Summary:
Advisory Committee on Blood Safety and Availability
Department of Health and Human Services
29th Meeting, May 9-10, 2006

At 9:05 AM, May 9, 2006, the meeting was called to order by Dr. Jerry Holmberg, who then called the roll. He invited the members to reveal any conflicts of interest. There being none he asked that any that arose during a public comment period be disclosed at that time. He then turned the meeting over to Dr. Bracey who welcomed members and thanked them for their attendance.

The chair announced that they would review the effects of the mumps epidemic in Iowa and other parts of the Midwest, the workshop on donor deferral for high risk behavior and the current status of the FDA bar code requirements to be followed by an overview by the Executive Secretary of previous recommendations from the Committee and the responses returned from the Assistant Secretary and the Secretary. He thought that the Committee would be re-invigorated by this reevaluation and an examination of today's needs. He indicated that the Committee would spend a significant amount of time during the meeting on strategic planning. Dr. Bracey also noted that there were press reports recently of unavailability of IGIV and that the Department is aware of the problems and is taking corrective action.

The first speaker was Hira Nakhasi, PhD of the FDA who outlined the FDA's current considerations on Mumps Deferral. His presentation represented the culmination of several teleconferences between the FDA and the CDC and a dialogue with the AABB Transfusion Transmitted Diseases Committee. As of May 4, 2006, there had been 2,869 mumps cases reported from the 13 outbreak-affected states. About half of these were from Iowa (1,552) and the others from seven other states (Nebraska, Kansas, Illinois, Wisconsin, Missouri, Pennsylvania and South Dakota). Additionally, there were 12 isolated sporadic cases related to travel (Colorado, Minnesota, Mississippi and New York). Thirty five patients have been hospitalized with complications (meningitis, encephalitis and orchitis). The majority of cases were in 2-dose MMR vaccine recipients (note that the current recommendation is first does at 12-15 months of age and the second at 4-5 years when entering school). The effectiveness of this regimen has been estimated at about 90%. The majority of cases thus far have been in ages 18-24. Between March 26 and April 23, 11 persons who were potentially infectious with mumps traveled on 33 different commercial flights involving eight airlines. Of 226 exposed passengers and crew, 117 have been traced for up to 25 days and two cases confirmed as a result of the travel. The source of this outbreak is still unknown, but it is from genotype G, which has been circulating in UK since 2004 more than 70,000 cases reported.

Dr. Nakhasi further stated that Office of Blood is concerned that mumps might be transmissible by blood. Infection is initiated in the upper respiratory tract and spreads via primary viremia in draining lymph nodes and to the salivary glands. It disseminates widely in a secondary viremia and can cause orchitis, arthritis, pneumonia and

meningitis. Nevertheless, 20-40% of the cases may be asymptomatic, so there is a possibility of asymptomatic viremia. No cases of transfusion transmission have been reported. The incubation period from infection to symptoms is usually 16-18 days, but the range can be from 12 to 25 days. Symptoms are usually resolved in 10 days. Mumps-specific antibody can be detected as early as 11 days (studies done in 1948) and plasma viremia seems to be terminated with the development of antibodies. It may be cell-associated (lymphocytes), so that the removal of lymphocytes could remove some of the virus. Susceptible and immuno-compromised patients may be at risk for serious outcome of transfusion transmission. Interventions considered included avoiding blood drives at institutions where there have cases for at least one month after the last case, providing information for donors to self-defer and adding a question to the donor qualification questionnaire to allow deferral at the time of presentation. Information for donors should include: existence of mumps locally, deferral for two weeks after disease resolution, deferral for four weeks after vaccination (MMR – measles, mumps and rubella with the latter being a live attenuated vaccine with the potential for 4 weeks of viremia) and deferral for four weeks after a known exposure. Post-donation illness reports should stimulate product quarantine and retrieval according to the same criteria. The effect on supply should be monitored and serious disruptions avoided. Plasma for further manufacture (source and recovered) is not affected because viral inactivation procedures are protective.

Dr. Bracey began the discussion by asking if monitoring of the blood supply in the affected states determined if there were any adverse effects on supply. Dr Nakhasi responded that monitoring did show an effect on blood supply; however, there was no data yet. Dr. Epstein remarked that the situation was unusual in that the lead came from the industry. Considerable discretionary judgements were involved in the absence of hard data on which to base decisions. This situation is a successful model for dealing with uncertainties in the face of the outbreak. Dr. Ramsey asked about the current trend in case numbers. Dr. Kuehnert responded that the Iowa curve was likely flattening but it is unclear what the rest of the country will look like. He added that in many institutions, people were going to be re-vaccinated to be certain that they got the preferred two doses. The re-vaccination and subsequent need for deferral would make it a bad place to hold a blood drive. He wondered if there were procedures in high risk areas to test recipients to help determine blood transmissibility. Dr. Nakhasi replied that the AABB task force was open to that approach although he didn't know if it was being implemented. Dr. Ramsey asked what was being done in the UK. Dr Nakhasi said that he was not sure, but it seems likely that little is being done in the absence of data on blood transmission. Dr. Pierce asked about plans for a re-vaccination program. Dr. Kuehnert replied that it was under way in Iowa.

