**Advisory Committee on Blood Safety and Availability**
**Department of Health and Human Services**
**27th Meeting Minutes**
**September 19 & 20, 2005**

Dr Jerry Holmberg called the meeting to order at 9:05 AM. He introduced a new Committee member (Dr Pearl Toy, School of Medicine, UCSF), called the roll and reminded the members of Federal Conflict of Interest Rules and Policies. He then turned the meeting over to the Chairman, Dr. Mark Brecher.

After welcoming the Committee Members, Dr. Brecher summarized the three major topics from the last meeting (May 16-17, 2005). 1) Efforts to reduce the risk of transfusion-transmitted diseases and coping with any consequent effects of availability needed further discussion before recommendations can be made; further discussion is planned for the current meeting. 2) Measures to avoid bacterial contamination of platelets and to extend the dating period beyond 5 days seem to be moving along well. Shortly, the New York Blood Center is expected to go "live" with 7-day platelet dating and the use of a bacterial contamination "release test." 3) Availability of intravenous immune globulin (IGIV) for patients with immune deficiency has worsened since the last meeting with a change in reimbursement methods leading to further disruptions in supplies for those patients. DHHS has not declared a "Public Health Emergency" to enable alternate reimbursement mechanisms. This issue will also be discussed at the current meeting.

The Chairman reviewed with the Committee the response to those recommendations from Dr. Beato (Acting Assistant Secretary for Health). She was encouraged by the progress toward preventing bacterial contamination of platelets, noting that this resulted from a public/private collaboration to improve safety and efficacy. She also noted the importance of vigilance toward infectious diseases, as important not only to blood transfusion safety but also to the safety of bone marrow, progenitor cells, tissues and organ transplant safety and efficacy. The Department has reviewed the availability of IGIV and concluded that the overall supply was adequate and that market-based adjustments in manufacturing and distributing were responsible for apparent problems with patients getting appropriate care. Off-label use, both evidence-based and speculative, is responsible for much of the increased use and apparent shortages.

Dorothy Scott, M.D. (FDA) described a potential disruption in the availability of varicella-zoster immune globulin (VZIG). It was licensed in 1981 and produced from plasma of normal donors selected for high levels of anti-varicella-zoster antibodies, with the indication to prevent or modify varicella (chicken pox) or herpes zoster ("shingles") by IV administration within 96 hours of exposure. It effectively reduces complications such as pneumonia, hepatitis, encephalitis and death when given to immunocompromised children or adults, including premature infants, non-immune pregnant women and

patients receiving cancer chemotherapy. The sole manufacturer (Massachusetts Public Health Laboratories) is ceasing plasma operations. It is estimated that there enough stock of adult-size (625 units) vials to treat appropriate patients through 2006. The entire supply is managed by one distributor, so that monitoring is simplified. Clinicians will be encouraged to place orders only for specific patients and not establish small stockpiles; shipments can be made promptly enough to suffice. There are two other firms that have shown an interest in producing and marketing VZIG. The FDA has encouraged them to apply for an IND and ultimately a BLA. The FDA Blood Products Advisory Committee (BPAC) addressed the scientific data needed to support licensure, considering that pharmacokinetics and titers after administration of the drug would suffice. There are too few patients who need the drug for a classic clinical trial for efficacy to be feasible. The product can be classified as an "orphan drug" as a result. FDA has also consulted with CDC about the possibility the standard IGIV preparations would suffice, but titers are quite variable and dosing is difficult without knowing the titer. If licensure can't be accomplished before current supplies are exhausted, it would be possible to use a preparation supported by preliminary data, using the treatment IND mechanism.

In the discussion, Dr Bracey asked if blood centers might be designated sub-depots to facilitate distribution. In response, the single distributor can ship needed supplies promptly so that sub-depots would not be necessary and might needlessly complicate distribution. It is something to keep in mind, however, should the need arise. Dr. Epstein asked about sub-aliquot adult-sized vials to provide doses for children while minimizing waste. Sterility could be a problem and it is preferable to avoid undue manipulation (e.g., freezing) if possible. Sub-aliquot is an option. Dr. Brecher asked if the dating period could be extended. Such an extension is acceptable, provided that the potency is demonstrated to be stable enough. It is most likely, however, that the current supply will be exhausted before outdating. Dr. Bianco asked if other companies were interested. FDA has had some discussion with two.

Jerry Holmberg, PhD (Committee Executive Secretary) elaborated on the opening comments by Dr. Brecher about the supply and reimbursement status of intravenous immune globulin (IGIV). The Secretary, DHHS, and its constituent Agencies are concerned and investigated the many parts of the problem: manufacturers, distributors, Plasma Protein Therapeutics Association (PPTA), Center for Medicare and Medicaid Services (CMS), the Immune Deficiency Foundation (IDF), hospital-based pharmacists, providers and individual patients. Problems are multi-faceted: market consolidation has reduced the number of manufacturers who have tailored production to reduce inventory costs; inventory reduction has limited the amount of product carried by the distributors; providers have had difficulties getting the best product for individual patients (e.g., lower salt content, reaction avoidance), although the overall supply may be adequate; reimbursement policy changes have reduced physician willingness to administer office-based therapy, shifting treatment sites to hospital out-patient departments; hospital pharmacists have had difficulty adjusting to their increased demand; and finally, off-label uses have increased the demand (e.g., FDA has approved only a handful of indications, while CMS will reimburse for about 30 clinical conditions). It is recommended that providers communicate needs directly to manufacturers (rather than through distributors)

so that they can respond better to need. DHHS is planning to develop evidence bases for off label clinical use. Payment rules have been published for hospitals and are still in the comment period for office-based (Medicare, Part B) and hospital out-patient treatment. Medicare reimbursement rules are usually adopted quickly by other third party payers and become standard.

