

Summary:  
Advisory Committee on Blood Safety and Availability  
Department of Health and Human Services  
32nd Meeting, August 22-23, 2007

At 9:05 AM, August 22, 2007, Chairman Arthur Bracey called the meeting to order and asked The Executive Secretary, Dr. Jerry Holmberg, to call the roll and introduce new Committee members. Present were: Dr. Bracey, Chairman, Ms. Benzinger, Dr. Duffell, Ms. Finley, Dr. Kouides, Dr. Lopez-Plaza, Dr. Matyas, Dr. Ramsey, Dr. Roseff, Ms. (Thomas) Wade, Dr. Epstein, CDR Libby, Dr. St. Martin and Ms. Ashton. Absent were Ms. Birkofer, Dr. Bloche, Dr. Haley, Mr. McGuire, Dr. Pierce, Dr Sandler, Dr. Triulzi, Dr. Kuehnert, Dr. Klein, Dr. Bowman and Dr. Burdick. Dr. Holmberg announced that a quorum was present, although a quorum was needed only if formal votes or other actions were taken.

Next, Dr. Holmberg recognized members who potentially will rotate off the Committee, potentially because the Charter permits extension of service, the nomination process is delayed, and the needs of the Committee require it. Those recognized are Dr Sandler, Dr. Rosa, and Dr. Bracey.

He also announced that Dr. Agwonobi, Assistant Secretary for Health, had resigned effective September 4. His leadership, knowledge and compassion will be missed.

LCDR Rich Henry has been promoted to Deputy Director for Blood Policy and Programs and Deputy Executive Secretary for the Advisory Committee. LTJG Jennifer Lunney has joined the Public Health Service and the Committee's Office from several years at an HIV/AIDS project in Zimbabwe in a Johns Hopkins Bloomberg School of Public Health project. Dr. Holmberg also recognized Ms. Renee Wilson, who handles logistics of the Committee meetings and other aspects of Committee business.

A call for nominations to the Committee has been published in the Federal Register. Members are appointed by the Secretary. The Committee Charter has been expanded and includes: "The Advisory Committee on Blood Safety and Availability shall provide advice to the Secretary and to the Assistant Secretary for Health, the committee will advise on a range of policy issues to include definition of public health parameters around safety and availability of blood, and blood products, broad public health, ethical and legal issues related to transfusion, and transplantation safety. And the implication for safety and availability are various economic factors affecting product cost and supply."

Dr. Holmberg then turned the meeting over to Dr. Bracey, Chairman.

Dr. Bracey welcomed committee members and expressed his gratitude that they participate in the important workings of the Committee. He noted recent activities that established the basis for the provision of blood and blood products to be considered a critical component of the medical infrastructure. There was also a strong recommendation for the establishment of a biovigilance system to improve the safety of blood, organ, and tissue transplantation under the expanded charter.

The first part of today's meeting will include updates of previous activities and evolving issues in blood therapies. In the remainder of the two day meeting, the Committee will hear from experts on the availability and elasticity of supply, the ethics of

distribution priorities, the current system for monitoring supply and strategies to improve readiness assessment and response to crises.

Before proceeding further, Dr Bracey read a letter from Dr. Agwunobi responding to Committee recommendations from the last meeting:

“Dear Dr. Bracey:

“It was a privilege to meet with the Advisory Committee on Blood Safety and Availability at the May 2007 meeting. I appreciate the leadership that you provide the committee and the thought for discussion of the proposed questions regarding the need, opportunity and the scope of the master strategy for transfusion, and transplantation safety.

"It is apparent from the response to the questions that there is both an opportunity, and a need to develop a process to enhance quality improvement, transfusion medicine and transplantation. As the Committee noted the benefit risk profile differs for transfusion, tissue, and transplant recipients.

"However, all patients treated with these modalities have the potential requiring life-threatening infections. This risk increases if good laboratory manufacturing tissue and transplantation practices are not followed.

"The Committee also noted that there needs to be a mechanism to detect and monitor emerging unknown diseases which may be transmitted by transfusions, or transplantations. The scope of a master strategy is very consistent with a previous recommendation made for biovigilance to include all transfusion and transplantation modalities.

"The department and its operating divisions are working with the private sector concurrently with internal discussions to move forward on these recommendations. Some activities such as biovigilance partnerships have already been initiated with AABB, and the United Network of Organ Sharing (UNOS) using HSS resources.

"Please express to the committee my appreciation for their service and valued recommendations. I look forward to the advancements in transfusion and transplantation safety which will be realized in the near future."

Signed John O. Agwunobi

Dr. Bracey then introduced the first speaker, Dr Basil Golding (Division Director, Hematology, OBRR, CBER; certified in Internal Medicine and Rheumatology), updating “Measles Antibody Standard for Immunoglobulin Lot Release.”

He discussed the presentation to BPAC on this topic, seeking advice on a proposal to reduce the minimum measles antibody titer required for release of Intravenous Immune Globulin (IVIG) or of subcutaneous immune globulins. Measles antibody has been decreasing in these preparations; lot release criteria failure leads to rejection of the produce and decreased availability for patients with primary immune deficiency diseases. The proposal is to reduce the requirement for antibody to that necessary for pre-exposure prophylaxis for patients with primary immune deficiency (these products are also indicated for post-exposure prophylaxis for non-immune deficient patients; these requirements will be considered separately).

Lot release requirements are: “Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures designed to assure that drug products conform to appropriate

standards of identity, strength, quality, and purity.” from the Code of Federal Regulations.

Potency testing for Immune Globulins provides a measure of Lot-to-Lot consistency, assurance of product integrity, especially tests that measure antibody function rather than just binding, activity that is relevant to the indication for patients with Primary Immune Deficiency Disorders. Current U.S. Immune Globulin Product Potency Test manufactures are required to measure antibodies to measles, diphtheria, and at least one type of polio. In addition, we’ve been asking for Hepatitis B surface antigen antibody testing. All of the above tests except antibody to Hepatitis B surface antigen are neutralization assays, functional tests. The anti-hepatitis B surface antigen provides additional assurance of viral safety. Measles functional potency tests, hemagglutination inhibition and plaque neutralization correlate with post-exposure prophylaxis in normal subjects, as measured by bioassay (years ago in measles epidemics).

Measles antibody in IgG preparations is decreasing because members of the plasma donor pool are increasingly likely to have been immunized by vaccination rather than by natural infection (data shown on slide 9). Measles vaccine was licensed in 1963 and progressively increased in use. The plasma donor population is also aging and more likely to be deferred. The last major outbreak of measles in the US was 1989-91, with more than 55,000 cases. Since 2001, US outbreaks come from exposures outside the US. The first standardized lot of IgG for measles antibody was done in rhesus monkeys that were susceptible to the virus. Subsequent lots were standardized every few years against that preparation or successor standards. Measles is still a serious disease in many parts of the world; world-wide, 21% of deaths from disease in children under age 5 were from measles.

Neutralizing antibody titers of 120 milli-International units provide protection against disease; titers greater than 1,000 mIU are needed to prevent infection (virus is cleared by CD8+ T cells)(slide 14). There are no published pharmico-kinetic data. Because there are more than 100 immune deficiency syndromes, making it difficult to determine antibody protective levels in that population.

Primary immune deficiency disease (PIDD) patients are treated with 200-800 mg IVIG per Kg every 3-4 weeks. It is rare for them to be given less than 400 mg/Kg. With a concentration of measles antibody of 1200 mIU/ml (0.48 of the current standard #176, the proposed new lot release requirement), these doses of IVIG would provide twice the protective level at trough (slide 15). (The current lot release requirement is 0.60 x this standard) Other strategies to prevent failure of lot release criteria include revaccination of plasma donors. Healthy individuals will get titers more than 1052 mIV/ml, but these are short-lived, making it unlikely that this strategy will work.

BPAC was asked if reducing the lot release criterion for measles antibody from 0.60 x standard 176 (current) to 0.48 x that standard was acceptable. There were 13 yes and 1 no votes. They were also asked to discuss and accept studies proposed by FDA as needed: to confirm that PIDD patients will achieve trough levels of measles antibody greater than 120 mIU/ml if treated with preparations meeting the proposed potency revised standard of 0.48 x CBER standard. There were 13 yes and 1 no votes. BPAC was asked to comment on alternate strategies.

BPAC action items are: 1) consider requiring tests for antibodies to

enterovirus, hemophilus influenzae and streptococcus pneumoniae and requiring that actual titers be part of the label; 2) should PIDD patients get IVIG before traveling? 3) educate physicians about these issues; and 4) IgIM needs attention; it was not part of this discussion. Severe immune deficiency patients (e.g., SCID before marrow transplantation, severe immune deficiency from HIV infection) may need larger doses providing trough levels greater than 1,000.

Discussion: Dr. Dufell asked if the 2 dissenting votes came from the same BPAC member. No; they were 2 different individuals. The dissenter for the first question was uncertain. The reason for the dissent on the 2<sup>nd</sup> question was not clear. The Chairman asked what effect the new standard would have on supply. In response, 100% of lots will likely pass the new standard. Although natural infections outside of the US will have increased titers, FDA requires that plasma protein derivatives be made from US licensed plasma. Donors from outside the US may be more likely to be deferred, e.g. possible exposure to vCJD. Dr. Holmberg asked if labeling requirements would be changed. The response was yes.

Dr. Bracey then introduced the next speaker, Ms. Mary Malarkey (Office Director, Office of Compliance and Biologicals Quality, CBER, FDA) to summarize the Human Tissue Task Force Report (available on the CBER website). The task force was formed in August 2006 as part of the risk-based system for regulating human cells, tissue and cellular-based products (HCTPs). Its goal was to assess the problems that arose after a “final” rule for these products was published, May 25, 2005. This FDA task force included the Office of Regulatory Affairs (FDA field staff), CBER, the Office of the Commissioner, the Office of General Counsel and the Office of Policy. They considered inspection and compliance activities, adverse reaction reports and the science of tissue safety to see if additional regulations, guidances or policy statements should be recommended.