The next speaker was Andrew Dayton, MD (CBER, FDA), who reported on the FDA Workshop on Donor Deferrals of High Risk Behaviors. As part of routine reexamination of criteria for donor deferrals the FDA held a workshop on March 8, 2006, to consider behavior-based deferrals in the nucleic acid technology test, NAT test era. There are now highly sensitive tests for many of the important transfusion-transmitted viruses. He

summarized the workshop highlights most directly connected with what to do next. At the workshop, Dr. Cees van der Poel of the Netherlands provided Europe's attitude toward these issues and said that the European Blood Alliance decided not to change the present policy of permanent deferrals for potential donors who have a history of male sex with other males (MSM). All 15 countries have permanent deferral for donors with sexual behavior which puts them at high risk of acquiring severe infectious diseases. There was a court case brought for four MSM against four blood banks complaining that the Equal Treatment Act forbids discrimination in offering goods or services and that MSM is a manifestation of sexual orientation. The verdict was no direct discrimination and the purpose of the selection was to prevent virus infections including HIV. Homosexual men are disproportionately affected by the selection, so there is indirect discrimination but it is objectively justified and not disproportional given the interest of blood recipients. Dr. Matt McKenna of the CDC updated the prevalence and incidence of HIV. There are about half a million MSM and 300,000 injection drug abusers infected with HIV in the US, about three quarters of whom are diagnosed. The incidence of HIV in MSM is about 2-3% per year in high risk and about 1% per year in low risk. The incidence of HIV in injection drug users is about 0.5-1.0% per year and declining with preventative measures. The general population and, especially, blood donors are ultra-low risk. Young and older MSM and injection drug users are depicted separately, showing increased prevalence with age. Dr. Ed Murphy from UCSF provided a similar update on the prevalence and incidence of HTLV-I infection including current blood donors (0.01%) and commercial sex workers (7%) and of HTLV-II, including injection drug users (0.5-17.6%, varying by city), sex partners of injection drug users (0.5%) and Native Americans (2-3%). HTLV-I and –II testing is not nearly as ironclad as for HBV, HCV or HIV. There is only one ELISA test, which is not nearly as sensitive as is NAT testing for the others. The residual risk for the HTLVs has not been estimated since 1996, but it probably remains at about 1-2 per million units. Risk may be reduced by cold storage and by leukoreduction, but this has not been formally assessed. Dr. Sheila Dollard of the CDC summarized the current status of Human Herpes Virus-8 (HHV-8). She stated that it probably is transmitted via transfusion (2-3% of sero-positive units, max). She also provided estimates of the seroprevalence of HHV-8 in various US populations (blood donors – 2-4%, general population – 2-10%, injection drug users HIV negative – 6-11%, drug users HIV positive – 13-18%, MSM HIV negative – 12-16%, MSM HIV positive 40-50% and patients with Kaposi'sarcoma - >95%). The FDA estimates that changing the MSM deferral to 1-5 years would increase blood recipient exposure to HHV-8 by 2-5%. Dr. Michael Busch estimated HIV ELISA and NAT tests each have a primary error rate of about 1/3,000. Doing both tests provides a redundancy that reduces the likelihood of a positive unit slipping by to 1/million. Similar redundancy and reduction in risk is true of other viruses for which two tests are routinely used. Dr. Busch also reported a REDS study (NHLBI) that in anonymous post-donation questionnaires, about 0.3% of donors reported MSM that they had denied at the time of donation. With abstinence for less than 12 months or for one to five years, the presence of positive infectious disease markers was 3-4 times that of the general donor population. With abstinence for longer, the marker rate was similar to that of the general donor population. First time and repeat donors did not differ. Some of the uncertainties could

be resolved with a prospective national study of MSM abstention history correlated with sexually-transmitted diseases and transfusion-transmitted viral infection positivity. Previous risk assessments have indicated the biggest single source of risk is quarantine release error. More recent assessment using biological product deviation reports showed that hospitals (7/10,000) had a log-fold greater frequency of release errors than did blood centers (0.4/10,000), probably because the blood centers, being larger, are more fully automated.

In summary, Dr. Dayton stated that changing the MSM deferral period from permanent to 5 years (of abstinence) would increase HIV risk by 1.7% (allowing 4 more infectious components to be transfused); to 1 year would increase the risk by 2.5% (6 components). These changes would result in a smaller increase of HBV infectious components. One can argue that these numbers are negligible. These estimates use the most recent three year biological product deviation reports; older data from NY state are manifold higher. Changing injection drug use from permanent to 1 year would increase the risk for HIV by 5% (12 components), HBV by 2.4%, HCV by 40% and HTLV by 2100%. Dialogue is under way to try to chart the future course.

At the workshop, Dr Roger Dodd (ARC) commented that emerging infectious diseases did not form a homogeneous group. Although all must necessarily have a blood-borne phase, they may not be transmitted sexually or by low volume non-parenteral routes. Consequently risk behaviors associated with those routes are not common to all transfusion-transmitted infections. MSM does represent a major risk factor for two of the five major screened infections. Dr. Kristen Miller discussed problems with questionnaires. Factors influencing the accuracy of responses include the effect of asking about sensitive/stigmatizing behaviors, donor motivation, donor literacy, time-frame/memory problems, and donor knowledge and understanding of risk.

Dr. Dayton concluded by saying that the FDA is having extensive discussion with the NIH and CDC to arrive at a consensus recommendation. Although it would be technically possible to make modifications in donor deferral criteria and see what happens, this poses a certain risk that to many may be unacceptable.

The Committee had no questions or discussion of this presentation.

Ms Judy Ciaraldi, BS, MT (ASCP), a Consumer Safety Officer from CBER, FDA reported on Bar Codes and Machine Readable Data, Guidance of April 2005, which has just been put into practice in blood and blood component establishments. This system replaced the old blood labeling regulation that allowed machine-readable information on labels as an option. As a result of the Institute of Medicine report, *To Err is Human: Building a Safer Blood System*, Secretary Thompson set up a patient safety task force in 2001. One objective was to apply bar code technology used in other industries to track drug distribution and prevent medical errors. The FDA was named as one of the Federal Agencies to lead this effort. The rule predicts that the number of medicine and

transfusion errors will be reduced by bar codes (502,000 over 20 years) and that there will be savings in health care costs ($93 million in 20 years).