In the discussion, Dr Roseff asked if there were a mechanism to track provider interaction with manufacturers about IGIV problems. Such tracking is outside of the Government's realm, but problems can also be referred to 1-800-MEDICARE (1-800-633-4227) where they can be tracked. The FDA also will track and help deal with problems. Dr. Sayers asked about the traffic on the web sites listed. Dr. Holmberg does not have those data.

Ms. Julie Birkofer (Executive Director, PPTA) reported on an IGIV Summit meeting, September 7, 2005. PPTA rapidly assembled an "IGIV Working Group" of physicians, consumers, distributors and manufacturers to address the specific issue of patient access to IGIV therapy in hospital outpatient departments. Previously, IGIV issues addressed involved physician office therapy supported by Medicare Part B. The Hospital Outpatient Prospective Payment System (HOPPS) is also supported by Part B, but with a different mechanism. IGIV reimbursement will be based on "Average Sales Price" plus 6%, which physician office experience suggests is not a sustain business model. Even adding 2%, as has been proposed, will not support continued patient access. One problem is the six month delay in assembling and analyzing price data for this fluid and dynamic market. Another is that products are not interchangeable; apparently minor differences in the production often are important for patient tolerance with minimal reactions or side effects. Recent changes in physician office reimbursements have resulted in a sizable shift in infusion sites to hospital outpatient departments (previously, 67% of 4-8 hour IGIV infusions were in doctors' offices and 32% in hospital outpatient departments). This has resulted in difficulties for hospital pharmacies to increase their product allotments and led to individual product shortages. It is not clear what the effect of 2006 HOPPS reimbursement is likely to have, but it probably will be negative for the patient. The 30-40 member working group made some consensus recommendations to correct the problems: 1) reclassify IGIV from "low complexity" infusions (e.g., saline) to "biological response modifiers." 2) Healthcare Common Procedure codes (HCPC) should be debundled and replaced by product specific codes (e.g., National Drug codes, which are drug and dosage size specific). 3) Bring FDA and CMS classifications into synchrony (e.g., FDA classifies IGIV as a "blood product;" CMS considers it heavily refined and a "drug").

In the discussion period, Dr. Angelbeck asked for clarification of the sustainability of the business model for ASP + 6% versus ASP + 8%. "Providers," including physicians and home care companies, find both to be problems. Manufacturers are committed to providing life-saving medications and are maintaining a robust emergency supply to cope with spot shortages of specific products. Mr Skinner asked how the system of physicians reporting problems directly to manufacturers would be monitored. PPTA is not involved at the interface between customer and manufacturer. Dr. Holmberg asked about NDC-based reimbursement (see above for a discussion). Dr. Bracey asked what actual

production costs were. PPTA has not specific data, but IGIV production is capital intensive and costly. Dr. Holmberg asked if an FDA posting about albumen (initial reports that albumen was unsafe in many circumstances were found to be in error: FDA clarified this information about the time of the last Committee meeting) had any effect on albumen demand and indirectly on costs and prices for IGIV. A strong albumen market helps other products, but changes had been incremental and not yet clear. Dr. Haas asked for additional clarification. PPTA has no comment on pricing. Dr. Sayers asked what proportion of IGIV use was "off label" (not approved by FDA, usually because data had not been submitted for review). The Immune Deficiency Foundation (IDF) has estimated that 40-60% of the use is off label.

Next, Ms. Marsha Boyle (President & Co-founder, Immune Deficiency Foundation: IDF; son being treated for Immune Deficiency) reported on surveys of IGIV use. By way of introduction, she thanked the Committee for its past work on behalf of ID patients and noted some Congressional interest. CMS had not seemed responsive to problems reported to their hot line. "Find another doctor" was not a satisfactory answer to problems getting IGIV in physicians' offices; referral to a hospital infusion site for care was not helpful either. To quantitate impressions obtained from phone complaints, the IDF did a telephone survey of patients and physicians known from previous records to be treated for immune deficiency. The summer 2005 survey was compared to previous ones, notable from 1997 and 2002. There was 91% cooperation from more than 6,000 patients contacted. Eighty-one percent were using IGIV. Reimbursement problems led to health problems for 39%. Problems included a product change with poorer tolerance for the new formulation, a decrease in the dose per infusion or in the frequency of infusions and a change in the site where the infusions were given. Decreases in overall dosing were accompanied by increased frequency and severity of infections. Out-of-pocket costs for patients were increased: hospital infusion sites always collected the co-pay, while physicians sometimes waived co-payment if the patient was needy. One fatality was recorded as the result of problems with treatment based on reimbursement changes.