The universe considered was 2,023 registered establishments which harvested material from living or non-living (856 of the total) donors. From October 1, 2006 through March 31, 2007, 153 inspections were performed at establishments that recovered musculo-skeletal tissues. The formal inspection program was supplemented with activities designed to detect inaccuracies or other deficiencies in records. The results showed some deviations from regulations, but no major inaccuracies or deficiencies of records. None required regulatory action. A few had gone out of business, but failed to cancel their registration. Some were inactive. There were 134 hospital adverse reaction reports. Large establishments (>50 employees) were involved in 22% of the reports and 54% of recoveries; most of these harvested organs as well as tissues. Medium-sized establishments (10-50 employees) generated 48% of the reports; and recovered 34% of the materials; some recovered both organs and tissues and some, just tissues. Small operations (<10 employees) were responsible for 30% of the reports and recovered 12% of the tissues. There were about 43,000 donors of recovered organs or tissues in calendar year 2005. Most establishments recovered organs or tissues at more than one location; 93% of establishments used operating rooms; 59% worked at funeral parlors; 59% used the medical examiner’ office and 26%, the morgue. A dedicated suite was used by 18%. Most went to more than one location and they usually had a contract or other agreement with the site of recovery. All used procedures designed for aseptic recovery. No recovery establishment had the final say in the eligibility of donors; this

final determination was most commonly done by the final processors of the organs/tissues. Forms 483 (deficiency report) was generated by 35 or 26% of the inspections, and this did not vary with the size of the establishment. "Cleaning and Maintenance of Equipment" was the most common deficiency cited, followed by record problems, failure to follow cGTP, facility cleaning and sanitization, and "quality programs."

Recommendations were made concerning training, time and human resources needed to improve the program. Partnering was suggested with CDC, HRSA, FTC, State health resources, the eye banks and the tissue industry, and academic/professional organizations. Most improvements will require additional resources, although interaction with outside experts and coordination with tissue activities of CDC can continue with present resources. A workshop on tissue safety is scheduled for October 10-11, 2007. Being drafted are Good Tissue Practices (GTP) guidances including responsibilities of establishments and their contractors. Improving the systems for tracking organs and tissues is important. Critical path analyses will be used to determine the most important activities to reduce the risk of transmitting infectious diseases by organs or tissues.

Dr. Bracey opened this discussion by asking if there were any organ/tissue retrieval organizations that were neither inspected by FDA nor accredited by another agency. In reply, registration with the FDA is required, as is listing the activities performed. The only exception was "research only" entities. Was there a requirement that tissue for transplant be obtained from a registered facility? No. Regulations address the determination of donor suitability and the training required for the individuals doing that. Ms. Birkofer then asked how many tissue processors were there in the US. Ms. Melarkey had no information about this, but Mr. Scott Brubaker from the American Association of Tissue Banks (AATB) thought there were less than 100 processors and most, but not all, were accredited by the AATB. Fifteen to 20 of these dealt with musculo-skeletal tissue. AATB has standards for accreditation. He didn't know the rates of donor rejection for all causes. Two to 25% of the tissues recovered were unsuitable; the most common reason for rejection (8%) was positive infectious disease tests. Ms. Birkofer asked if CMS did (or could) require that tissue be obtained from registered establishments. Neither Mr. Brubaker nor Ms. Melarkey knew the answer and referred to CMS (no answer).

There was a question about traceability of tissue from donor to recipient. FDA is looking into this, but tissues are handled in many different places in hospitals, with no central location like the blood bank responsible. Dr. Kuehnert (CDC) commented that this was changing, with blood banks becoming more involved. The Joint Commission was developing requirements for traceability. Nevertheless, some tissues were handled outside of hospitals, e.g., dental offices. Ms. Melarkey commented that legal analyses were always a problem when new regulations were being developed.

Dr. Holmberg commented that it was good to see so many HHS agencies involved in tissue transplant issues. He asked who did the inspections, the field or FDA headquarters? Field office staff. He then offered any help his office could provide to move these issues along. Dr. Epstein noted that other tissues than musculo-skeletal were involved, e.g., reproductive tissues, stem cells, cord blood cells and eye banks. FDA was currently focusing on musculo-skeletal tissues. Sterility was a major problem. Product

irradiation was one approach, but it wasn't acceptable to all.

The next speaker was Ms. Robyn Ashton, RN, MS (Division of Transplantation, Blood Stem Cell Program, HRSA) to provide an update on the new Advisory Council on Blood Stem Cell Transplantation (ACBSCT). The Stem Cell Therapeutic and Research Act of 2005 (PL 109-129), signed into law 12-20-1005, aims to increase the number of unrelated-donor transplants, increase the inventory of high quality cord blood units from diverse populations for use in unrelated-donor transplants and increase to cord blood units available for research. Key elements were the National Cord Blood Inventory (NCBI) by 150,000 additional units and establish the CW Bill Young Transplant Program to facilitate cord blood and bone marrow stem cell transplantation and collect data on outcomes. The Act required the establishment of a new HHS Advisory Council on Blood Stem Cell Transplantation for these programs. This Council would consider and make recommendations to the Secretary on matters related to the CW Bill Young Program. The committee charter was published in the Federal Register 1-23-2007 and nominations for the Council solicited by 2-22-2007 (more than 100 nominations were received). Up to 25 voting members were to represent marrow donor and transplant centers, cord blood banks, birthing hospitals (or labor and delivery sections of general hospitals), stem cell transplant recipients or their families, individuals with expertise in typing, matching and transplant data outcome data analysis, social science experience (e.g., bioethics), basic scientists in the biology of adult stem cells and members of the general public. Ex officio (non-voting) members would represent the DOD Marrow Program (run by the Navy), HRSA's Division of Transplantation, FDA, NIH, CDC and CMS.

Brainstorming came up with examples of topics to be considered by the Council: targets for optimum size and composition of the NCBI and adult registry; research priorities; criteria for the release of CB and BM for research; informed consent; accreditation, confidentiality, key cord blood characteristics to improve outcomes; criteria for stem cell source for various different diseases; demographics of the registries; public and professional education about donation and strategies to encourage pregnant women to donate cord blood to public banks; regulatory policies and harmonization for importation; public and private insurance; and actions to increase patient access.

Council nominations are still under departmental review and it is not clear when the Secretary will make appointments. A contract for logistic support of the Council has been awarded and it is hoped that the first meeting will be held in the fall. Slide 12 lists important references for this topic and slide 13, contact information for Ms. Ashton.

Dr. Bracey began the discussion by asking if the Council would address issues of availability. Yes; nothing is currently out of bounds for the Council. Dr. Holmberg promised that a CD with Committee material on it would be available in two days.

After a short break, the next speaker was William Riley, PhD, from the School of Public Health, University of Minnesota (co-author, Jeffrey McCullough, MD), discussing the US Donor Pool. He began by saying that their study didn't uncover anything new, but merely took what has been recognized by blood banking experts about the donor pool and put in numbers. Current estimates of the blood donor pool are simply based upon the population between the ages of 18 and 65. They refined that estimate

slide 6) by subtracting 31 major deferral factors, weighted by prevalence and duration of the deferral (18 permanent or > 1 year; 9 long term or 60 days to 1 year; and 5 short term or < 60 days). These were listed in the briefing book provided to the Committee. Of the US population, 294 M, 117 M are outside the age range and 66 M fit other exclusion factors, leaving 111M or about 38% of the population. Conventional wisdom estimated that collections should be about 81/1,000; the estimate from the present model is potentially 128 units per 1,000 population. Unknowns include increasing or decreasing exclusion effects, possible regional variation, the effect of superimposing the known donor profile (white male, college educated with higher than average income), the effect of an aging population on supply and demand, and the effect of new donor exclusions. The prevalence of deferral factors was estimated, not epidemiologically derived. Comorbidities were not factored in. Some of the criteria were selected arbitrarily.

Dr. Bracey opened the discussion by citing Willie Sutton who “robbed banks because that was where the money was.” Except for acute illness, the largest criterion for donor deferral was low hemoglobin. Addressing this issue would improve public health by decreasing iron deficiency and could increase the blood supply. Dr. McCullough replied that low hemoglobin was a short term exclusion in their model, but that it has been known for at least 20 years that this could be addressed by giving anemic donors iron, something that blood bankers have been loath to do. Dr. Epstein asked how the present estimate compared with a number of international estimates and how did it address the issue that the gap or cushion between supply and demand was narrowing? Neither the chair nor an unidentified speaker was able to answer. Ms Finley asked how this applied to platelet donors and the availability of platelets. In response, the same exclusion factors generally apply to platelet donors, except that they may donate more frequently. An unidentified Committee member asked about the age cut-offs, 18 and 65, noting that airline pilots had just generated some publicity about delaying their mandatory retirement from flying beyond 60. What is the effect of geography on the effect of the age cut-off? A respondent noted that neither age is a regulatory requirement and some states have allowed 17 year olds to donate on their own recognizance and that many blood banks are accepting as donors those over 65 who are healthy.