The new rule, effective February 26, 2004 (69 FR 9120), mandates machine readable information on the label. New products approved after that date have 60 days to comply with the rule. Previously approved products had two years from April 26, 2006 to comply. Three regulations were affected by the new rule. The first is 21 CFR 201.25, which applies to most prescription and certain over-the-counter drugs regulated under the FD&C and PHS Acts, requires that the National Drug Code (NDC) number displayed as a linear bar code but doesn't apply to hospitals, clinics or public health agencies. The FDA's legal authority extends to products and not to hospitals, which are encouraged to use new automated bar code technology but not required to do so. The second affected rule change is the inclusion of a new regulation, 610.17, which requires biological products to comply with 201.25. Devices are not included and blood and blood components must comply with §606.121. Products exempt from the rule include those for further manufacture, source leukocytes and autologous blood collected and used in the operating room, recovery room or ward always staying with the patitent. Required machine readable information is the unique facility identifier which is the FDA registration number, lot number relating the unit to the donor, product code and ABO and Rh of donor. "Machine readable" does not specify a particular symbology so as to accommodate new bar codes and changes in technology. The FDA recognized Codabar in 1985 and approved ISBT 128 (v.1.2.0) in 2000. Some issues are not consistent with regulations; hence variance submission is needed. The bar code rule applies to tissues subject to pre-market approval under §351 of PHS Act, but not to hematopoietic stem/progenitor cells from peripheral or cord blood, which are regulated under §361 of the PHS Act. Requests for exceptions will be considered if complying with the rule would affect safety, purity, potency and effectiveness of the product or if it isn't technically feasible. Exceptions for financial reasons or claims for a low error rate will not be considered. Questions should be directed to the Office of Communication, Training and Manufacture Assistance at CBER (E-Mail: matt@cber.fda.gov).

Dr. Bracey opened the discussion, asking what it would take to get hospitals (exempt from the regulation) to adopt these new technologies. Ms. Ciaradldi replied that it is hoped that use in pharmacies and blood banks will encourage hospitals to take the additional step. Dr. Kuehnert asked about tissue requirements. They must comply. In her talk, Ms Ciaraldi separated items by the sections of the Public Health Act that regulate each. Special products (e.g., leukoreduced red cells, irradiated products) have specific names, which are included in the bar code. Ms. Ciaraldi wasn't sure; Dr. Holmberg reported that the ISBT North American working group has joined the HL7 working group, whose concept is that until there are standards, local agreements must exist between computer systems within a hospital information system. Dr. Kuehnert emphasized the importance of these systems working together. Dr. Duffell asked about the difference between §351 and §361. It was explained that §351 requires licensure; §361 requires only infectious disease testing, not licensure. Dr. Epstein clarified that §361 was promulgated under the requirements for control of communicable disease, but

includes issues of donor eligibility and good tissue practices. There are standards and inspection for compliance. Under §361, a product can't be distributed unless it is licensed (or only in intrastate commerce). Premarket review is required for licensure. Dr. Duffell further asked for examples of exemptions. Only one has been granted: a batch made at the time the rule became effective for products that would outdate before the compliance date. Dr. Ramsey asked what proportion of blood components in the US actually use bar codes. The response was that all the major blood and blood components have some type of bar code but their actual use at the bedside was unknown. Dr. Bracey reported that only 80 of the 4,000-5,000 hospitals in the country are using these systems now. Dr. Epstein noted that the FDA had cleared three device systems for performing an automated crossmatch, which should facilitate use but the major barrier seems to be cost. Dr. Bracey noted that hospitals pay particular attention to "health grades," but that misadministration of blood was not included in the 20 or so parameters that go into the grade and perhaps the blood industry should get more active in promoting this need. Dr. Epstein reemphasized that the blood machine readable systems are different from those used for pharmaceuticals. After considerable discussion during rule-making, it was decided to let blood banks continue use of their systems rather than make a complete change. Technology does permit the use of two parallel systems, but it requires an additional investment to make that accommodation. Dr. Holmberg noted that most distribution of plasma derivatives (e.g., albumen, IGIV, coagulation factors) takes place from the pharmacy. He asked if these considered biologicals under "machine readable?" or as pharmaceuticals? Ms. Ciaraldi stated that they fall under pharmaceutical and need a linear bar code with the NDC code. Dr. Epstein commented that in some areas there is movement to radio frequency identification systems. For many drug products there may be an issue of the effect of radio frequency energy delivered to the product. This needs to be answered for blood components as well. Ms. Thomas asked that they not forget about the people who need this technology the most, the patients. Working with patients, she has seen first hand errors in blood delivery. She opined that we can really do much better than we have been.

After a short break, Dr. Holmberg provided a progress report of the recommendations of the Committee from 2001 through 2006. He noted that the response letters are being prepared in PDF format for the web page and would be available soon. In addition to a review of the recommendations he provided insight about what has happened behind the scenes. These recommendations are on the DHHS web site.

Dr. Holmberg then described DHHS Secretary's 500-day plan for implementing the Department's mission provided by President Bush at the time of Mr. Leavitt's appointment which is to help Americans live longer, healthier and better lives, and to do it in a way that protects our economic competitiveness as a nation. Dr. Bracey asked if there were enough budgetary support to have a stand-alone plan, since many items are likely to be costly. Dr. Holmberg noted that resources were always an issue and that possible constraints should be noted as the strategic plan is developed. Furthermore, Committee recommendations are just that: the Secretary may or may not accept them as stated. The common goal is blood safety and availability. The Secretary's plan is based

on 10 principles: 1.) care for the truly needy but foster self-reliance; 2.) have national standards but neighborhood solutions; 3.) collaboration, not polarization; 4.) solutions that transcend political boundaries; 5.) markets before mandates; 6.) protect privacy; 7.) use science for facts and progress for priorities; 8.) reward results, not programs; 9.) change a heart, change a Nation; and 10.) value life. There are six parts to the plan: transform the healthcare system; modernize Medicare and Medicaid; advance medical research; secure the homeland, protect life, family and human dignity; and improve the human condition around the world.

Many of the recommendations made by the Committee in September fall within the top four. They have played a role in how the working groups have been organized. The others are a bit more in social aspects, somewhat exemplified by work in the Department under PEPFAR in Africa and the Caribbean. As far as blood safety and availability is concerned, about 80% of the Executive Sec's Office' work is to convene people to discuss issues and develop the consensus. There is responsibility for policy and less time directly devoted to products. The BASIS inventory tracking system deals with product availability.