In the discussion, Dr. Brecher asked about off-label use. IDF from various sources believes that about 30-34% of IGIV is being used for immune deficient patients and about 50% is being used off label for other purposes.

Ms. Jan Hamilton (Advocacy Director, Hemophilia Foundation of America) began the Open Public Comment period with a Discussion of Patient Access to Care in a disaster situation (Gulf Coast and Hurricane Katrina). The destruction and disruption from Katrina was unprecedented. Pre-storm evacuation was recommended but not mandated. Some with their own transportation left early and relocated without difficulty. Others had transportation, but delayed leaving and were faced with massive traffic jams. Still others did not have their own transportation, but preparations for them were incomplete. For example, hundreds of New Orleans school buses were left in their usual low lying parking areas and were flooded out and useless. There was a shortage of qualified drivers for the few buses that were available. Some called it a black/white issue, but she does not believe it to be the case. Governor Blanco did not seek Federal help in timely fashion,

although President Bush offered. There were serious communication problems: land and wireless phones did not work. Ham radio operators were excellent, but problems with security of their equipment blunted their capabilities. When access was available, the internet provided some helpful communication. Ms. Hamilton lives in Lafayette, LA, where many refugees from the New Orleans area landed. Shelters were set up for people in the Cajun Dome, for pets in the Blackham Coliseum and for special needs medical care in the Heymann Center next to the Lafayette General Hospital. Dr. Lessinger from the Tulane Hemophilia Treatment Center relocated to Lafeyette ofter a short delay. Conference calls with manufacturers helped with supplies of anti-hemophilia factors and drugs and other materials for diabetics, hypertensives, patients with multiple sclerosis, immune deficiency and alpha-1 anti-trypsin deficiency. There was unfortunate friction between the Red Cross and local medical personnel that seemed to interfere with smooth functioning. Both Red Cross and FEMA were very slow to enter the Lafayette area. In planning for the next disaster: 1) Federal assistance should be requested early; 2) evacuation should start early and be mandatory; 3) backup communications should be planned and ready; 4) nearby medical facilities should be identified that might suffer less damage and be helpful; 5) medical facilities should have off-site backup records. The OMB stated that a disaster response should be unified, coordinated and effective, pretty much the opposite of what happened on the Gulf Coast.

The next speaker in the Open Comment Period was Ms. Tamie Joeckel of ASD Healthcare, a Dallas-based division of AmerisourceBergen that specializes in the distribution of blood derivatives. They are one of the largest drug distributors in the US, publicly traded and number 23 on the Fortune 100 list. Its workforce is more than 14,000. They distribute a third of the US supply of derivatives to more than 4,000 providers, including physicians, home care providers, Department of Defense, and hospital in- and out-patient departments. Diseases treated include primary immune deficiency, neurological diseases and autoimmune disorders. ASD is happy to work with ACBSA to gather data to support a message to CMS to reevaluate the effect of changes in Medicare Part B and the January 2006 changes relating to IGIV. Not only must the drug be reimbursed but also related services need to be covered. They are getting calls not only from providers about supply, but now also from patients. The unpredictable and somewhat erratic shift of patients from other sites of infusion to hospital outpatient departments' results in allocations based upon historical information being inadequate. Infusions, taking anywhere between 2 to as many as 8 hours, require constant supervision. Adverse events take place about 61% of the time, with 44% being unpredictably serious. Thirty-four percent occur with the first infusion; the rest are seen with later treatments. Neither for-profit nor not-for-profit operations can afford to lose money on these treatments. She believes that CMS has the authority and the flexibility to change reimbursements to support adequately infusions at all sites.

During the discussion, Dr. Sayers asked for clarification of production waste and testing for hepatitis D as source for some of the rise in production costs. Ms. Joeckel had no direct or specific answer, but as the demand for some plasma-based products decreases (due to a shift to using recombinant proteins), production costs, overhead and profit (or

difference between revenue and costs) must more and more be covered by the continuing use of others (i.e., IGIV).

Continuing with Public Comment, Ms Michelle Vogel (IDF) echoed what Ms. Boyle has said earlier, but added concern about what patients will face when and if hospital reimbursement rates are ratcheted down to approach those for physicians' offices. CMS' hotline suggestion to find a physician that will accept Medicare reimbursements to replace those that won't is neither a satisfactory nor a viable solution. She requested that the Committee send a letter to Mr. Leavitt (DHHS Secretary) seeking his assistance.

Ms. Theresa Lee (Advanced Medical Technology Association – AdvaMed, Blood Products and Technology Section) reported that her organization was working in coalition with AABB, ARC and ABC to support reimbursement for all blood and blood products. CMS' APC Advisory Panel recommended that blood and product reimbursements be frozen at 2005 levels for 2006. Nevertheless, plans are afoot to reduce payment for leukoreduced red cells by 10%. Furthermore, blood has lost its status in a separate class and is now coded in a miscellaneous category of many unrelated products and services. She did thank CMS publicly for Guidance #496, clarifying their approach to blood.