The next speaker was Louis Jacques, MD from CMS, updating the Committee on a recent National Coverage Determination for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications. Dr. Jacques has been on the Faculty of Georgetown University Medical School, including a stint as Associate Dean for Curriculum from 1998-2003. His research interests include issues in medical education. In November 2006, two publications in the NEJM (clinical trials “CHOIR” and “CREATE”) raised questions about the safety of erythropoiesis stimulating agents (ESA) in patients with cancer, especially if the hemoglobin was stimulated to greater than 12-14 gm/dl. There were two issues: possible thromboembolic episodes and possibly greater disease progression and hastened death. In March 2007, the FDA ordered a “black box” warning for these ESAs and some other labeling changes. Shortly thereafter, CMS opened a National Coverage Analysis (NCA) of the use of ESAs in cancer patients. In May 2007, the FDA Oncology Drug Advisory Committee (ODAC) discussed the issues and made some recommendations: “further marketing authorization be contingent upon additional restriction in product labeling; further marketing authorization be contingent

upon additional trials; labeling should specifically state that ESAs are not indicated for use in specific tumor types that may include breast cancer, head and neck cancer, and non small-cell lung cancer (NSCLC); the current evidence is insufficient to determine a lower limit different from the current level of 10 g/dl; the current evidence is insufficient to determine an upper limit different from the current level of 12 g/dl; and product labeling should recommend discontinuation of the ESA following completion of a chemotherapy regimen and re-evaluation of the degree of anemia with subsequent chemotherapy regimen.”

A few days later, CMS proposed a Decision Memorandum (DM) which generated considerable comment. For this DM, CMS reviewed over 500 publications, although very few described prospective randomized double blinded trials. It was more common to compare ESA dose levels than to use placebo controls. Mostly, there were retrospective post hoc analyses. Others reported small trials that were under-powered to detect safety issues. Some were stopped prematurely before statistical significance could be determined. None of the protocols standardized the indications for transfusion, yet the labeled indication for the use of ESAs in cancer patients was to avoid red cell transfusions. No attention was devoted to other possible causes for anemia in these patients, i.e., iron, vitamin B-12 or folic acid deficiency and chronic inflammation. Patients with higher hemoglobin values “felt better,” but no consideration was given to the idea that higher hemoglobins may have resulted from being less sick: circular reasoning. The few attempts to measure quality of life had problems and were difficult to interpret. There is some evidence that transfusion to higher hemoglobin levels is not beneficial and likely is harmful. There was no methodological rigorous evidence that the changes made in ESA coverage would change the demand for blood.

The statutory requirements for NCDs include a proposal no later than 6 months after starting an NCA, a 30 day allowance for public comments and the final NCD within 60 more days. In practice, expert comments are usually solicited when the NCA is opened. The NCD for ESAs in cancer patients did not cover (“non-covered”) off label uses. It restricted coverage for “anemia of cancer” by specifying the duration and intensity of treatment. The original proposal did not cover ESA treatment for myelodysplastic syndromes, but public comments suggested that this was a “pre-malignant” condition, and that it should be omitted from the NCD (covered as previously). CMS’ final decisions were: “noncover specific off label indications; restrict the coverage of ESAs beyond specified duration and intensity and remove MDS from the scope of the NCD.” The list of “noncovered” situations is: “any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis; the anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers; the anemia of cancer not related to cancer treatment; any anemia associated only with radiotherapy; prophylactic use to prevent chemotherapy-induced anemia; prophylactic use to reduce tumor hypoxia; patients with erythropoietin-type resistance due to neutralizing antibodies; and anemia due to cancer treatment if patients have uncontrolled hypertension.” In the 3 weeks since the NCD was finalized, there have been 3 requests for CMS to reconsider the decisions.



The first discussion question asked if there were any information to assess the effect of the coverage changes on specific types of patients. In response, this presents a challenge in that the information on current use of transfusion is short on specifics. Most transfusions are covered on the hospital side (Medicare, part A). A practicing oncologist who uses ESAs requested clarification of the requirement for measuring hemoglobin or hematocrit values. In practice, after ESAs are indicated, repeat measurements are not done for 4 weeks or so. Answer: no hemoglobin check is required in the first 4 weeks. The Procrit label recommends weekly checks until the hemoglobin level stabilizes. The NCD does not require biweekly hemoglobin tests. What if the 4 week hemoglobin is 11 gms/dl? Answer: if known, there is no coverage for a hemoglobin of 11 or more. There are often multiple physicians involved with treating the patient; if one gets a hemoglobin test, the others (ESA user) are not accountable for knowing the result. Don't most local insurers require a CBC at least every 2 months? What about coverage if the hemoglobin is >10 but <12? In response: CMS is not covering continued ESA treatment for patients whose hemoglobin is known to be 10 or more. The Tax Relief and Health Care Act of 2006 (TRHCA) requires that all claims for ESAs after 1/1/08 include the most recent hemoglobin or hematocrit. In the proposed rulemaking for the fee schedule for next year, there is regulatory language to implement that statutory requirement. CMS will develop contractor instructions to implement. Another discussant asked if there were data to support the 10 gm hemoglobin level vs one of 12? The reported problems with ESA therapy occurred when the hemoglobin was greater than 12. Dr. Jacques replied that the labeled indication for ESAs in cancer patients was to prevent or reduce the need for transfusion. There is no evidence-based reason to believe that patients between 10 and 12 require transfusion. The Chairman asked about the practical difficulties in forecasting the effect of a change in ESA policy on blood requirement. Most transfusion services have a good feel for the need for blood for specific surgical procedures; for medical patients, the use is a little fuzzier (e.g., MDS). In response, CMS believes the blood supply is flexible and could respond to legitimate changes in need. Although one should not read too much in the absence of comment, but none of the public comments on the NCD came from major blood suppliers. Those comments that addressed the blood supply came largely from one segment of the physician population. Dr. Epstein asked if there were plans to monitor prospectively the blood needs of patients who might have been given ESAs but will not under this NCD? CMS has had on-going discussions with many in the stakeholder community that have proposed ways to do that. When needed, CMS performs a post coverage analysis. They are concerned that such an analysis be not just post hoc, but include judgments about the appropriateness of any change in transfusion practice. Ms Finley commented that Dr. Epstein's topic deserved more discussion and might lead to a recommendation from the Committee. Ms Thomas asked how ESA treatment might be reinstated, noting her (sickle cell patient) experience with higher hemoglobin levels making patients feel better? If the patient's hemoglobin drops below 10, ESA treatment could be restarted as before. This is certainly true if there were another course of chemotherapy. If the peak hemoglobin represented an overshoot, the dose might be modified downward.

The first speaker in the Open Public Comment session was Matthew Farber, MA, Manager of Provider Economics for the Association of Community Cancer

Centers (ACCC). After thanking the Committee for listening to public comments and CMS for working with them on the issue of the NCD on ESAs, he noted that the ACCC is a membership organization that includes about 650 hospitals and 550 oncology practices. Included are physicians, oncology nurses, social workers, pharmacists and administrators – everyone involved in the scope of cancer care. Member hospitals were polled: “What is the new NCD going to mean to you?” Anecdotal information was obtained from a convenience sample (those 150 that responded) that included facilities of varying sizes, in rural, suburban and urban locations, community-based and teaching. Although the question was aimed at those with some knowledge of transfusion, the responses came from many sites within the institutions, including pharmacies and administrative staff. At what level (e.g., 10% increase, 30%, etc) would you be concerned that it would cause reductions in other services, knowing that transfusions require extra hospital beds, dipping into the blood supply, more personnel for blood typing and an increase in administrative resources? The largest number of respondents said that a 30% increase in blood transfusions would potentially cause problems for hospital resources. Twenty-two percent of the respondents said any increase would potentially cause problems. It would present more problems for small institutions than for larger ones who could absorb most of the increase. Some (16.5%) said that just a 10% increase in transfusions would be a problem. Although we don’t know what the increase in transfusions might be as a result of this NCD, the consensus of their membership was that there would be some kind of an increase. The level of concern varied from “some” or “slightly” (44%) to “very” much (30%). The information has been shared with CMS and ACCC is looking forward to trying to track what actually happens.

In the discussion, he was asked what the typical transfusion trigger was among his membership? In response, it wasn’t asked, since it varies greatly from member to member and from patient to patient. The questioner noted that the information would be useful and could be obtained in response to various scenarios. The concern could be overblown. Dr Farber agreed. Dr Epstein asked if the respondent’s level of concern correlated with the size or type of hospital and may reveal how facilities face blood shortages, without regard to the ESA issue. In response, no correlation was recognized, other than that the larger hospitals (e.g., >600 beds) could more easily take any kind of transfusion increase without adverse effect on other services. Ms. Benzinger asked for clarification as to what kind of cuts might be forced if transfusions were increased. In response, the example used in the question was cutting elective surgeries. Ms. Benzinger expressed concern as to how blood apportioning was prioritized. The Chair commented that this might be addressed later when the Committee discusses focal shortages. Dr. Jacques commented that the proposed decision cited a hemoglobin below 9 (below 10 for patients with significant cardiovascular disease). Hence, the context hemoglobin level for the ACCC survey was the proposed 9 rather than the final 10 gm. Ms. Birkofer noted that the NCD had broad national coverage implications, including patient access to transfusions, blood supply, etc. and wondered what may have prompted CMS to move in this rather sweeping fashion. Dr. Farber responded that this was not part of the survey. It seemed to stem from the black box warning to the NCA and then the NCD. Ms Birkofer expressed concern that reimbursement or cost controls not effect patient safety. Dr.

Bianco asked if there were a transfusion trigger in the Chairman's hospital. Reply: It's variable. Hospitals may have guidelines, but adherence to the guidelines varies and they have few teeth. Notably, the Society of Thoracic Surgeons, the Society of Cardiovascular Surgeons and the Society of Cardiovascular Anesthesiologists have put together a nice joint guideline on the use of blood in cardiovascular surgery, recognizing that improvement was needed. The onus is on other specialty societies to promulgate similar guidelines. Responding to the question about cost, Dr. Jacques said the Medicare Coverage Group does not consider cost in making a reasonableness determination in an NCD. Coverage has been extended to a whole lot of expensive things, including implantable cardio-defibrillators, bariatric surgery and all sorts of stuff.

The Chair started the Open Committee Discussion by reading specific questions that the Assistant Secretary of the Department wanted to know.