After lunch, the Committee will broke into working groups to address what can be done to improve Blood Safety and Availability as part of transforming the Healthcare System, as part of modernizing Medicare and Medicaid, as part of research efforts and as part of securing the Homeland. Groups were charged to consider blood issues in transforming the Healthcare System include transfusion practices, donor recruitment and retention, policy and bio-vigilance and aspects of Medicare and Medicaid that need attention involve mainly reimbursement.

Dr. Epstein commented that much Committee discussion over the years has been devoted to reimbursement, including contingency funding for new needs. Should those be part of the modernization of Medicare and Medicaid? Dr. Holmberg responded that things not specifically addressed should be included; if pertinent, i.e., reimbursement topics raised by Dr. Epstein. Dr. Bracey reiterated the need for a coordinated system for hemovigilance. He encouraged thought be devoted to blood conservation and alternatives to transfusion. The technology advances with automated systems to help reduce error might be included. Finally, the groups should address the National Blood Policy, even though it had been reexamined in 1998 and in 2004. Regional blood distribution issues have not been completely resolved. Mr. Walsh expressed his appreciation that this sort of review was being done. Nevertheless, there doesn't seem to be a safety issue in current donor deferral practice that merited any change nor is there an availability or an accessibility issue needing a donor qualification change. Dr. Epstein replied that the lifetime exclusion for male sex with males has been repeatedly reexamined, partly because it was originally put in place despite the limitations of supporting data and partly because new technology, e.g., pathogen inactivation for plasma derivatives, may question its utility. In a broader view, it is necessary to reexamine the entire framework of donor recruitment incentives and deferrals to be sure that the rationale hasn't changed as the science changed. The Committee is also

empowered by its charter to examine ethics and social choice. Part of the male sex with males issue is a perception that this is discriminatory, a reality to the everyday activities of blood centers. This must be balanced against a primary concern for recipient safety. This was addressed by at an earlier FDA workshop. There is a generation of young people who are turned off by the perception of discrimination based upon life styles and simply perceive that the science-based policies are misplaced. Dr. Holmberg highlighted some other issues that remain unresolved, such as leukocyte reduction, many related to reimbursement through CMS Medicare/Medicaid, blood reserves and their linkage to disaster and shortage management, products for rare diseases and many technology issues. More issues include expanded multiplex testing for infectious diseases, strategies to interdict TRALI, improvements in controlling bacterial contamination, 7-day pooled platelets and pathogen inactivation strategies. A new item, not previously discussed, is prioritization of a research agenda. Antigen-free red cells or a blood substitute would revolutionize transfusion medicine. The donor-base, how we recruit and defer donors, merits discussion. Practices that have been in place for many years that may not be evidence-based need reexamination (the National Association of Transfusion Alternatives is focusing on this). Finally, there is "off-label" use. Once a product is licensed, it is perfectly legal for doctors to use it for additional indications that may have had limited study and no controlled trials. With reference to Mr. Walsh's comments, Dr Pierce supported current donor acceptance criteria as satisfactory. Does the Committee need to review every workshop and take a stand? Drs. Bracey and Epstein replied that currently we are gathering and reviewing data and in the future there may be a need for the Committee to take a stand. Dr. Pierce continued, asking how much the Committee should do to promote a research agenda, such as reducing the use of blood during surgery or by using cells (e.g., stem cells or stem-like cells for heart disease) or tissues that might obviate the need for surgery. Dr. Holmberg replied that the field was wide open for what the Committee might recommend for possible Department support through NHLBI. Dr. Bracey agreed. Dr. Kuehnert suggested studies of the epidemiology of off-label product use. Dr. Bracey suggested that this could be part of the larger picture of efficient resource utilization. Dr. Epstein noted that the Committee might deal with threats and opportunities, identifying the former and suggesting candidate interventions.

Dr. Bracey then called for an open public comment period. Dr. Barbee Whitaker, the Director of Special Projects, AABB read a statement strongly supporting a US biovigilance program to capture and analyze data regarding infectious and non-infectious risks associated with receiving a blood transfusion or a tissue transplant. The UK, Canada and France have such programs in place. The US, unlike these countries, does not have a national blood program and is five to ten times larger. The AABB recommend that a US biovigilance program work to coordinate and integrate existing efforts to reduce duplication and be a public/private initiative. Current data on the magnitude and scope of the problems unreliably underestimate them because the information is based on passive reporting. AABB believes it alone cannot implement a comprehensive national program but it can serve a critical role in the development and implementation of a program. The Bacterial Contamination Task Force, the West Nile Virus Task Force, the Interorganizational Task Force on Domestic Disasters and Acts of Terrorism and the

Nationwide Blood Collection and Utilization Survey are examples of the ability of the AABB to bring organizations and interested parties together toward a common goal. On June 1, then AABB will initiate a pilot project to collect needed early warning data on the threat of transfusion-transmitted West Nile Virus. The AABB has a unique perspective representing nearly all of the nation's blood collecting facilities and the hospital transfusion services responsible for transfusing most of the blood in the US. The AABB is prepared to establish an interorganizational task force and work with interested parties, including HHS and international organizations who have many years of experience in managing hemovigilance networks. A larger goal is to expand to a biovigilance program to include data on tissues and cellular products, including hematopoietic stem cells. AABB urges the Advisory Committee and the Department of Health and Human Services to support the concept of a public/private initiative to address this important need. Dr. Epstein asked if the Committee could get a copy of the 2006-2007 AABB strategic plan for work group deliberations.

Mr. Corey Dubin of the Committee of Ten Thousand expressed concern that consumers have been dropped out of the equation, leaving only government and industry. He opposes remodulation back to old methods, just because the AIDS blood crisis is over. Users have made positive contributions and have not been disruptive. He urged the establishment of a national blood policy to help deal with issues such as male sex with males (MSM). His group has concerns about implementation. With all the advances in safety, the Red Cross is still working under a consent decree and there are regional differences about how individual banks are implementing tests and procedures. The Committee recommendations described earlier are impressive and address critical issues, but how they are taken to the next step and implemented or otherwise disposed of is not clear.

