Dr. Roseff open the discussion with two questions: 1, how many people to you have for tissue management? Answer: At the Beaumont Hospital, we have one full time person with 11 years of experience plus part of the medical director, who covers both blood and tissue. 2. What cultural and historical issues were involved in moving tissue management from the OR to the blood bank? Response: Some OR staff were reluctant to give up a service they liked doing, but many of them realized that the details involved were becoming too much for them. They lacked leadership and often asked if what they were doing was OK or needed to be changed. Besides, the move to the blood bank was a good thing to do, so they would do it. Ms. Bensinger pointed out that the surgeon rarely saw the patient very many times after a successful operation, so that he was unlikely to have much responsibility for following up on adverse reactions. The patient's responsibilities for keeping their primary physician informed should not be forgotten.

The next speaker was Marc Germain, MD, FRCP(C), PhD, Vice President, Human Tissue, Hema-Quebec, and a microbiologist by training, who discussed the Quebec and Canadian Blood Service experience with hemovigilance. In Canada, the exclusive responsibility for providing blood services lies with Hema-Quebec (population 7.6 M) and Canadian Blood Services (population 25.8 M). Both are members of ABC. Regulations come from Health Canada (similar position as FDA) but the provinces finance medical care. Blood establishments are licensed, much like in the US. Canadian blood centers adhere to AABB Standards. There is a proactive hemovigilance surveillance system for adverse events related to transfusion, which began in Quebec and is now spreading throughout Canada. Most major hospitals have a Transfusion Safety Officer who is responsible for collecting event data and submitting it to a central repository (for all of Canada). These data are analyzed and findings fed back to the hospitals for action, if needed. Blood transfusion is very safe, as safe as possible with present knowledge, and is considered a benchmark for cells, tissues and organs (CTO) for transplantation, which are not as fully developed. Health Canada has moved into CTOs relatively recently, asking in the year 2000 the Canadian Standards Organization to develop standards for cells and tissues (organs are managed by a separate organization; in Quebec, it is Quebec Transplant). The CSO in Canada develops standards for multiple

disciplines. These standards are similar to those in the US CFR, except at the start they were voluntary. In 2003, these standards were issued as a "Directive" which is one step below regulations, but does have the force of law. A National Review of known tissue banking operations asked each to describe their level of compliance with the Directive. Regulations were developed referencing the standards – "standards-based regulation." Health Canada has no authority over the hospitals, which are controlled by the provinces. However, there are few comprehensive tissue banks in Canada and the banking process is decentralized. Only a few are AATB accredited. Some of the problems with tissue banking and tissue transplant safety include: lack of standardization, limited traceability, no real provision for look-back, no control over importation of tissues from outside of Canada (90% from the US) and the practice of sending specimens to the US for testing. He would like to see tissue banking developed similar to blood, although it would not have to be by the same agency. In this, he supported the approach taken by the previous speaker (Dr. Eastland).

Dr. Holmberg started the discussion from the standpoint of readiness and preparedness, asking about the availability of skin in Canada; it's in short supply here. Answer: not in his province. They can't find skin on the US market, but fortunately haven't had any major disasters that would require skin for transplant. Dr. Holmberg then asked if Canada was involved with the ISBT 128 advisory group. In response: ISBT is being put into place for blood; he is part of the AATB group that is trying to adapt it to tissues. Dr. Holmberg then asked if AATB standards would require all to use the same numbering system. Dr. Germain referred it to Dr Brubaker with the comment that AATB was pushing for a uniform numbering system, but hadn't settled on ISBT 128 yet. Dr. Brubaker confirmed the involvement of the ICCBBA in the challenge of adapting ISBT 128 to the different types of tissue grafts. Ms. Finley asked what steps the Canadian Government had taken to achieve greater self-sufficiency for blood-derived and plasma products and tissues and organs? She noted problems with that for at least 12 years, especially with IVIG and anti-hemophilia products. She clarified that she wanted a general discussion, not specific to IVIG. Dr. Germain was not part of the Canadian Consensus conference on the self-sustainability of blood derived products, with a focus on IVIG. The recommendation was to reduce dependence on US source plasma, recognizing that that was likely not possible, but suggesting that complete self-sufficiency was not necessary. There has been no similar exercise concerning tissues. There is the Canadian Counsel for Donation and Transplantation to advise the federal and provincial governments toward improving cell, organ and tissue services in Canada.