To open the Committee discussion, the Chair asked for discussion whether another message about difficulties with patient access to IGIV needed to be sent to the Assistant Secretary for Health and the Secretary (DHHS) or had the message already been delivered and further action is awaited. Dr. Epstein commented that the problems had not been solved and that the consensus proposal reported by the PPTA earlier today deserved to be discussed, although he wasn't sure how that proposal would help. Ms. Lipton agreed, but suggested that the market shift toward increasing use of recombinant proteins was a bigger but unclarified issue. This change is seriously affecting the business model that had been describing the derivative manufacturing process. Dr. Bianco also agreed. Upon query from the Chair, the group decided that they would like to react tomorrow to a proposal developed overnight.

The Committee then opened the major topic for the meeting, the Development of a Strategic Plan for Improving Blood Safety in the 21st Century with a report from a Strategic Planning Subcommittee (Dr. Linden). The Subcommittee's task was to raise issues involved in risk reduction and in improving safety and availability. They built on and supplemented the Blood Action Plan, originally developed at FDA and later adopted by the DHHS. Risks can be divided into Infectious and Non-infectious. Eight issues were identified:

1. Processes for developing policy and decisions should be structured, open and transparent and the blood system(s) should be integrated into the Public Health infrastructure;
2. Improved surveillance and adverse event reporting, both infectious and non-infectious;
3. Plan focus on blood or blood products or should tissues, organs and hematopoietic progenitor cells (HPC);

4. Improve and coordinate risk communication and error prevention
5. Improve availability by better recruitment and retention of donors;
6. Develop and publicize clinical practice standards to limit risk from unneeded transfusions and reduce pressure on recruitment;
7. Establish and manage a suitable scientific research agenda;
8. Continue and improve upon the Disaster Planning process started after 9/11.

The plan should include what needs to be done, who will do it and the role of DHHS. Clarification of these tasks should be done whenever it is needed. Dr. Holmberg asked the full Committee to develop answers to questions that will be posed at the end of the discussion. Does the Committee believe that there is a need for the Department to develop a strategic plan for detecting and preventing transfusion-transmitted complication, both infectious and non-infectious? If a strategic plan is recommended, what scope of issues should it address and what role should the ACBSA play in the development of the plan. The object is to build on what has gone before, e.g., the FDA-Departmental Blood Action Plan, NHLBI's increasing emphasis on the study of Transfusion-related Acute Lung Injury (TRALI), a workshop on rare blood disorders, platelet concentrate bacterial contamination, the "critical path" FDA initiative for approving new procedures, products or devices and equipment and the rapid study, deployment and approval for West Nile Virus testing, now considered a model for improving safety. An IOM Report on microbial threats to health provides excellent background for future planning. It commented that we have a fragile Public Health system. Dr. Beato has appreciated the previous Committee discussions, is pleased that there has been no headlong rush to recommendations and always has emphasized the need for data and logical support for the recommendations that have been made.

The Committee Report continued with a presentation on each of the other issues. Dr. Epstein spoke about the structured process for policy and decision-making. He noted that good discussion was likely to lead to effective action, integrating scientific, economic and social factors. The process has an outcome focus with a needs assessment, the development of scientific evidence to support selected policies and actions, the active engagement of all stakeholders and clean communication of risks and benefits, including their uncertainties. It is useful to study the process, although in the real world you often find yourself concurrently at different stages. Dr. Sandler asked if this could be accomplished by expanding current resources at the FDA or would it be better to go external to his office to create a plan. Stressing a personal opinion rather than an Agency policy, he thought that the structure in place could do the job, especially if encumbrances to action were reduced. Ms. Lipton commented that the revision of the advisory committee structure was positive and effective, but asked if decisions were sufficiently evidence-based. Dr. Epstein agreed that they might do better in marshalling evidence, although often some decisions must be made with limited scientific groundwork. Dr. Bianco suggested that the objectives of safety and availability be better defined. Dr. Sayers noted problems with the Blood Products Advisory Committee in that prospective members who had the special knowledge necessary often also had potential conflicts of interest. Dr. Epstein agreed that keeping the BPAC free of taints was difficult to balance with having enough expertise and information. The FDA covered some of this delicate

balance by holding workshops of experts whose conflicts of interest could be exposed and understood. Ms. Lipton asked if FDA had enough resources for the workshops desired. In response, it was noted that other groups (e.g., industry, associations) could sponsor workshops where FDA could attend and participate.

Dr. Judy Angelbeck summarized thinking about the integration of the blood system within the Public Health structure. Within the Federal Government, the Public Health Service (CDC, FDA and NIH-NHLBI) and the Department of Defense have blood safety concerns and activities. In DHHS, this Advisory Committee oversees issues of blood safety and availability. National private sector organizations who are concerned with blood issues include AABB, ABC, ARC and PPTA. Also concerned are various local health agencies, such as State and Territorial offices, tribal offices, county and city health departments and various local health boards. The blood and plasma collection and distribution system is a free enterprise network of non-profit and for-profit organizations. The 9/11 attacks underscored the need for a coordinated message about blood needs (and non-needs). Discussions about widespread vaccination for smallpox emphasized a need for advance planning which included consideration of the effect of such immunizations on the blood supply. Concern about the transmission of West Nile Virus by blood transfusion fostered a successful collaboration of the various entities in the public and private sectors and addressed the problem in model fashion. Nevertheless, the Hurricane Katrina natural disaster exposed continued weaknesses and led to a serious system breakdown. The potential for an influenza pandemic pointed to a continuing need to address how best to cope with blood supply disruptions. When there is a major event, would attempts to integrate the disparate public and private sectors lead to change for the better? Or would it be better to enhance and expand collaboration as appears to have been the case with West Nile Virus?