Dr. Holmberg referenced two communications about the availability of IGIV, one of which he read and the other was part of the Committee packet and should be considered. The statement he read described how a patient with CVID was refused to continue IGIV in a hospital out-patient clinic because of insufficient reimbursement to the internal medicine physicians who "owned" the clinic. Her private insurance company asked that every two week infusions be stretched to every three weeks; she then required hospitalization for pneumonia. Recently she was required to be admitted to the hospital for infusions, but could not get set appointments for them. She now has been told to go to the cancer center at the hospital for her infusions. The stress accompanying these frequent changes has been difficult. She pleaded for herself, relatives and other similar patients that the Medicare rules be changed to allow them to return to previous approaches which have been successful.

At 12:34 PM, the Committee adjourned for the day. Sub-groups of the Committee met in the afternoon of the May 9 and the morning of May 10th to deliberate. The sub-groups were instructed to report deliberations to the full Committee when it reconvened on May 10th in the afternoon.

The Committee reconvened at 1:10 PM, May 10, 2006 to hear sub-group reports and conduct further deliberation. After a roll call, the first report was presented from the Policy Group by Mr. David Matyas.

Development of a Strategic Plan for Increasing Blood and Blood Product Safety and Availability

First Stage Recommendations:
Structured Process for Policy and Decision Making

1. Adopting a set of Principles that define a Federal Strategic Policy for Blood and Blood Products that is relevant to the 21st century (the "Principles").

   By way of example, the World Health Organization has suggested the following:

   Needs and Outcome Orientation. Prioritize blood safety and availability within the health system and clearly identify desired outcomes and goals based on an assessment of the national need for blood and blood products

   Transparency. Clear and open policy processes help ensure the legitimacy and effectiveness of blood policy.

   Evidence Based. Health outcomes are maximized if decision making is based on robust evidence.

   Efficiency. Ensure limited human and financial resources are being used prudently and to maximize the health impacts.

   Participation and Partnership. Involve relevant stakeholders in the policy process to ensure legitimacy and effectiveness.

   Communication. Pro-active communication ensures public awareness of the needs, benefits and risks.

2. Using the Principles to evaluate/benchmark the system for the purposes of (i) conducting an initial gap analysis of the current system and (ii) performing ongoing reviews of progress and setbacks in the policy and decision making processes. In this process, would propose that there be various scenarios developed that test the weaknesses and strengthens of the system

3. The Secretary of the Department of Health and Human Services demonstrating a commitment to the Principles

4. Holding DHHS and its multiple agencies accountable for following and achieving improvement in the Principles by ensuring:

- Decision makers are not only *empowered* but also *involved*
- Coordinated activities among DHHS and agencies

In discussion, Dr. Bracey asked if these suggestions were expected to be on-going with continuous review of decisions with reevaluation as needed. Mr. Matyas replied yes. There would be gap analysis as part of continuous improvement. Ms. Birkofer asked if the intent was only to impact the strategic plan or as guidance for making decisions and policies for all activities of the Committee. Mr. Matyas replied that it wasn't specific to the plan nor was it specific to the Advisory Committee but could be guidance for all decisions. Ms. Birkofer noted that the consumer and patient organizations were missing, as was an assessment of assuring access to care. Ms. Pahuja thought that consumer needs were implicit in the whole process. Mr. Matyas noted that the fifth principle, participation and partnership, involves the relevant stake-holders.

Bio-vigilance Working Group Recommendation Summary

The next presentation was by Dr. Matt Kuehnert on behalf of the Working Group and Hemovigilance. The two main foci for this group was to evaluate ways for surveillance of adverse events related to blood donation and transfusion and to prevent errors in blood collection centers, transfusion services and clinical transfusion settings.

1. Bio-vigilance should encompass a comprehensive definition of biologic products (e.g., blood, organs, other tissues), donor and recipient surveillance of outcomes associated with these products, and intervention if event rates rise above a pre-determined threshold.
2. Donor surveillance data, focusing on both deferral and laboratory testing results, should be collected and analyzed in a national scope.
3. Recipient surveillance data, focusing on transfusion/transplantation outcome, should be implemented using both comprehensive and sentinel data collection models in a national scope; reporting by the end user should be as simple and clear as possible, and there should be adequate incentives to ensure compliance.
4. Emerging Infectious Disease (EID) monitoring should be accomplished using a hypothesis generating algorithm for newly discovered threats, then assessed using virtual repositories or other suitable rapid investigative research methods if needed.
5. Comprehensive tracking of all biologic products that include critical data elements is needed, with application from source to the end user.
6. A system to evaluate use and availability is needed to measure products used, products requested but not received, and intervention to respond to inequities.
7. Collaborative partner involvement and education is needed that includes federal government, industry, trade organizations, patient advocates and consumer organizations, accrediting organizations, healthcare organizations, clinical practice organizations, IT companies, media, and community, with the Secretary of HHS coordinating.

He concluded by noting that now was the time to get started with hemovigilance; most other developed countries have some such system. Dr. Bracey asked if plasma derivatives were included. Dr. Kuehnert replied that the group wanted to be inclusive, recognizing that each product (plasma protein or an analogue, tissues and cells) may have unique characteristics. Dr. Klein commented that the US was disturbingly deficient in hemovigilance or, as used here, biovigilance. From a research prospective, there are two issues: the collection and the analysis of the data. We collect considerable data but what they mean are unknown because they are not analyzed. The Research subgroup considered approaches for data on emerging infections current adverse events to be analyzed scientifically using new technology, to develop a system that might work in a huge country like the US. Dr. Kuehnert replied that this was a great suggestion; his subgroup considered it important to develop intervention strategies as well. Ms. Lipton noted that errors were listed, but not accidents or near misses: was this omission intentional. Dr. Kuehnert replied that they should be included. Ms. Lipton also encouraged to the program avoid the collection of data without providing feedback.