1, A: will restricting recombinant erythropoietin until the hemoglobin is less than 10 increase transfusion demand in general?

B: will restricting recombinant erythropoietin until the hemoglobin is less than 10 increase transfusion demands specifically in the chemotherapy induced anemia cancer?  
And

2: will restricting human recombinant erythropoietin until the hemoglobin is less than 10 increase transfusion demand in ESRD, end-stage renal disease patients?

3, A: what is the current demand for transfusion in general and sub item 1, A? what is the current demand for transfusion in cancer patients and sub item 1, B? what's the current demand for transfusion in chemotherapy induced anemia of cancer patients?

4. Is there a blood shortage and if so, does it affect a particular patient population?

In opening these questions for discussion, the Chairman noted that the Committee recognized that there was lack of reliable data. There was considerable doubt that the target hemoglobin of 10 was low enough to affect the demand for blood. Only a few patient subsets (e.g., cardiac disease, congestive failure) were likely to need it to be higher (Epstein). It seems unlikely that cancer patients need a higher transfusion trigger. Fatigue was a common symptom in patients with cancer, but it seemed likely to be related to disease activity or therapy rather than to a specific hemoglobin level. Transfusion guidelines have long been an issue. NHLBI has addressed it in the past and Ms Finley asked if it were a current priority for that Institute (no answer was presented). Many hospitals have put forth their own guidelines, but the problem seems to be non-adherence and limited enforcement. CMS does not need the Committee to address the use of blood in patients with kidney disease and it should be left out of today's discussion. The Committee should not base any recommendations on their effect on the blood supply, but only on patient needs. The elasticity of the blood supply is more important than the absolute level; this will be considered in the afternoon session. There developed a consensus that the Committee should limit their recommendations pending further assessment of the status of current guidelines and collection of more data on current use of blood. CMS data bases are of little help, focusing mostly on administrative issues. In-patient transfusions are funded as part of DRGs and there are no specific data. Large cancer hospitals may have internal data that could be evaluated. Blood shortages, when they occur, tend to be seasonal or focal, involving red cells and platelets. Later in

this session, the Committee will try to develop recommendations addressing the first two questions posed from the Assistant Secretary.

After the lunch break, the Committee addressed the ethical considerations and risk-benefit issues for ensuring transfusion (and transplantation) safety during focal periods of shortage. This includes the elasticity of the blood supply and reducing barriers to receiving transfusion therapy.

The first speaker was Theresa Wiegmann, JD, Director of Public Policy and Special Counsel for the AABB, reporting on behalf of the AANN's Interorganizational Task Force on Domestic Disasters and Acts of Terrorism. She reminded the Committee that the Task Force was comprised of national blood banking organizations: AABB, Red Cross, America's Blood Centers and Blood Centers of America. There was government liaison with DHHS, FDA, CDC and others. In addition, other interested parties participated.

Her presentation addressed the question, is the blood supply adequate to deal with potential shortages including those arising from disasters. Is it generally sufficient and is there adequate elasticity? As background, the Task Force used the National Blood Collection and Utilization Survey from which the latest data is from 2004 (every 2-3 years from 1989 – 2004)(graphically illustrated in slide 2). The most important figures represent blood available for transfusion (after collection and passing screening) and the actual transfusions given. The margin between red cells available and that actually used has decreased from 6.3% to 4.5% by 2004. Demand appears to be leveling off. Overall blood banking efficiency has improved, with less outdated and a 42% decrease in the postponement of surgical procedures and less time when "needs were not met." True shortages were less frequent, but more severe when they did occur. The shortages, however, were no longer nation-wide, but local and seasonal in the summer or around holidays. They could be eased with increased collections or with importing blood from other blood centers with a more adequate supply. With financial support from DHHS, the next survey seeking 2007 data is just starting.

Problems when a disaster occurred were with allocation of blood supplies, communication, transportation and getting authorities to recognize the needs of the blood banking community in supporting disaster relief efforts. Most disasters do not result in an increased need for blood, rather there is more likely a level or even decrease in demand. There are three groups, ABC, ARC and BCA that monitor supplies within their systems daily and arrange for shipments as needed to balance need and availability. Data most pertinent to share with DHHS include total red cells, but especially group O positive and O negative, expressed as "days of supply," collected and reported at least weekly. Many blood centers regard this information as proprietary, so that sharing with Federal authorities should be regional or national rather than local. In the past, there had been discussion about creating a "national blood reserve" of 10,000 units, but this has been reconsidered because of cost (estimated at \$2.6 B startup and \$675 M annually to maintain) and the current abilities of the blood organizations to move blood around daily, as needed.

Barriers to successful management of blood in time of disaster include logistics and the states need to provide help with communication, transportation, fuel and other resources with blood given sufficient priority. Regulatory restrictions concerning blood

counts of donors and training of staff may need to be relaxed – this is expected to be covered by Dr. Alan Williams tomorrow. Controlling usage and creating guidelines for use are complicated issues that are being addressed by some medical organizations, notably the thoracic surgeons and associated specialties. Data to support the development of such guidelines are often quite limited. Funds are needed to support donor awareness campaigns on the need to donate blood and, probably, to accept more outdates of certain components as the supply becomes more sufficient.

The Chair led off the discussion by asking what proportion of centers were included in these annual surveys. Neither Ms. Weigmann nor an unnamed associate had this information, but the “vast majority” of centers were involved. The sampling was “weighted” to be overall representative of the 15 million red cell units collected. Dr. Epstein asked if the figures represented mainly blood centers or if there were hospitals involved. Blood for urgent use drew upon what was on hospital shelves more than in what was in blood centers. In response, the AABB was looking into how to address this issue and have data on all inventories. There is no such data source currently and there is little incentive for hospitals to report. Another question addresses the specifics of urgent shipment to hospitals or from one blood center to another. The Task Force had discussed the choice between increasing “total” inventory and having a physical “reserve.” Blood centers have a mind-set to help as much as possible, using the present systems, which were considered better than a “virtual” reserve. Establishing a “National Reserve” was not realistic at this time, largely for financial reasons. Dr Alan Williams (CBER, FDA) noted that the narrowing of the “cushion” between collections and demand was long considered a warning that serious shortages were in the offing. Is this no longer considered likely? In response, better utilization with less out-dating and blood group targeted double red cell collections had decreased the likelihood of national general shortages. Ms. Finley asked Ms. Weigmann to characterize the response to a large scale and possibly continuing disaster such as an acute radiation syndrome attack, especially with regard to a potential need for platelets over a longer period. In the past, disaster responses need to be short term and relatively constrained. In response, the blood centers have been counting on the continuing good will of the American people and hard work at regional blood centers. Ms. Finley further asked if the failure to continue recommending a National Blood Reserve differentiated between we don’t need it and we can’t do it. The blood communities thought we didn’t need it. Ms. Birkofer asked about the source of information that there hadn’t been national blood shortages. What about the previous recommendation that there be a 7 days’ supply? How is “shortage” defined? In response, the current blood center inventories were a 3-4 day supply and assumed a 2-3 day supply in hospitals. Blood centers each had their own definition of “shortage” (more information may be presented later by Ms. Sylvester, ABC). Ms. Lopez-Plaza asked if inability to supply orders or actual cancellation of surgery in a hospital was the critical factor. Ms Weigmann responded that she wasn’t sure how the survey questions had been worded, but at least one question asked about “unmet surgical demand.” Between the last two surveys (2001-2002 and 2004), there was a 40% decrease in unmet needs and in outdating. The Chairman noted that problems with surgery were probably underestimated, because not all such instances were reported to the blood center. He suggested that “days’ supply” was not very precise and probably differed from one to another center or metropolitan area. Why can’t absolute numbers be made available?

The Task Force thought that “days’ supply” was a more “usable” number.

Dr. Holmberg noted that the Committee had previously recommended supply monitoring and that it was in the FDA Blood Action Plan. The BASIS internet-based program for monitoring the blood supply had been active since October, involving more than 100 hospitals (135) and a small number of blood centers. There has been a pilot program in Boston getting daily information via BASIS. Dr. Bianco later asked that the uses of the BASIS data be shared with the Committee. Mr. Matyas asked if BASIS was voluntary (yes). Should CMS be asked to make providing BASIS data a condition for participating in Medicare? He suggested that hospitals already have these data and that it would be a minimal burden. Dr. Sandler, representing the American Hospital Association, said that hospitals were manpower stretched, especially in transfusion services, and additional burdens (e.g., transfusion statistics, biovigilance information) would be hard to cover. It was suggested that funds could be added to HRSA hospital grants, but those funds have been moved to the Assistant Secretary for Operation and Response, who will report to the Committee tomorrow. Dr. Duffell noted that blood banking, along with many industries, has moved to a “just in time” procurement and delivery scheme. Has the Task Force considered the availability of equipment and supplies for a surge in donations? Ms. Sylvester will likely cover this information and Dr. Bianco suggested that further discussion be deferred until after presentations from the Red Cross and America’s Blood Centers.

The Chairman then introduced Ruth Sylvester, Lt Col, USAF (Ret), Director of Regulatory Services, ABC to discuss “The US Blood Supply; Is it Adequate?” After brief description of ABC, Ms. Sylvester noted the questions Dr Holmberg posed to help guide her talk:

What is the elasticity of the blood supply and how is it monitored by ABC and BCA?

What is member preparedness for major disasters, natural or man-made?

Comment on the flu pandemic; experience with past disasters; considerations about other potential strategies to meet shortages, including a National Blood Reserve; ethical considerations

Challenges include the short shelf life of red cells (42 days) and platelets (5-7 days), precluding any ability to stockpile, low reimbursement rates insufficient to cover costs, increased costs for safety that can’t be passed on to customers (hospitals). Three lessons are repeatedly observed with each new disaster: problems with communications, transportation and fuel. When they are learned, planning will permit them to be avoided.