In discussion, Dr. Bianco asked that “integration” be better defined as an example; the Canadian system has formal risk assessments and coordinates the results through the regulatory process to implementation by users. The US is much more fragmented. Dr. Epstein noted that the US public health structure was also fragmented. With regulations and volunteer trade organization activities, the blood system is probably less fragmented than is public health. He suggested that the need was for a better interactive dialog to lead to decisions about blood safety and availability. Dr. Brecher said that despite our system, the US has had greater success than most other countries with protecting the blood supply.

Next, Dr. Holmberg (speaking for Dr. Kuehnert, who was on assignment near the Gulf of Mexico) discussed Surveillance for Adverse Events Related to Blood Donation and Transfusion. He noted that some activities related to hemovigilance directly while others were of a more general nature. In the US, there are multiple systems (e.g., CDC, NIH and NHLBI) that are poorly integrated and minimally interactive. Other weaknesses include passive reporting with no information about the denominator, little apparent attention to unknown pathogens and future threats, limited activities to educate clinicians and others about transfusion transmitted infections and little coordination of global vs. domestic needs. He recommended standardizing and integrating existing data collection

and analysis into an adverse event reporting system. Ideally, this should include, in addition to blood, hematopoietic progenitor cells, organs and tissues. Dr. Bracey asked if non-infectious complications could be given similar emphasis placed to infection transmission. Dr. Holmberg noted the possibility of developing a sentinel hospital program for more focused collection of data.

Ms. Lipton then discussed the Coordination of Risk Communication. The presently constituted Committee has had no formal presentation on risk communication. She listed the following barriers to effective risk communication: lack of a formal integrated process for developing and communicating risk; lack of optimal harmonization and coordinated globally; problems with timeliness (various groups may prematurely make statements that need more thought); questions of accountability (who has the primary role?); and conflict with lack of communication between stakeholders. Risk communication should be a 2-way, interactive process, treating the public as a full partner. She recommended that the roles of various organizations be defined and the message developed for specified target audiences.

Dr. Jeanne Linden summarized thinking about Error Prevention in Blood Centers, Transfusion Services and Clinical Transfusion Settings. Many errors appear to be preventable and relate to underlying systems factors, sometimes called "latent system pathogens." Blood transfusion should be viewed as a process going from donor to recipient. She noted that transfusion errors have parallels in the aviation and in the nuclear power industries, which also have very significant adverse events. They have good evaluative reporting systems to identify factors that can be addressed. The transfusion process, however, is different in that many people with various levels of expertise are involved. More than half of the errors happen outside of the blood bank. The present surveillance system is neither coordinated nor comprehensive and focuses on fatal or sentinel events. Assuming strategies can be developed to prevent errors, they must be acceptable to stakeholders, who must be involved in planning, if they are going to be implemented. One goal is to make doing things correctly easy and doing them the wrong way difficult. The root cause analysis of errors should identify the system failure(s) that allow them to happen.

After a lunch break, Dr. Bianco reported on approaches to donor recruitment and retention. Previously, the Committee has focused primarily on shortages and how to alleviate or prevent them. In April 1999, there was pressure to accept blood from therapeutic phlebotomies of patients with hemochromatosis (weekly or maybe more often). The practice was approved, with safety safeguards. Nevertheless, the expected flood of blood from this source never materialized. The lack of complete and timely data on collections and use of blood made it difficult to understand and correct the apparently problem of insufficient blood supplies and frequent shortages. The 911 disaster brought about considerable reevaluation and soul searching. It was concluded that the country needed a strategic reserve of blood and blood components. Public promotion of blood donation was sought, but it was never clear who should do it and how. In January 2004, the Committee suggested that a nationwide supply of blood to cover 5-7 days of use was desirable, although there was considerable debate. There may be a delicate balance

between shortages and glut with increased wastage. Funding was suggested for a public/private partnership, but funds never materialized. Should blood centers accept full responsibility or should government help and promote blood donation as a social responsibility. Discussion should focus on the respective roles of transfusion services, Federal government (FDA, CDC, NHLBI, CMS, Homeland Security and FEMA) and state and local government, as well as the blood centers. Should funding come from users (e.g., hospitals) or from a larger portion of society?