Donor Recruitment and Retention

Dr. Bracey then reported for the donor recruitment group. This group addressed donor recruitment and retention using a gap analysis process: 1). the establishment of a national Donor Deferral Registry to include deferrals for high risk behavior and other transfusion safety matters. 2). It will be increasingly important to expand efforts to recruit donors among minority groups. 3). Data are being collected by the Westat group (REDS) on the motivation of blood donors and the barriers to donation; these need to be integrated into practice to improve the yield. 4). It is important to reevaluate and possibly modify reasons for excluding some donors, e.g. hemoglobin level, iron balance management and some hemoglobinopathies. 5). There should be more sharing of strategies to promote "best practices" for recruitment and retention. 6. Consider treating the donor center as a community health resource, beyond that of collecting blood; e.g., improving quality of life through health promotion. Instead of outsiders recruiting donors among various communities, it might be better to have health educators promote both health issues and blood donations (combined with the group's #8). 7). Attention should be directed at minimizing adverse donor outcomes. 8). Now is the time to embrace existing information technologies so that real-time data can help guide collection plans to cover future needs. 9). Research needs include methods of making blood more interchangeable (less restricted by blood group) and even tissue culture methods to alleviate problems with certain blood groups or products. 10). Begin to educate the public on the need for blood donations at an early age. 11). Currently available automated systems need to be fully utilized from the donor to release for transfusion to eliminate errors. 12). Utilize repeat donors or selected transfusion recipients as ambassadors (advocates) for blood donation (and health promotion). 13). Active participation of the public and private sectors in disaster drills and their analysis, focusing not only on the movement of blood to areas of need, but also on the recruitment of volunteer donors as needed. One suggestion was for a group of committed donors"

("minutemen") who would be rapidly available in time of need. Systems need to be as interoperable as possible. Ms. Lipton commented that the American Donor Recruitment Professionals (ADRP) do share techniques and "best practices." The AABB has made efforts to deal with schools, but there is no central control and dealing with each school district is daunting. Furthermore, curricula are so crowded that to add material is a problem. In disaster planning, the models used (pandemic flu may be exceptional) were transshipping for immediate needs and recruiting to "backfill" what was shipped. In emergencies it is the blood on the shelf that is important; recruiting donors, collecting blood and processing it for transfusion all take too much time. Pandemic flu may be different because multiple cities are likely to be affected and over a longer period of time. Ms. Birkofer asked if the group focused only on blood donation. Dr. Bracey replied that they did focus mainly on blood donation, but most of what was said could easily be broadened. Ms. Birkofer pointed out that plasma donors also undergo rigorous screening. It is important to assure a continual supply of plasma for further manufacture. In addition, there is a National Donor Deferral Registry for plasma donors that has been in place for years. Dr. Epstein commented that other countries have found peer relationships to be useful and it is surprising that there is no donor organization here. Dr. Bracey responded that the group did consider the use of donors as ambassadors. Dr. Klein noted that his research subgroup would not need to report if all others addressed research as well. Between 25 and 50 percent of healthy Americans go through a donor center at one time or other, but only five percent of them donate each year. This might be an outstanding resource for genomic testing for healthy life-style issues but there may be legal issues in using it.

Dr. Holmberg followed on Ms. Birkofer's comment by opining that the plasma industry had set a good example of seeking dedicated and pedigreed donors with healthy lifestyles, moving beyond the stigma that plasma donors had years ago. Much can be learned from both plasma and whole blood donors.

Clinical Practice Standards for Transfusion

Dr. Roseff then reported for the Work Group on Clinical Practice Standards for Transfusion. They were joined by the Donor Retention and Recruitment Group.

1. The group recommended that data from multiple hospitals be collected and subjected to on-going analysis. To ensure this be done, incentives would be needed, such as a requirement by CMS or some other accrediting agency. The plan would include prospective monitoring of transfusion outcomes to determine if expected results were obtained. Is the science behind transfusion use acceptable? If the data were patient focused, a patient with chronic transfusion need and problems (e.g., red cell antibodies, non-hemolytic reactions) could be treated appropriately anywhere in the country.

2. National transfusion guidelines should be developed for both cellular and plasma-derived products and their analogs, evidence-based and implemented.

3. A focus should be developed where patients could obtain quality information to help them participate in their own transfusion care. Such a site would be of use to physicians outside of the specialty of Transfusion Medicine. More education about blood use is needed for physicians in general medicine, surgery and various specialties.

4. Adverse events should be included in the data-bases.

5. A position should be established for a blood safety officer with defined roles and responsibilities; although frequently recommended, few such positions exist in the US at present.

6. There should be a national collaboration to develop and certify information technology to expand the use of machine-readable information. It may be possible to find technological fixes so that the myriad of approaches in various facilities can be used together.

Dr. Ramsey opened the discussion by noting that not all products are used in hospitals, nor are they subject to CMS jurisdiction. Dr. Roseff agreed to the need to take this into consideration. Ms. Lipton reported that the AABB is going to start issuing transfusion guidelines. The research needed in developing these guidelines needs to be extensive and probably will be costly. She suggests that the proposed position be called a "transfusion safety officer" rather than "blood safety officer." Dr. Roseff agreed.

Medicare & Medicaid Modernization

Dr. Gregory Bloche then reported for the group, Modernizing Medicare and Medicare (originally called the Reimbursement Work Group). They worked under the concept of the great philosopher, Yogi Berra, "Open all these boxes of Pandora."

Members: John Walsh, Linda Thomas, Jerry Sandler, Gargi Pahuja, [CMS representative – Ms. Newman], David Matyas, Jonathan Goldsmith, Jim Bowman, Julie Birkofer

To modernize Medicare & Medicaid and to provide high-quality health care in a financially sustainable way, we recommend:

1. Coverage decisions, where possible, should be national and based on empirical evidence.

2. Where empirical evidence supports coverage of a product, device, or service, CMS should act quickly to issue a coverage rule.