ABC monitors inventory in member centers daily, expressed as red -- < one day supply; yellow – 2-3 days’ supply; and green -- > 3 days’ supply. Blood Centers of America, an independent subset of ABC, has developed a “dashboard” monitoring system that collects numbers rather than symbolic color levels. Both suffer for being only supplies in blood centers without accounting for blood on hospital shelves. The DHHS BASIS program will help fill this gap. Review of numerical data collected as a pilot project by ABC between 2002 and 2006 shows fluctuation and distinct seasonal variation: a winter decrease because people don’t have time to donate during the holiday season; a January scarcity because of colds, flu and other viruses lead to donor deferrals;

a spring upsurge when blood is plentiful; and a summer decrease again because of vacations. “Just in time” logistics tends to exacerbate the shortages.

The 9/11 terrorist attacks and the hurricane Katrina natural disaster provided wake-up calls leading to the development of the Disaster Task Force and review of previous episodes. The latter was published (summarized on slide 14; Schmidt, P, N Engl J Med 346: 617-620, 2002). Regardless of the number killed or injured, these disasters each used less than 300 units of blood (red cells). The blood that was used was shelf stock in the affected hospitals or that moved relatively short distances from nearby stocks. There was a large public response and large quantities of blood were collected in a short period of time (e.g., 475,000 in the days following 9/11). Several years ago, Dr. Shenar (ph) of the Israel Blood Bank Agency reported similar information to the Committee. Individual patients may use a large amount of blood, but the overall use in a disaster situation is likely to be 100-300 units. Hence, the surge capacity for the blood supply is in the donor (the best place to store it) who responds to the disaster by flooding donation sites.

Longer running disasters such as a flu pandemic require somewhat different planning assumptions: red cell demand will likely decrease by 10-25% (during SARS in Toronto, demand fell by 25% in affected hospitals; less so in non-affected ones); platelet demand is unlikely to change, as is the case for frozen components. Prospective donors should be vaccinated annually. Red cell stock should carry through the first wave; utilization triage and postponement of elective surgery will be needed later, posing some ethical issues. Platelet collections will need to continue; antivirals and pandemic flu vaccinations may need to be considered for committed apheresis donors.

In case of terrorist attacks using dirty bombs, radiation or nuclear explosions might need (historically) 200-300 units of red cells, but could cause the deferral of donors throughout an entire metropolitan area. Shipping blood in from unaffected centers will require attention to transportation, fuel and communications. ABC has made contact with “Angel Flights” to transport blood if commercial flights are grounded.

The capacity, the will or desire of the blood bank industry and the US population comprise a suitable blood reserve. The baseline inventory can be increased, but the weak link is determining who will pay for it and how, because the capacity is there and could be tapped more.

In the discussion, Dr. Holmberg asked for clarification of the horizontal scale on slide 10 and why there were green centers at valley low points. Are some facilities that are more efficient at pulling themselves out of a shortfall? In response, there are a few centers that seem always to be red; rather than inefficiency, some move most of the inventory to hospitals by choice, intentionally keeping their own stock at or below a one day supply. Dr. Duffel queried the apparent paradox that in the past, not only were donors available when asked, but also bags and other supplies were sufficient to collect the blood. Yet in the pandemic flu situation, one of the “unmet needs” was adding blood collection bags and venipuncture supplies to the strategic stockpile and providing government funds to do this. Answer: in pandemic flu, not only will the blood industry be affected, but so will transportation and various suppliers as well. Hence, the need here for a stockpile beyond what might be used in a single point disaster.

Dr. Bracey then introduced Richard Benjamin, MD, PhD, Chief Medical

Officer of the American Red Cross, to present Blood Supply Challenges and Red Cross' Strategies and Response. He started by reminding new Committee members that the Red Cross Blood Service was started about 65 years ago by Dr. Charles Drew and now collects 9 M blood components serving 3,000 hospitals. Fifty thousand organizations support 135,000 blood drives, collecting 6 M red cells from 4 M donors each year. They maintain the largest inventory of antigen negative and rare units in the world. Following two superb presentations on disaster planning and response, he will focus on seasonality and challenges in producing an adequate and regular supply.

The Red Cross concurs with the AABB and ABC that single disasters find the blood on the shelf to be most useful, while expecting that within 18-24 hours, depending on availability of transportation, additional blood can be moved in as needed. Public response has been good and sometimes difficult to control. Pandemic flu and multiple site terrorist attacks are different, but covered well by Ms. Sylvester. In the pandemic flu situation, the Red Cross expects their normal nationwide inventory of 100,000 units will dwindle during the first wave and 12 weeks to 20,000 units. There is likely to be sufficient time between waves to rebuild inventory.

A major challenge to a constantly available blood supply is seasonality of collections; demand tends to remain relatively constant. Much of the seasonality in collections is due to increasing dependence on high schools and colleges, mirroring the school year. This is exacerbated in summer by many potential donors taking vacations. Other factors include an aging donor-base with increased deferrals, e.g., geographic to reduce the risk of transmitting variant Creutzfeld-Jakob disease (vCJD) and malaria. Adoption of the Uniform Donor History Questionnaire has resulted in a 1% increase in donor deferrals in the Red Cross system. Increased safety from these and other deferrals has been difficult to measure. Nevertheless, those who actually donate are a small percentage of those who are still eligible to donate (NB the presentation by Dr. Riley). The number of new donors added to the system each year has also decreased. An increasing focus on minorities has not helped overall, since minorities tend to donate less frequently than Caucasians. New stresses likely include the use of male-only plasma and platelets to prevent TRALI and new tests under development, e.g., Chagas' disease and babesiosis. The Red Cross response to these challenges has been the use of Ad Council Public Service Announcements and partnering with the National Athletic Association, Greek Fraternities and hospitals to increase blood collections.

"Blood Shortages" really only affect blood group O (Rh pos and neg) red cells and platelets. There is "never" a shortage of group AB and just about never a shortage of A+. Indeed, he opined that the use of group O red cells (50% of demand; 46% of the donor population) was constrained by the supply: the more made available, the more would be used (?abused). Responses to these imbalances include increasing collections of double red cell units from group O donors and the diversion of A and AB donors to plasma and platelets. Red Cross has begun to use incentives (usually financial) to decrease "abuse" of group O. Red Cross has also adopted "demand-driven planning" to balance the supply and demand for blood components.

Regarding hospital use of blood, there is great variation in the use of red cells from country to country (US is highest), from hospital to hospital and for the same procedure in different hospitals and sections of the country. It is unlikely that these have sound scientific bases.



Dr. Bracey began the discussion by wondering how to put teeth in utilization guidelines: could CMS put leverage on hospitals to increase proper utilization? Dr. Benjamin replied there was a good opportunity to influence appropriate practice, but wondered if JCHO would be a better choice, working through accreditation. In his section of the country (SE Texas), the predominant minorities of Latin American and Mexican. Dr. Benjamin replied that many minorities have increased frequencies of group O, so ARC is seeking them as donors. Nevertheless, the imbalance in the use of group O is widespread throughout the country, even where minorities are not prominent. Ms. Finley asked Ms. Sylvester about storing bags with the Strategic National Stockpile (SNS) (medical equipment and supplies)? or at one place? Or at several places with easy access? In reply, the SNS has multiple sites located within 8 hours drive of anywhere in the US. Blood banks usually maintain a 2 week supply and could be supplemented from the SNS quickly. She chose that as an example because it exists and focuses on medical needs.

Dr. Epstein was struck by the absence of donor organizations in the US, whereas they are active in many other countries. Dr. Benjamin agreed that we in the US have not done as good a job here as we might. Ms. Sylvester noted that committed donors are much like clubs, e.g., gallon donors, 10 gallon donors, apheresis donors. Dr. Bianco said that these donor clubs vary around the world: some, like Norway, are very active in recruiting donations; others are more like unions than clubs (in France, donations decreased sharply when the blood service began to require that donors sign their history forms and the informed consent document).

Dr. Bracey commented that it would be necessary to get the word out if there were blood needs following one or more disasters. The Assistant Secretary for Health (ASH) is expected to perform this role, but how should he function when there are spot shortages? Ms. Sylvester replied that the Task Force was involved from the start and would make the decision to approach the ASH for help. Dr. Bracey reported that in Seattle, the Puget Sound Blood Center uses text messaging and other means to communicate with donors. Ms. Sylvester commented that the Task Force has subgroups dealing with this communication issue. For example, to communicate with teenagers, one uses text messages on a cell phone. For older adults, a laptop and E-mail is more suitable. Blood bank movement to use these communication devices has been slow, largely due to limited resources, including funds. Dr Benjamin said it took 6 requests to bring a donor through the door and there were multiple ways to make those requests.

Dr. Roseff-Dickerson suggested that more effort should be devoted to defining "shortage." It varies from one hospital to another. In her hospital, failure to receive their full order can be ignored unless it occurs repeatedly over several days. They then begin to triage products, especially platelets: screening orders, reducing them as needed, to postponing or cancelling elective surgery. Cancelling surgery can be a real problem for a hospital in today's competitive environment.

Ms. Thomas-Wade asked if donors were screened for Chagas' disease and if those positive were deferred. Dr. Benjamin reported that there is now a licensed test available and that effective January 29, Red Cross began a universal screening program, deferring all positive donors. There were more false positives than true ones, but they decided to defer anyway.