Dr. Arthur Bracey then discussed the need for Clinical Practice Standards for Transfusion. The Committee has never discussed proper use of blood, blood components or plasma protein derivatives. The literature carries many studies that 20-50% of transfusions are inappropriate. Even if individual unit risk is low, inappropriate use increases the population risk and that for individual patients. Unneeded transfusion also has an effect on availability. In general, we have a permissive system that is not proactive in controlling inappropriate use, except in times of blood shortage; many transfusion services scrutinize individual requests for urgency of need. The use of blood often varies from hospital to hospital; for example, a study of heart surgery showed that as few as 25% of patients were transfused in some hospitals, while as many as 100% of heart surgery patients in others received blood. The reasons for this disparity should be studied. There are no uniformly accepted guidelines for determining the need for blood. Several NIH Consensus Development Conferences address the use of red cells, fresh frozen plasma and platelets, but there as seemed to have been little effect on practice. Several subspecialties and professional societies have developed guidelines, but although they weren't divergent, neither were they uniform. There has been a paucity of clinical trials addressing the decision to give blood. This may change, however, because NIH-NHLBI is supporting a clinical trails network for transfusion medicine and hemostasis. This group will be studying some of these issues. There are no good tests to define the functional capability of the red cells (e.g., oxygen delivery). Near-site laboratory testing seems to improve practice by allowing decisions to be based on data. In general, our diagnostic systems are inefficient and not geared up to provide such timely information. Another evolving issue is measuring the effect of increasingly potent antiplatelet drugs. Another problem is that the accountability for the use of blood is usually in the Pathology Department, while clinicians actually write the orders. Clinicians in general have been poorly trained in the use of blood and are largely unfamiliar with available resources (e.g., Circular of Information, AABB materials).

Dr. Bracey made four recommendations: 1) educational efforts should be increased, although it is not clear how durable the benefits are; 2) hospitals should be encouraged to use benchmarking, often based on outcome data; 3) experts should interact more with clinicians to influence practice using available data; and 4) the role of government in improving practice should be determined and implemented.

Dr. Merlyn Sayers then discussed the Research Agenda. Although he was not part of the group dealing with this issue (Drs. Klein and Heaton were not available), he had access to their notes. His discussion will be influenced by his own thoughts and prejudices. Transfusion research has been very strong in immunohematology and in transfusion

transmitted infectious diseases. There have been a few studies on the motivation and altruism of donors (e.g., Dr. Jane Piliavin). Nevertheless, the national inventory seems to lurch between surplus and insufficiency (currently, it is full, as a result of donations after Hurricane Katrina). The "dogma" that 60% of the population is eligible while only 5% donate has been a lament that hasn't helped and should be abandoned. The Committee has recently discussed a number of research topics: 1) the treatment of rare disorders; 2) bacterial contamination of blood components; 3) transfusion-related acute lung injury (TRALI); 4) universal leukoreduction; 5) various infections such as made cow disease, HHV8, babesiosis and Chagas' disease; 6) pathogen inactivation; and 7) bioterrorism agents. Some of these are quite rare. Chagas' disease was called an "unmet challenge;" is seven cases in the US and Canada since 1987 really that important? In the search for "zero risk," the problems of getting the right unit of blood to the right patient have not been solved, representing one of the larger risks. Preventing the misidentification of recipients will take a multidisciplinary approach, including hospital administration, nursing, information management services, physicians, pharmacies and the blood bank. He also recommends an interdisciplinary approach to understanding altruism for the recruitment of donors. His overall plea was to focus on common problems as well as the unusual ones.

Dr. Susan Roseff reported on issues surrounding disaster planning. As a new member of the Committee, she wasn't present for the discussions that followed 9/11. The AABB coordinated Interagency Task Force of Domestic Disasters and Acts of Terrorism that was formed in December 2001. Initial discussion involved the importance of managing collections after a disaster to avoid over-collecting with resultant wastage and loss of public trust. A consistent message to the various publics should be developed and used. A national inventory management system was needed, but there was dispute on how much was adequate (5-7 days of supply were most common numbers). Blood used in disasters must be available; that collected from the public's response to the disaster will be too late for the emergency itself. In the winter of 2002, the Committee sent a letter the then Secretary Thompson endorsing the work of the Task Force and suggesting its incorporation into the Federal structure. Blood reserves should be monitored. Attention should be paid to infrastructures, especially supporting the movement of blood, reagents and testing and storage cites. A certain amount of redundancy is necessary. Regulations should be scrutinized to see if revisions would be useful or necessary. Donors should be regarded as a national resource. The Task Force functioned during and after Katrina with a consistent message about the need (or lack of need) for blood. Questions remain about the Task Force structure, whether its resources are adequate. What is the status of a national blood reserve?

The Chairman then asked Ms. Lipton for an update on the activities of the Task Force. Most of its issues involved support for the areas hit by Hurricane Katrina. They are still in the process of evaluating what was needed and done. A full report should be available for the next meeting of the Advisory Committee.

Dr. Brecher asked about the availability of an alternate site for coordination, should the Washington, DC, area be part of the disaster. The Task Force is not particularly people

dependent in that there are a number around the country that could help with coordination, but there is limited redundancy of servers. Communication would likely be a problem. At present, the Task Force is using resources that are within the AABB. Additional support would be needed to develop more redundancy.