3. The Secretary should have special authority to adjust reimbursement rates to prevent and to cope with breakdowns in the chain of distribution and administration of blood products and plasma derivatives, when the breakdowns impair access.

4. Develop a comprehensive and effective program of post-approval, post-market surveillance and analysis of adverse events arising from administration of blood products and derivatives. Manufacturers should be required to comply with this program in order to continue to distribute their products.

Ms. Birkofer opened the discussion by noting that there are about 23-25 Medicare carriers who reimburse on local practice patterns. This posses a problem in the development of national guidelines. The effect of this variability on patient access is unknown but needs to be studied. Dr. Holmberg questioned opposition to national guidelines since now decisions are more regional than local. Dr. Bloche asked if a practice based on empirical evidence was good in one area, why wouldn't its expansion nationally be a good idea? Ms. Birkofer agreed, especially if there is evidence that it is not effective or harmful. Dr. Bloche pointed out that practices and costs vary tremendously across the country. Citing studies by Dr. John Wennberg, Dartmouth Medicare spending per patient in Miami is about twice as much as in Minnesota and in Boston it is twice as much as in New Haven. There is no known empirical basis for this. This supports the development of a national rule. Ms. Birkofer thought that the opinion of the provider should take precedent. Dr. Epstein raised questions about paying for performance; this may penalize poor performance to the extent of its ability to improve, in somewhat of vicious circle. Dr. Bloche replied that maybe some poor performing institutions should be closed, especially if the services could be provided by better performing ones. Dr. Bracey noted that local task forces have been able to orchestrate changes in clinical practice, stimulated by pay-for-performance. Ms Berkofer noted that there is post-market surveillance for plasma derivatives in that companies do report adverse events to the FDA; however, only fatal adverse events from fresh component transfusion are reportable. Dr. Roseff presented two examples of the adverse effect of incentives. To try to obviate increased deferrals toward the end of the day, various operations were compared. This provided an incentive to take donors, irrespective of their qualification and the incentives were promptly abandoned. In a hospital pathology department, bonuses based upon cost reduction resulted in decreasing the supply of blood, not always in the interest of good patient care. This idea was also reversed.

Ms. Wiegmann of the AABB commented from the public, recommending that CMS use reliable data when making payment decisions. The AABB has data that the cost of blood components has increased dramatically in the last few years get at the same time, APC rates have been going down. Mr. Walsh opined that the passive surveillance system for plasma proteins and their analogues is not effective. Patients are discouraged from reporting adverse events, there by eroding confidence in the system. Dr. Epstein noted that not only do fatal events regarding transfusion products need to be reported, but also

biological product deviations must as well. The FDA is considering revising regulations to require mandatory reporting of serious adverse events from transfusion. He then asked if there were any discussion about linking CMS reimbursement policies to the FDA product approval or to the CDC clinical practice recommendations. Mr. Matyas replied that this was the point of recommendation number two. Ms. Lipton found a problem in the language used; it may not necessarily be adding coverage for a product or service, but instituting a safety enhancement that increases cost without appropriate increase in reimbursement. Drs. Bracey and Epstein agreed that this was a problem that needed to be addressed. Ms. Thomas commented that local practice did not always work well from her perspective. Mr. Walsh noted that there was a representative from the CMS in their working group and that she was very useful and helpful. As for recommendation three, at present the Secretary must declare a "Public Health Emergency" before rates can be adjusted. Item three addresses easing this requirement. Ms. Pahuja commented that the changes were meant to avoid public health emergencies. This will require a statutory change. Ms. Birkofer noted that post-market surveillance for safety differed from surveillance for efficacy. Dr. Epstein asked if consideration was given to recommending a DRG for blood, rather than embedding its use in other DRGs. Ms. Pahuja replied that this had been discussed, but no formal recommendation considered. Dr. Epstein suggested that such a change would convert hospital thinking about blood as a cost center to a revenue center, increasing the visibility of blood services. Making surveillance activities reimbursable would also improve the likelihood of developing such an activity. Dr. Holmberg suggested that there was a deeper issue, blood utilization, possibly by DRGs, focusing on those that intensely use blood or blood products. Changes over time would be important. He noted that a planned final rule on hepatitis C look-back is expected to provide for some reimbursement for the time and effort needed. Dr. Klein said that a DRG with reimbursement attached would stimulate reporting; now blood is considered a cost-center, but if it were to become a profit center, accurate reporting would follow promptly. Dr. Duffell agreed. Dr. Kuehnert suggested that blood was regarded much as is a drug, while it might better be considered a procedure, like a tissue transplant. Dr. Bloche pointed out that DRGs were developed in health policy to get control of costs by giving hospitals and physicians making clinical decisions the task of managing resources within set budgets. You could gain or lose for individual patients but overall you had to come close to breaking even or be in big trouble. A case could be made that blood is unique because clinical decisions and purchasing decisions are separated and they present different sets of values.

After a brief break, Dr. Bracey noted that this current meeting was intended to provide background for the drafting of a strategic plan to be reviewed at the next meeting. Hence, he proposed: **"The Committee recommends that the Executive Secretary take the recommendations of the work groups as discussed before the whole committee for drafting a strategic plan for review at the next ACBSA Committee meeting."** Dr Epstein suggested making it the next suitable or available meeting, since there are already other issues for the next meeting. Dr. Bracey accepted "the earliest feasible." This recommendation was passed unanimously.

Advance Medical Research

Dr. Klein then reported for the Advance Medical Research workgroup. This group looked at the blood transfusion process from beginning donor recruitment through post-marketing surveys. Donor motivation for new and repeat donors should be studied and changes through the years noted. Other donor-related items include:

1. Should the donor room be a healthcare demonstration project, addressing such things as life styles and iron deficiency or the need to replenish iron lost through donation. Most research is unlikely to be a 500 day deliverable, as in the Secretary's plan; more likely is a 5,000 day horizon.