After a break, Dr. Bracey opened the meeting for Public Comment, introducing

Mr. Dave Cavanaugh, representing the Committee of 10,000 (COT). Patients do not want to see standards lowered, even in time of shortages. COT has alerted FDA to the operation of plasma apheresis centers near the Mexican border in Texas. They pay Mexican citizens with tourist visas \$25 for the first donation of a week and \$56 for the second. COT believes this is exploitation of a population living in serious poverty. The collection of source plasma from developing rural countries presents an ongoing safety risk for the users of plasma derivatives because of Dengue, dengue hemorrhagic fever, becoming more prevalent. These collections seem designed to circumvent the collection of source plasma in the developing world. Ms. Birkofer (disclosed that she represented the plasma collectors and fractionators on the Committee) commented that dengue virus was a flavivirus with a lipid envelope, similar to the West Nile virus. Plasma derivatives are subject to inactivation procedures to inactivate those and similar viruses. Mr Cavanaugh interrupted with a question if dengue were viremic during incubation. Dr. Bracey noted that the Committee's influence here was indirect and that FDA was addressing these issues. Ms Birkofer summarized a statement from the plasma protein therapeutics industry which works to ensure that comprehensive safety measures are in place to collect plasma used to produce lifesaving therapies for consumers and rare diseases. All collection centers meet stringent requirements by the FDA and voluntarily adhere to their own policies concerning safety.

The Chair closed the open public discussion and moved the Committee to a discussion of the questions that were presented earlier this morning:

1, A: will restricting recombinant erythropoietin until the hemoglobin is less than 10 increase transfusion demand in general?

B: will restricting recombinant erythropoietin until the hemoglobin is less than 10 increase transfusion demands specifically in the chemotherapy induced anemia cancer?  
And

2: will restricting human recombinant erythropoietin until the hemoglobin is less than 10 increase transfusion demand in ESRD, end-stage renal disease patients?

3, A: what is the current demand for transfusion in general and sub item 1, A? what is the current demand for transfusion in cancer patients and sub item 1, B? what's the current demand for transfusion in chemotherapy induced anemia of cancer patients?

4. Is there a blood shortage and if so, does it affect a particular patient population?

After considerable discussion and wordsmithing, the Committee passed the following recommendation unanimously:

“The Committee believes that there is inadequate information to accurately assess the impact of CMS's National Coverage Determination (NCD) for Erythropoiesis Stimulating Agents (ESA) on the management of anemia in the general patient population and in cancer patients.

“Whereas, the revised position on ESA coverage may increase blood demand, ACBSA recommends that

1. HHS perform an analysis of the impact of ESA NCD on blood demand in affected patient populations. The information needed should be derived from prospective data collection.

“Whereas current demand for transfusion in various patient groups is not well characterized and varies with local practices, including adherence or non adherence with available transfusion guidelines, the ACBSA recommends that

2. HHS support studies to identify and characterize transfusion practices in relation to clinical outcomes in patient groups affected by the NCD, e.g., survival, quality of life (using validated instruments), adverse events, including cardiovascular events.”

The Chair then asked the Committee to begin a general discussion about how elasticity of the blood supply is to meet unexpected needs, following the presentations by the AABB, ABC and ARC. One conclusion is that there is no national shortage, and focal regional shortages can be covered in time by the movement of blood between centers. Dr. Roseff questioned these assumptions, pointing out that very little had been heard from the transfusion service perspective. Furthermore, Dr. Benjamin said that 53% of Red Cross customers reported shortages. Dr. Kuehnert reminded the group of the importance of defining what a shortage is. This was an issue during a recent pandemic flu exercise at CDC when it was suggested that all elective surgery be postponed because of lack of blood. How was blood shortage defined and what data supported the conclusion? It was said that 50% of the blood used was for elective surgery, but it was unclear what the source of this figure was and how reliable it was.

Dr. Holmberg noted that the monitoring system that was in place when he arrived focused on the effect of policy decisions, such as changes in donor deferrals. This was hospital-based and involved 26 hospitals and 2 blood centers. It appeared that shortages at the hospitals were promptly covered by shipments from a blood center. It became apparent that both supply and demand were important and BASIS was developed. The present system involves reports from 100 hospitals and permitted the detection of local shortages and proactive interaction with ARC, ABC and AABB to see if a national appeal for donors was needed. Both quantitative data and qualitative information (did you receive your complete blood order?) were obtained. There were transplant centers forced to close because of lack of blood. To follow through with the suggestion that blood bags be added to the National Strategic Reserve, data are needed about quantities, costs, etc., and information from BASIS helps with these calculations.

Dr. Bianco commented that data collection should focus on actionable items: what use is to be made of the information? Some of the information suggested seemed more of a satisfaction survey.

Dr. Bracey closed by asking Committee Members to consider the remainder of the questions for this meeting: Is the public aware of blood inventory status and what is the appropriate role of media and government in informing the public of this information? How does the system prevent disparities in blood availability? What are the ethical issues related to donor recruitment and blood distribution. Dr. Holmberg

promised to provide everyone with a copy. The meeting adjourned at approximately 5:00 PM.

The Advisory Committee reconvened at 9:00 AM, August 23, 2007. Dr. Homberg called the roll; present were Dr Bracey, Ms Bensinger, Dr Duffell, Ms Finley, Dr Kouides, Mr Matyas, Dr. Ramsey, Dr. Roseff, Ms Thomas-Wade, Dr. Kuehnert, Dr. Epstein, Dr. Klein, Cdr. Libby, Dr. Saint-Martin, Ms. Ashton. He pointed out that two documents had been distributed: testimony by Mr. Cavanaugh and questions posed for today and reminded the Committee of the Conflict of Interests statement read yesterday.

Dr. Bracey suggested that a subcommittee would perform a gap analysis to determine what might be missing from presentations but be important toward formulating recommendations for the Secretary from the Committee. Dr Kuehnert handed out for the Committee's information copies of a UNOS proposal for public comment about biovigilance and organ/tissue transplant safety. It tries to balance safety issues against the urgent need for transplant organs, and includes an advisory group to collect reports and analyze data on organ transplant adverse events (the TTSN). Dr Holmberg asked if this topic should be presented at the next meeting of the Advisory Committee.

The Chairman then introduced the first speaker of the day, John Armitage, MD, President and CEO, Oklahoma Blood Institute (himself a >100 times blood donor), speaking on behalf of the Association of Donor Recruitment Professionals (ADRP), to address the question: "Who represents the volunteer blood donor?" The ADRP was founded in NY State in 1977, but now has offices in Austin, TX. As the worldwide industry leader in the field of donor recruitment, its mission is to provide education, development and resources for the donor recruitment professional. It is committed to shaping international policies and standards and developing marketing strategies and specialized resources for donor recruitment. ADRP membership is comprised of more than 600 individuals at all levels from blood centers or agencies, the marrow program and associations, who are Public Relations or Communications specialists, field representatives, physicians, administrators, vendors, etc. It has an international scope, including, for example, members from Canada, Finland, Germany, Kenya, New Zealand, South Africa, the United Kingdom, the United States and Vietnam. (information: [www.adrp.org](http://www.adrp.org)).

Appeals are needed from time to time for most blood centers when, for whatever reason, the inventory shrinks to a critical level. Nevertheless, if not done carefully, there may be negative consequences. Personal experience in 6 different blood centers shows great heterogeneity, from rare events to cyclical occurrences to use as a marketing tool, fostering media access, motivational activities for staff and promotions. Care is needed in planning for appeals to preserve credibility and maintain truthfulness (the ethics of using an appeal as a primary marketing tool may be questionable). Appeals may be general or targeted to donors with certain blood groups.

It's important to recognize that an appeal is really a failure indication, that your fundamental recruiting and collecting processes have not been sufficient. The appeal is patch for weaknesses which are not corrected; the energy put into the appeal may detract from longer term planning and efforts to improve supply stability. It is a sign of weakness that appeals are allowed every summer and every holiday season. Little has been done on the effect of appeals. It is a well known anecdote, unsupported by data, that

you shift donors during appeals, e.g., “normal” September donors make a donation in August instead (not in addition). You may not create new first-time donors, and those that are created may not often be retained.

There may be negative effects on patients, e.g., someone planning surgery learns there is a blood shortage that could curtail surgery. The public may be confused by lack of coordination between blood supply agencies, especially in a competitive environment. Potential donors may not understand that blood is not being supplied by one collecting agency.

There is no “owner” of an appeal, someone or some group that can be approached to mastermind the process. There may be some “champion,” Surgeon General, HHS Secretary, celebrity spokespersons, etc. There could be cultivated communication channels, e.g, government agencies, patient advocacy groups, corporations. There may be community preparedness messaging. The public may not understand certain nuances, e.g, “urgent” vs “emergent;” “critical” vs “serious.” The outcome of an appeal is rarely tracked, as to timing, duration, effectiveness. Appeals should be carefully planned and coordinated, including all staff (especially front-line staff), hospitals and surgical centers, etc. It strains credibility for a center to put out an appeal while hospital inventories are apparently unaffected. Hospitals may have to participate with patient triage, double or triple cross-matching, etc. In any event, they should let the blood center know what effect, if any the apparent shortage has on hospital activities. Most of what I have said pertains to red cells, but platelets may also be a problem; their short shelf life likely means that the effects of shortage and recovery are much more volatile. Very rare but possible outcomes could be diversion of patients from a hospital that had a limited blood supply to one with more blood and delaying or cancelling an organ transplant because of insufficient blood.

Recruiting donors is essentially a marketing activity and requires a different type of research than epidemiology. It would be desirable to support with seed money some centers of excellence that will test modern techniques such as text messaging and blogging. For example, the Puget Sound Blood Center is making excellent use of technology, possibly because of their location near Microsoft. These centers of excellence should be required to make their products, deliverables, available to the whole community.

Donor recognition is important: e.g., giving an award to high school students who donated 4 times before graduating went over well in Oklahoma.

Dr Armitage called for rationalizing deferrals, in particular reviewing each reason for deferring a donor to be sure that the condition the deferral was meant to avoid is still pertinent.

Finally, we must pay attention to usage of blood, leveling out the amounts used for the same procedures throughout the country (? and world). It would be important to be able to say that every last unit, especially of O negative, is used to its best advantage before or when appealing to the public in emergency fashion. We know, however, that this is not the case.