There followed a Public Comment period. Mr. Corey Duban, President, Committee of Ten Thousand (COTT), discussed the history and future of this Advisory Committee. COTT and Ms. Louise Ray asked Senators Kennedy and Graham for a Congressional investigation of the contamination of the blood supply by HIV. As a result, Ms. Donna Shalala, then Secretary of DHHS, commissioned the Institute of Medicine (IOM) to develop a report. One of the recommendations of this report, praised by Mr. Dubin, was to form this Secretary's (DHHS) Advisory Committee on Blood Safety and Availability. Its mission was to coordinate the Federal response to threats to the safety and availability of blood and blood products. The COTT board is concerned that senior department officials are not aware of the Committee's history and its role in providing advice. Early in the history of the Committee, all stakeholders participated in an intense dialogue on the issue discussed (stakeholders include: 1) blood banking – AABB, ABC & Red Cross; 2) manufacturers: fractionators, source plasma, biotech companies; 3) health/medical: home health care, clinicians & treaters, psycho-social care & research; and 4) community: end users & advocates). COTT believes that the early participation of user communities and advocacy groups has diminished as the Committee composition has shifted toward more professionals and fewer lay stakeholders. There have been more presentations by Committee members and fewer from outside sources.

COTT was formed as a support group for patients with hemophilia infected by HIV from blood products and grew into an advocacy group for patients infected by HIV or HCV from "tainted" blood or future patients threatened by other contamination of the blood supply. It is not if a new pathogen will affect blood safety, but when. At one time, hepatitis (now known to be hepatitis C virus, HCV) was considered an "acceptable" risk of blood transfusion and treatment of hemophilia with factor concentrates. He believes there has not been an adequate explanation of how HCV infection became so widespread without more publicity (>4 million in US). Risk assessment should include consumers. He sees a possible parallel in the situation with Creutzfeldt-Jakob Disease (CJD), especially the variant form (vCJD), a human counterpart of made cow disease. There has been a lack of coordination between FDA (blood) and USDA (food), with what he believes is testing of too few cattle at the time of slaughter.

COTT had hoped that the Advisory Committee would lead to proposals for Congressional action. Two items specifically mentioned were no-fault compensation for patients harmed by blood or blood products and the formulation of a National Blood Policy. Unique among advanced countries, the US has no national blood policy or program. Instead, the Committee is dealing now with some of the same issues as were discussed in 1998 or before, e.g., supply and allocation of IGIV. COTT is concerned that the Committee's communication with and influence over the Secretary has diminished over time to very low levels.

There then ensued Committee discussion of the day's overall agenda. Several members supported Mr. Dubin's disappointment that they had gone through a period of limited response and little apparent action from the Secretary to their recommendations. Mr. Skinner commented that as a prelude to strategic planning it was useful to recall why the Committee was created (problems with blood safety at the beginning of the AIDS epidemic) and for whom it was to be advisory (Secretary, DHHS). Addressing the original issues has gradually given way more to ad hoc problems. Dr. Epstein said that the Committee was advisory to the Department and the Secretary, who decide where they want advice. The results of the Committee's deliberations have sometimes been good (the government and/or the private sector have been responsive) and sometimes frustrating because responses have not been evident. Dr. Brecher noted that the Interagency Disaster Task Force, dealing with bacterial contamination of blood and HCV "lookback" have been among the successes, while reimbursement recommendations have had more limited effect. Dr. Bracey pointed out that many beneficial treatments of modern medicine have been made possible by the availability of blood; blood becomes important if it is in short supply or if unexpected dangers arise. There was some expectation that the Committee would take leadership in examining and updating National Blood Policy and that this might be a suitable project for 2006.

The Chairman noted that two projects needed to be addressed during this meeting: what new or additional message should the Committee send regarding the IGIV issues and strategic planning and policies for mitigating adverse diseases and other problems that might enter the blood supply. The former should be completed today; the latter formed the agenda for tomorrow. The Committee had sent two messages about patient access to IGIV therapy with little apparent action from the Department. There is confusion about the adequacy of the supply of IGIV: distribution has been flat for the past year or so, but usage historically has trended upward. PPTA figures consistently show a "four week supply" on hand, but manufacturers have been allocating medication based upon historical usage. "Off label" use has been increasing, but use for indications not approved by FDA is not inherently bad. Regardless, there is occurring a shift of the administration sites of IGIV from home or physicians' offices to hospital settings. This can increase exposure of immune deficient patients to serious infections, decrease the provision of care by long term treating physicians, adversely affect patient access to care, disrupt the present allocation system and possibly increase costs. Increased patient problems have correlated with changes and decreases in reimbursement policy, suggesting a cause and effect relationship. It was suggested that there were only two "fixes" for the problem: declaration of a Public Health emergency, permitting additional leeway in setting reimbursement schedules; or Congressional action. Reclassifying IGIV as a biological response modifier would also increase reimbursement flexibility.

Dr. Epstein proposed the following resolution:

> "The Committee remains highly concerned that disruptions to access for IGIV, including a shift to hospital-based therapy, continue to compromise quality of care for many patients. We further are concerned that a change to hospital outpatient reimbursement, to ASP plus 8 percent, effective January 2006, will further aggravate an already difficult situation and that this shift will not be sustainable.

"We therefore recommend that the Secretary take immediate steps to:

1. Increase reimbursement for non-hospital IGIV therapy to a level consistent with current market pricing.
2. Reconsider the current program to hospital outpatient reimbursement to ASP plus eight percent in January 2006.
3. Re-examine the extent to which current IGIV supplies are or are not meeting demand."