2. A current "hot topic" for research being the deferral of males who have had sex with males.

Increase and improve the use of technology applied to donor recruitment and retention. Long-term research issue "deliverables" might include

1. Transfusion alternatives & blood substitutes, but not just for red cells, but for other components as well. This might include an ability to expand blood cells in vitro to replace some of the blood supply. Replacing 13 million units with in vitro production would be difficult but developing special cells for hard-to-transfuse subjects might be more feasible.

2. Long-term research is needed to determine if all of the reasons for donor deferral are indeed appropriate. In the collection a processing of blood, there are many knowledge gaps.

3. The importance and necessity for universal leukocyte reduction needs further study.

4. Research is needed on TRALI.

5. Technology for infectious disease testing needs continuing evaluation, e.g., multiplex technology, chip-based techniques, nanotechnology or some other platform. A screening test for prions is likely important.

6. The development and routine use of pathogen reduction must be evaluated.

7. Current typing and compatibility testing uses early 20th century technology; immunohematology at the genetic level for identifying blood groups and patients likely to develop antibodies needs to be pursued. There are research issues in the storage and release part of the chain.

8. All, or nearly all, blood cells develop a storage lesion(s), which need to be further defined to improve their quality and shelf life. The effect of irradiation needs to be better defined.

9. In the short term, validation of 7 day storage of pooled whole-blood-derived platelets is needed. Are buffy-coat or platelet-rich-plasma derived platelets similar or different?

10. Possible toxicity of DEHP needs to be studied and defined.

11. Evaluate the release systems, bar coded or RFID (?effect of radiofrequency waves on the storage of blood components).

Over the long term,

1. Transfusion outcomes should be studied, including indications, effect of short or longer storage before transfusion

2. Should there be a national blood reserve and, if so, how should it be structured. Finally, there needs to be a permanent research infrastructure for use as projects are developed. Now, it takes some time to put together the infrastructure for each individual study before data collection can be started.

Ms. Thomas asked for more information about the MSM issue. Dr. Klein responded that it is not clear what lifting the restriction would do for blood availability or for transmission of other viruses, e.g., HHV-8. Ms. Starkey of America's Blood Centers commented that the concept of developing therapy for orphan diseases might be expanded to include "orphan" laboratory tests, e.g. confirmatory tests for HTLV. The questions was asked if some tests be required universally, e.g., for malaria? Manufacturers are unlikely to develop tests for a small market. Dr. Klein agreed that the problems needed attention. Tests for bacterial contamination may not be orphan, but improvements are needed. If use is limited, development may be slowed. Dr. Bracey asked about the NHLBI research planning meeting. Dr. Klein replied that the NHLBI recommended prioritization on the basis of science. The ACBSA Workgroup is interested in good science also, but approached the issues from a "what's best for public health" perspective. Ms. Lipton noted that physiology of red cells needed further study. Dr. Klein agreed, saying that it was not clear whether the patients first reported to be transfused (James Blondell, 1818) lived or died because of or in spite of the transfusion and whether the fatalities were due to toxicity. We are not too much further along today. Dr. Epstein asked about a discussion of the long-term effects of donation. Dr. Klein agreed that that was important and should have been included, since it was discussed. Factors to be considered are: cell depletion and iron deficiency, plasma protein depletion, infusion of citrate in apheresis procedures, and effect of steroids and various cytokines on the granulocyte donor.

Secure the Homeland

CDR Libby then reported on the "Secure the Homeland" working group. The three topics were: 1. integration of the blood system and the public health structure; 2. risk communication; and 3. disaster planning. The functional leadership of the blood system needs definition. Stratification for the circumstances provides flexibility. One person or office needs to be in charge. Local integration will be essential. The role of the Interorganizational Task Force needs to be formalized; it has become an important part of the blood response to disaster. Other organizations that should be integrated include the American Association of Tissue Banks and the National Marrow Donor Program. Redundancy needs better development; e.g., the Internet for communication, transportation and testing facilities. Threat analysis plays a role, including who might be affected. Regulatory standards need modification to balance threats and risks.

Ms. Birkofer began the discussion by touting the importance of the plasma industry in disaster planning. Dr. Epstein supported that notion, pointing out that the timeline for replenishing plasma products was relatively long, compared to fresh blood components. Discussion revealed that the question of a plasma product reserve has not been discussed. Dr. Holmberg noted that this would likely be a serious problem for disasters with a long time frame, e.g., pandemic flu. Dr. Duffell asked about disposables, since most blood centers are operating on a "just-in-time" basis for supplies. CDR Libby replied that the group did consider that issue. Dr. Bracey asked just who was in charge. Dr. Holmberg replied that the responsibility was in the Office of the Assistant Secretary for Health. There will be considerable reliance on local blood banks. Dr. Ramsey asked how would it be mandated that local facilities do their preparations and how were they to be reimbursed for it? Dr. Holmberg said that HRSA has contracts with hospitals for preparedness and also support hemophilia treatment centers. Reimbursement for preparedness would be handled by HRSA. The Gulf hurricanes spotlighted problems when Medicaid (a state program) patients moved from one state to another and needed care. Dr. Bloche commented about increasing reliance on the military, which makes sense, but asked if the military have the surge capacity to treat large numbers of civilians in a disaster situation. CDR Libby replied that he has asked for guidance in the case of blood and blood products on this issue, and it is not set. The Secretaries of Defense and Homeland Security (with FEMA) work this out ad hoc depending on the circumstances. It is a bit complex: FEMA has to request DOD aid in order for DOD to be reimbursed by the states. More than one state was involved after Katrina. There was no stoppage in the availability of blood in the US or in overseas operations, even with this confusion. Service came first; money issues were worked out later. Dr. Holmberg added that an understanding between DOD and DHHS was being worked out.

Dr. Bracey reaffirmed the recommendation resolution that was passed earlier in the day and a motion for adjournment was made, seconded and approved at 4:03 PM.