Dr. Bracey began the discussion by asking the speaker’s perspective on the public’s awareness of blood and the needs for it. In response, it’s variable around the country. For example, he heard from Dr. Roseff that in Richmond they use a scroll across the bottom of the TV screen. One problem is that it is patch work and different in

every community. Another problem is that an appeal is tantamount to an admission of failure, and the blood industry is reluctant to do this.

Dr. Bracey then introduced the next speaker, Matthew Payne, Deputy Director, Assistant Secretary for Preparedness and Response (ASPR, DHHS), to provide an overview of ASPR. I plan to discuss the various components of ASPR, talk about the Pandemic and All Hazards Preparedness Act, which has had a dramatic effect on us and finally focus on the Planning and Emergency Operations Group and the Biomedical Advanced Research and Development Office.

The Mission of ASPR is to *“Lead the nation in preventing, preparing for, and responding to the adverse health effects of public health emergencies and disasters,”* with the Vision of *“A Nation prepared to prevent, respond to, and reduce the adverse health effects of public health emergencies and disasters.”*

The ASPR organization chart (slide 4) represents 400-450 people divided among the Office of Policy, Biomedical Advanced Research and Development (working on medical counter measures), Office of Science, Medicine, and Public Health (International Preparedness) and Office of Preparedness and Emergency Operations (response group, including hospital preparedness transferred from HRSA), in addition to the Immediate Office of the ASPR.

In various ways, including the Hospital Preparedness Grant program, they play a major role in enhancing state and local preparedness. They recently sent notices to all state emergency management officials encouraging them to interact with community blood centers on preparedness activities. From a variety of responses and exercises, we’ve learned about gaps in blood center preparedness, such as getting generator power in timely fashion in case of a general power failure, transportation of blood and blood products in time of emergency and maintaining communications.

Playbooks are being developed for a variety of disaster response scenarios, such as pandemic influenza, an anthrax attack, a hurricane, an earthquake and a radiological event. An all-hazards approach is used. Collaboration is encouraged, not only within the Department but also between various governmental agencies (e.g., Homeland Security, Defense, Veterans Affairs).

The Pandemic and All Hazards Preparedness Act (PAHPA) codified HHS as the lead Federal Public Health and Medical Agency to respond to emergencies. It directed DHHS to engage DHS, the VA and the Department of Transportation in developing inter-agency agreements to assume control of Federal Public Health and Medical personnel and assets during incidents. The Department of Defense is not included, since they always retain control of their own assets. The bill created a new Senate confirmed position, the Assistant Secretary for Preparedness and Response, currently filled by Rear Admiral Craig Vanderwaghen (long service with the Department, serving in the Indian Health Service, as senior health official during the Katrina response, working in Iraq and deploying to SE Asia following the tsunami, etc). He has deployment authority for Federal personnel.

Another important part of PAHPA is the National Disaster Medical System. NDMS was originally established within HHS as a partnership among four agencies, DOD, VA, FEMA, DHS and HHS. When DHS was created, NDMS became part of that agency; PAHPA transfers it back to HHS. NDMS is comprised of thousands of physicians, nurses and other medical providers, organized into teams that can deploy to a

disaster site, be self-sustaining for at least 72 hours and provide field medical care. It includes the Patient Evacuation System, led by DOD and the VA. ASPR coordinates, but does not lead the Medical Reserve Corps (MRC) program, the emergency system for advanced registration of volunteer health professionals, the strategic national stockpile and the cities' readiness initiative. The MRC is managed by the Surgeon General. The uniformed officers of the Public Health Service can be mobilized and deployed to disaster situations, as was the case with Katrina. Others are by CDC and HRSA. The bill requires every four years, starting in 2009, the delivery of a National Security Strategy, similar to the Quadrennial Defense Review, on the status of public health and medical preparedness activities.

Primary response assets within the Department include the Secretary's Operation Center and sub-centers at the FDA, CDC and other elements. HHS is the lead agency for Emergency Support Function 8 that deals with public health and medical responses, under the overall coordination of DHS. Encouraged is cooperation between states and communities rather than just a Federal initiative.

The Biomedical Advanced Research and Development Authority (BARDA) was established by Title IV of PAHPA to facilitate collaboration among US Government, industry and academia, to support advanced research and development of medical countermeasures and to promote innovation to reduce time and cost of medical countermeasures. It established a Biodefense Medical Countermeasure Development Fund to bridge the development of products across the gap between initial basic research (NIH supported) and the procurement through Bioshield legislation. It makes reforms to the Bioshield procurement program and establishes the National Biodefense Science Board. BARDA supports ASPR in leading the Public Health Emergency Countermeasures Enterprise (ASPR, CDC, FDA and NIH) and drives medical countermeasure analysis and prioritization for HHS strategy and implementation plans for chemical, biological, radiological and nuclear (CBRN) threats. This includes acquisition under Project Bioshield and with direct appropriations for pandemic influenza. Some draft plans have been released (more information at: [www.HHS.gov/disasters/](http://www.HHS.gov/disasters/)). The director for BARDA is being sought, but not yet hired.

Dr. Epstein began the discussion by asking where blood systems and securing their needs fit into the larger picture. He noted that providers of blood had felt marginalized. Mr. Payne noted that a letter to all local disaster coordinators placed the provision of blood and blood products as part of the critical infrastructure in response activities. DHHS and DHS were working together to ensure that this was made part of local planning. Dr. Kuehnert commented that cooperation locally was most important. Does the blood center know the Health Department and vice versa? And most importantly, do they talk to one another? What is being done to make that connection happen? ASPR has emergency coordinators and 3-4 staff members in each of the 10 Federal regions, representing growth from those transferred along with NDMS to HHS from Homeland Security. The letter sent to these coordinators emphasized blood as part of the local activities within their purview. The Chairman asked about the role of the Committee, for example, would the Committee's recommendations to the Secretary, if approved, be passed on to ASPR? Where would implementation funds come from? In response: the Enterprise Governance Board is the managing body that includes FDA, NIH, CDC and the Assistant Secretary in making those decisions which include the

Strategic National Stockpile. They would discuss such recommendations and guide the Secretary or make decisions when appropriate. Mr. Payne wasn't sure of the specifics, but thought that resources could be made available as needed. Dr. Ramsey asked how the interorganizational task force fits into this structure. In response: the role of the task force is unchanged. Once ESF8 is activated, it is our responsibility to reach out and communicate and interact with the task force. Dr. Epstein pointed out that historically, the ACBSA (this Committee) made recommendations to the Secretary, but these were largely addressed by the Assistant Secretary for Health. To the extent this Committee has been dealing with disaster preparedness and response in its recommendations, it raises the question whether these recommendations are getting or should get equal audience with ASPR. Dr. Holmberg reported that they were: on several occasions, he briefed both Dr. Agwonobi, the Assistant Secretary for Health, and Dr. Vanderwagen (ASPR) on various issues and recommendations and based on those meetings, one was referred to the Enterprise Governance Board. His office was under the Office of Public Health and Science and reports directly to the Assistant Secretary for Health. Hence, this Committee's recommendations would go first to the ASH and then over to ASPR. Ms. Finley asked if the FDA was represented on the BARDA Blood Working Group. Dr. Holmberg replied that yes it is.

After a short recess, the discussion continued with a question about the maximum amount of blood that could be collected in one day. It is at least partly dependent on the availability of equipment, supplies, testing, etc. Vendors said yesterday that they could supply those things, but it is not part of our business model ("just in time" supplies); with funding, stocks could be increased. Dr. Bianco added that after September 11, capacity was increased at least three-fold (at least 500,000 units more than was required to maintain the system, or 15,000 – 20,000 units daily). There were local shortages of reagents or bags that were compensated for by other centers. For a radiation incident, the blood and marrow will suffer first, followed by a GI syndrome. A lot of supportive care will be needed. Dr. Epstein asked for clarification if blood and tissue needs were considered separately or in conjunction with a rad-nuke accident/disaster. Dr. Holmberg replied that there was cross reaction between groups and harmonization of their needs. Dr. Epstein further commented in the context of a blood reserve (now not supported by the blood organizations), there may be a greater need for blood to address radiological disasters and the question of going to the Enterprise Board for support for a reserve. Dr. Holmberg agreed that there was confusion about the position of the blood organizations concerning a blood reserve. The Department is asking for a recommendation from this Committee as to how to proceed.

Major considerations about the need for a blood reserve were cost and historical information that blood demand in a disaster situation is not very high. Ms. Wiegmann commented that the Task Force reconsidered their position on the need for a blood reserve based on past experience. They have not seen detailed modeling of a rad-nuke scenario and should defer their recommendation until they have reviewed those figures. She asked Dr. Holmberg to clarify the parameters of a reserve, virtual vs real and which products. Dr. Holmberg responded with a model of 2,000 units strategically located around the country, utilizing blood centers that could compete for a grant or contract; for each, the added recruitment would be minimal. One scenario might be multiple vendor-managed inventories of 500 units of Group O red cells that would be rotated in and out to



preserved dating (the Government cannot purchase blood). Release of that blood would be at the discretion of the Assistant Secretary for Preparation and Readiness. Hence, it is an actual reserve with a 2 week cycle, not a virtual one. This would move from the current three day supply upwards for a five or seven day supply. Dr. Bianco suggested that the effect of such a reserve would be small. He also expressed concerns that these 500 units must be in addition to what they already maintain, and not be part of the regular inventory kept by the center. ABC now has a hub and spoke system, with the hubs supplying urgently needed blood and replenishment coming from the spokes. Maybe the funds to support the reserve could be employed somewhere that would be more useful.