After considerable discussion about the inclusion of "Public Health Emergency" and long-term vs. short-term fixes and suggestions that IGIV be designated a "biological response modifier" rather than a drug (scientifically satisfactory), the following resolution was put to a vote and passed unanimously:

Recommandation Subject: Immune Globulin Intravenous (IGIV):

After new input from patients, medical professionals, distributors and manufacturers, the committee remains highly concerned that persistent disruptions in access to IGIV, which include a progressive shift to treatment in a hospital, continue to compromise quality of care for many patients. In particular, we believe the transfer to a hospital may impair continuity of care by their usual medical provider and may add otherwise unnecessary cost, logistical complexity and nosocomial infectious risk. We further are concerned that a change to hospital outpatient reimbursement to ASP + 8% effective January 2006 will further aggravate an already difficult situation and that this shift will not be sustainable.

We therefore recommend that the Secretary take immediate steps to:

1. Increase reimbursement for non-hospital IGIV therapy to a level consistent with current market pricing.

    a. Consider reclassifying IGIV as a biological response modifier.
    b. Consider declaring a public health emergency to address the short-term problem.

2. Modify the current plan to change hospital outpatient reimbursement to ASP + 8% in January 2006 in such a way as to prevent any sudden and large decrease in reimbursement.

3. Reexamine whether the current IGIV supplies are meeting patient needs.

4. Work with Congress to establish a long term stable and sustainable reimbursement structure.

The Committee adjourned at 5:30 PM, to reconvene at 9:00 AM the following day.

The Committee was called to order at 9:05 AM, September 20, 2005 and the roll called.

Dr. Holmberg posed two questions to the Committee to help guide the discussion: "1) does the Committee believe there is a need for the Department to develop a strategic plan for detecting and preventing transfusion transmitted complications in the 21st century? And 2) if a new strategic plan is recommended by the Committee, a) what scope of issues does the Committee believe that the plan should address? And b) what role should the ACBSA and its subcommittees play in the development of the strategic plan?" He also supplied an E-Mail from Dr. Haas that the Committee should consider potential fiscal constraints when developing recommendations and "submit (them) with full recognition of needed resources," but not a full cost-effectiveness study. Committee members were chosen because of their expertise and not to represent and lobby for a constituency's particular point of view.

The list of issues developed by the Strategic Plan Subcommittee was projected on the screen. After considerable discussion and rewriting, the following recommendation was made:

Recommendation Subject: Strategic Plan for Blood Safety

Blood is a critical element of modern medical care, and ensuring an adequate supply of safe blood is a national responsibility. Although there have been dramatic improvements in blood safety and availability in the United States in the last two decades, the Committee finds that there are compelling needs for improvement in some areas:

Minimizing disruptions in the supply of and access to blood products and their analogues,

Meeting the product development needs for patients with rare disorders,

Timely funding to ensure appropriate utilization of new technologies,

Integrating presently fragmented systems for monitoring blood safety and availability,

Aligning reimbursement and funding policies with product approvals and other decisions intended to optimize blood safety and availability,

Modifying reimbursement policies as needed to sustain access to blood products and their analogues for all patient groups (e.g. IGIV),

Reassessing policies and their related interventions based on evaluation of their impacts,

Intensifying efforts to influence clinical practices related to blood transfusion and alternative therapies, based on scientific evidence,

Accelerating responses to threats (e.g., patient /specimen/unit misidentification) for which there are available interventions,

Utilizing formal risk communication strategies targeted to blood donors, patients, and care providers to enhance scientific comprehension and public trust,

Pursuing opportunities to enhance public health in the management of blood donors,

Promoting comprehensive disaster planning including sustaining the inventories necessary for an effective crisis response,

Establishing a proactive, prioritized, and goal- oriented research agenda,

Utilizing formal assessment tools more routinely in policy development and decision making,

Further clarifying the respective roles of government agencies and the private sector in management and oversight of the blood system,

Therefore the Committee believes that the Department should develop, in collaboration with stake holders and interested parties, a strategic plan for increasing safety and availability for blood products and their analogues. This plan should include a review of the process of policy and decision making for blood issues and its integration with broader public health policy making.

Such a plan should encompass:

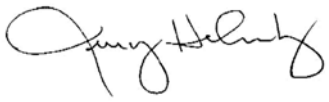
- Structured process for policy and decision-making
- Integration of blood system within the PH Infrastructure
- Surveillance of adverse events related to blood donations and transfusions
- Risk communication
- Error prevention in blood collection centers, transfusion services and clinical transfusion settings
- Donor recruitment and retention
- Clinical practice standards for transfusion
- Strategic research agenda
- Disaster planning
- Stable and sustainable reimbursement
- Funding for promising new technologies

A motion to accept this and forward it to the Secretary was made, seconded and passed with 13 for and none against.

The next meeting of the Committee will be the 5$^{th}$ and 6$^{th}$ of January at the Crystal City Marriott. After a brief discussion of the likely replacement of a number of Committee

members whose terms were expiring and of the need for some continuity on the Committee, the meeting was adjourned (1:35 PM).

Submitted by:



Jerry A. Holmberg, Ph.D.
Executive Secretary, Advisory Committee for Blood Safety and Availability

Certified by:

Mark E. Brecher, M.D.
Chairman, Advisory Committee for Blood Safety and Availability

Prepared by: Paul McCurdy, M.D.