Dr. Bracey opened the general discussion and recommendations period by quoting the August 2006 recommendation by the Committee:

> "Whereas promoting the safety of the U.S. blood supply's principle activity, the advisory committee inclusion of efforts to improve organ and other tissue safety and availability also need to be considerably recommended to the secretary that the secretary coordinate federal actions and programs for support and facilitate by a vigilance in partnership with initiatives of the private sector.
>
> "'Biovigilance' is defined as a comprehensive and integrated national

patient safety program to collect, analyze and report on the outcomes of collection, and transfusion and/or transplantation of blood components derivatives, cells, tissues, and organs. The program should be outcome driven with the objectives of providing early warning systems of safety issues, exchanging of safety information, and promoting education and the application of evidence for practice improvement.

"Formation of an HHS and PHS biovigilance taskforce would be an important step for identification of the vision, goals, and processes needed to advance these objectives. This task group should participate with private sector efforts, including the AABB inter-organizational taskforce on biovigilance to advance public health in this effort."

From that, he, Dr. Kuehnert and Dr. Holmberg drafted the following:

"The HHS ACBSA heard presentations on the status of safety systems for transfusion, tissue banking, and transplantation from major blood collectors, accrediting agencies, and practicing physicians in its May 2007 meeting.

"The committee was impressed by the number of common issues facing these activities and the opportunity for a process improvement. Whereas, the Assistant Secretary for Health accepted the Committee's August 2006 recommendation to pursue Biovigilance by expanding the role of the Committee's oversight in its new charter and by establishing a PHS Biovigilance task group, the Assistant Secretary requests additional input from HHS ACBSA.

"The Committee responds to the following question posed by the assistant secretary.

1. Is there an opportunity to lay out a process for transfusion and transplantation safety for the future? The answer or the response being yes, there is a need to develop processes to enhance quality improvement in transfusion medicine and transplantation. While transfusion medicine laboratory processes function at a high safety level, there is a great need to enhance and further develop quality systems in tissue banking and transplantation. Recognizing the difficulty in acquiring some tissues and organs a careful risk benefit analysis should serve as the foundation of such quality systems.

2. Is there scientific evidence to support the need for a master strategy? Yes. While the literature is in need of expansion, available infectious disease transmission and error reports substantiate the need for quality improvement noting the benefit risk profile differs between transfusion, tissue, and transplant recipients. All patients treated with these modalities have potential for acquiring life-threatening infections if infectious disease screening is flawed or emerging unknown diseases evolve unchecked over time.

Non-infectious hazards with potential for implant/transplant failure through host rejection or graft failure due to faulty preparation, processing or testing are also important hazards in this patient population.

3. What should be the scope (rubric) of a master strategy for recipient outcome surveillance (biovigilance system)?

A. identify all donors using common identification numbers linked to biological products that are uniquely identified.
B. trace all biologic products to the clinical user and recipient.
C. recognize transmissible events resulting in adverse outcome, including: i. infection agents; ii. malignancies; iii. toxins.
D. build a communication network to share data from users and to disseminate data to users.
E. allow efficient trace forward and trace back algorithms across all product types.
F. given large gaps at the user level, i. there is a need for healthcare based programs to coordinate adverse event reporting. i. there is a need for new approaches to infectious disease monitoring including informatic tools and evidence-based research. iii. other strategic plan elements should include a) donor recruitment, b) donor screening, c) research coordination, d) emergency preparedness.

4. What are the areas of commonality with blood products, core blood, progenerative cells, and bone marrow tissues and organs? And what we offer here in essence are these elements, donor recruitment availability, donor screening, collection, infectious disease testing, transport, much of what we've seen on the various slides, storage, processing, labeling, traceability, surveillance, outcomes analysis, adverse event reporting.

5. How best should this be done with the stakeholders? How do we begin? Develop a forum for developing common priorities using evidence-based decision making. Stake holders should include regulators, accrediting agencies, manufacturers, clinicians, and recipients. This considerable regulatory overlap, the efforts of OBRR, OCGT -- OCTGT, HRSA should be coordinated within the department. These efforts need to be public-private partnerships with transparency, collaboration, and data sharing, but the task of biovigilance is inherently a public health mission and government-based origin, and structure of the system should reflect that premise. And under d, which is not really flashed out much, it says what resources are needed, and, basically, what are the estimated costs.

This was extensively discussed and edited. Drs. Kuehnert and Bowman suggested a pyramid approach. The base or first foundation was a common donor ID number which was linked to all tissues, organs and recipients. That linkage does not now exist. The next step was tracking to the recipient. The third level was recognizing and reporting of adverse events. The weak link here currently is

recognition of events by clinicians, although the reporting chain has not been clear. The fourth level of the pyramid is communication. Finally, system education ties it all together. In their presentation, the AABB suggested a voluntary reporting system that was non-punitive. Dr. Klein opined that hemovigilance was a public health responsibility and that mandatory event reporting was important. There was controversy about voluntary or mandatory reporting, but a large majority of the Committee believed that reporting had to be a requirement. Enforcement of mandatory reporting was an issue; it was suggested that the Joint Commission could play a role in this.

In response to a question as to why blood was licensed and tissue registered, Dr. Solomon noted the history. Regulations are based upon Section 361 of the PHS Act, which focuses primarily on the prevention of infectious disease transmission. The requirement for licensing is in Section 351. Tissue, eye and blood banks are all inspected. For blood, one must submit an application for a license, following which an inspection is done, compliance with regulations assessed and only after a license is issued may they market their products. Tissue and eye banks may market their products and compliance with regulations is assessed at the time of periodic inspections. Dr. Bloche commented that DHHS did not have global statutory authority to impose requirements.

Ms. Finley asked that risk/benefit analysis not be heavily based upon scarcity of materials (organs).

The Committee passed the following responses to the questions asked by the Assistant Secretary for Health and then adjourned:

The HHS ACBSA heard presentations on the status of safety systems for transfusion, tissue banking and transplantation from major blood collectors, accrediting agencies and practicing physicians in its May 2007 meeting. The Committee is impressed by the number of common issues facing these activities and the opportunity for process improvement.

Whereas the Assistant Secretary for Health accepted the Committee's August 2006 recommendation to pursue Biovigilance by expanding the role of the Committee's oversight in its new charter and by establishing a PHS Biovigilance Task Group, the Assistant Secretary requests additional input from HHS ACBSA. The Committee responds to the following questions posed by the Assistant Secretary:

1. Is there an opportunity to lay out a process for transfusion and transplantation safety for the future?

Yes, there is a need to develop processes to enhance quality improvement in transfusion medicine and transplantation.

2. Is there scientific evidence to support a need for a master strategy?

While surveillance evidence is limited, reports of infectious disease transmission and errors substantiate the need for a master strategy for safety. Noting that the benefit-risk profile differs between transfusion, tissue and transplant recipients, all patients treated with these modalities have potential for acquiring life-threatening infections if infectious disease screening is flawed or emerging, unknown diseases evolve unchecked over time.

3. What should be the scope (rubric) of a master strategy?

I. Recipient Outcome Surveillance (Biovigilance System)

a. Identify all donors using common identification numbers, linked to biological products that are uniquely identified

b. Mandatory adverse event reporting process for tissue, organ, and blood therapy through appropriate mechanisms to designated public health authorities and to recipients and donors.

c. Timely and efficiently trace all biologic products to the clinical user, recipient and donor.

d. Recognize transmissible events resulting in adverse outcomes, including:
   i. Infectious agents
   ii. Malignancies
   iii. Toxins

e. Build communication and education network to disseminate data to users

II. Develop informatic tools to support surveillance, process improvement and evidence-based research

III. Include other strategic plan elements as needed, such as:
   a. Donor recruitment
   b. Donor screening
   c. Research coordination
   d. Emergency Preparedness

4. What are the areas of commonality with blood products, cord, progenitor cells and bone marrow, tissues and organs?

Key elements in common with transfusion required for ensuring high quality include:

a. Donor recruitment - availability
b. Donor screening and eligibility
c. Collection

d. Infectious disease testing
e. Transportation
f. Storage
g. Processing
h. Labeling
i. Traceability
j. Good Manufacturing Practices / Good Tissue Practices
k. Outcomes analysis
l. Adverse event reporting

In addition to these commonalities, there is a need to evaluate the differences

5. How best should this be done with the stakeholders? How do we begin?

HHS should convene a forum of stakeholders to include public health agencies, accrediting agencies, manufacturers, clinicians, consumers and end users. HHS should be responsible for implementing a master strategy with appropriate resources based on input from stakeholders.

6. What are the resources needed? What are the estimated costs?

See number 5