Ms. Finley said that the comments of Ms. Weigmann and Dr. Bianco were well taken, but emphatically pointed out that they were based on past experience and may not have considered other scenarios. For example, multiple acute radiation incidents at multiple locations would result in many fleeing in disorganized fashion, overwhelming local facilities of all sorts and it may not be possible to ship from another section of the country. The responsibility for modeling these scenarios belongs with ASPR. The Committee doesn't have adequate information to take a position on a blood reserve. Contrary to the situation in other countries where blood collection is part of the government, we need to have a firm number from ABC, ARC et al about how much elasticity they have and work that into the various models. There is a great deal more to be done, including having the blood organizations consider scenarios beyond what they have done to date.

Dr. Kouides posed two questions: is there a consensus as to how much blood is needed (e.g., 500 units or ?); and what time-frames have been considered for radiation problems (with total body irradiation prior to a bone marrow transplant, you don't become transfusion depended for 5-10 days). Dr Holmberg replied that the 500 figure was hypothetical and might be refined depending on the availability of blood centers. The DHHS current model is 2,000 compared with the original 10,000 units that would cost many millions of dollars. It was 500 per location for four different locations, strategically located. There are 15 different scenarios that DHS has asked be considered. There are three different modeling teams working on this presently.

For the second question, there will be blast injuries, combined blast and radiation injuries and finally radiation injuries from fall-out. Pressure injuries from the blast include tympanic membrane rupture and injuries from building destruction from that blast pressure change. A house can be destroyed by as little as five psi. Dr. Bracey reminded the Committee that there would be burns involved, and these could use large amounts of blood. Dr. Holmberg confirmed that there was a concern about the limited availability of burn beds.

CDR Libby noted that the Uniformed Services Blood Program was set up in 1952 to guarantee an available supply to our troops operating around the world. We do plan for disasters, potential disasters or conflicts. It may be more important to define what an available supply is rather than what constitutes a shortage. They have contracts with ARC and ABC, as do many hospitals. Contracts may be supplied with higher priority than those without contracts. Even in the military, arranging for blood products to be shared is not easy; those that have blood are reluctant to deplete supplies in expectation of prompt resupply. Dr. Bianco wanted to clarify that the ABC lack of a blood reserve

did not mean that they would oppose its establishment. Their issues are transportation, fuel and communications and he wants them addressed first.

Dr. Kuehnert thought that we're poorly educated on rad-nuke events and consequences. Estimates of potential needs vary from hundreds of units to 40,000 units of red cells alone. What plans are there to educate the Committee and the communities about the effects of a nuclear disaster? Dr. Holmberg promised to provide information to the Committee as it became available to the public. Ms. Weigmann agreed with that need for further education. She also thanked Dr. Holmberg for encouraging blood centers to interact with state and local governments. Dr. Roseff asked that consideration be given to what might happen if donors did not mobilize after a disaster or if the disaster situation continued for longer than a few days. Rad-nuke disasters will use more than red cells and we must plan for that (platelets, etc). Dr. Ramsey asked what the health system could absorb: how many ORs, ERs etc. Dr. Holmberg commented that some additional footnote like issues may surface, e.g., following a rad-nuke event the public may be told to stay inside. If it becomes necessary to irradiate all blood, red cell dating will decrease to 28 days. Burn patients may need large amounts of albumin and immune globulin.

Ms Finley summarized what needs to be done: the issue is the interplay between current availability and what might be needed, recognizing that the Committee doesn't have many of the scenarios and may never get them. Threat assessments might be restricted in who has access to them. We don't have a ton of elasticity in the existing blood supply and although we know that donors are willing to step up, there are concerns about some of the potential scenarios. We might want to consider the issue of a reserve in more detail with more specific information at the next meeting of the Committee. Maybe some key people should get security clearance to view and provide some input into various scenarios.

In response to Dr. Kuehnert's suggestion that many players need more information and training, Dr. Holmberg noted that a web site accessible through the National Library of Medicine (REMM) is designed to help clinicians walk through a rad-nuke event and what therapies might be needed. It is evidence-based and reference documented. Dr. Klein was the primary reviewer for the blood part.

Dr. Bracey opened general discussion of the above presentations by posing two questions: Is there a current system in the US for managing blood inventories? Does it include both blood centers and hospitals? There was a consensus that data about hospitals was very limited and to make appropriate recommendations, the Committee needed more and better data. Furthermore, the Enterprise Committee would need this information to consider if a national blood reserve was needed and if so, how large should it be.

Some blood centers get hospital inventory information, but it is sparse and of questionable reliability. The incentive is for each hospital to protect its own blood inventory and not share information. The DoD has a Defense Blood Standard System that all facilities are required to use, as part of the Joint Medical Asset Repository Program. DoD can query this system one or more times each day to determine each site inventory, including status and dating. The DHHS BASIS system gets daily reports about inventory from many hospitals. "Inventory" is not rigidly defined; each reporting facility is asked to provide data consistent from day to day for that facility. BASIS is not a management system and does not threaten to shift blood around the country arbitrarily,

as is feared by some centers and hospitals. Because of competition between blood centers, individual data are considered proprietary and not in the public domain. The Critical Infrastructure Information Act (Sept 2006) protects shared data, but in general it is anonymized and aggregated before becoming public. The responses of treating physicians, e.g., surgeons and anesthesiologists, to inventory problems are important and should be considered. Donor motivation is incompletely understood. Would publicizing the status of blood inventories be stimulating or counterproductive. Dr. Holmberg offered to make available a HRSA study on organ donation, which is lengthy but has some parallels to blood donation.

Dr. Bracey summarized the discussion that the Committee wanted more transparency and more data about the status of the blood supply. It is likely necessary that some work be done between meetings to facilitate discussion and the development of recommendations. There are provisions under the Federal Advisory Committee Act (FACA) for subcommittees, provided they report back completely to the full Committee, and note decisions that are made by the subcommittee. Recommendations must be accepted by the full Committee. The charge to any subcommittee should be defined: the principal question is the elasticity of the blood supply, with subsidiary problems with equity and fairness in distribution. Many people have been asking that question for many years with no clear result. After 9/11, the General Accountability Office was asked to assess if there was an adequate blood supply; it was looking at that question in the wake of vCJD risk based deferrals. The HHS Inspector General could also do such a study; the IG has mechanisms to compel data that aren't available to us, and Advisory Committee. What can be expected of a subcommittee in a few months.

After the lunch break, the Chair introduced the next speaker, Kathy Brinsfield, MD, MPH (Medical Director of Emergency Preparedness, Boston EMS System and for Boston MMRS and the DelValle Emergency Training Institute) to discuss Reserved Donor Strategies. She's been working for about 16 months on a disaster planning committee with representatives of the American Red Cross, CDC/COTPER, FDA/CBER, DHHS, Boston EMS, US Military, Hospital Blood Bankers, Trauma Surgeons, Emergency Medicine Physicians and ICU Physicians. She also had first hand experience with disasters as Deputy Director of the First Team at Ground Zero. From these perspectives, she will discuss disaster preparedness, where we stand with a one-day blood supply and what the transfusion needs will be for casualties based upon the numbers produced elsewhere and the possibilities with potential weapons.

In her home area, the blood supply is often a bit low in that they shuffle surgeries and aren't as well stocked as they'd like. Rough calculations suggest at the beginning of the day prior to beginning elective surgical procedures the Boston metropolitan area has about 5,000 units of red cells available, were there to be a disaster. They are working on having a statewide count of red cells and, maybe, a four region blood inventory. The region has numerous planned events with concentrations of people that are difficult to secure. Moving about in the crowd can be slow going. They have used a model developed at Johns Hopkins (EMCAPS) to simulate the explosion of an improvised explosive device (IED) in an open area with 25 feet per person (open area = no confounding by building effects). This would result in 15% moderate to severe injuries (2,829) in the model, comparable to direct experience in Israel – about 20% severe traumatic injuries. Using 3.85 units of packed cells per casualty, one can estimate 10,891

units as the need (Israeli experience was for 6.7 units per casualty, or 18,955 units), or considerably less than was the on hand estimate.

In the national planning scenarios, most are working with 10,000 – 25,000 casualties. The first 2 – 12 hours will be a critical period. Her area estimates that there will be enough blood on hand for initial transfusion in the first 2 hours. They are very concerned that there won't be enough blood for the 12 hour window, unless it is moved in from other parts of the country, a formidable task in the chaos and lockdown that will be present. It will be 72 hours before blood collected and fully processed will be available locally. The disaster is "instantaneous," unplanned for which makes it different from the military experience. Nevertheless, the military has considerable experience with recruiting volunteer donors in the fighting area, type them in batches, do limited rapid infectious disease testing and transfuses the whole blood immediately. In the Boston disaster planning, they are considering doing something fairly similar. After considering at the hospital level the blood inventory, the likelihood of resupply, ability to facilitate resupply and melding this into regional terms, at some as yet undetermined decision level (Federal?), a whole blood waiver will be sought to pursue the military approach. They would activate a pre-screened (and rescreened every 3-6 months) donor pool for this rapid procurement procedure, using it if resupply from outside the area was slow or non-existent. Both patient and blood would be retested completely when it becomes possible. This approach balances the risk of exsanguinations against the 0.01% or so risk of transmitting an infectious disease.

Dr. Duffell opened the discussion by asking about the need for plasma or platelets, noting that she focused only on whole blood. In response, the severity of the disaster scenario discussed was such that they thought there would not be the capability to consider platelet or plasma needs. It would be interesting to expand the modeling, however. Dr Bracey asked her to comment on the differences between the experience that 200-300 units are all that most disasters require and the model that suggests a considerably greater need. In reply: it is important not to "fight the last war." Terrorists are hitting 5-6 rail stations at once and they are learning how to be even more troublesome. CDR Libby (Head of DoD Blood Program) said that in Iraq there wasn't time to do any infectious disease testing and get the result prior to transfusion. They also must plan for what's coming next, possibly over reacting from time to time. How does the speaker plan to do AB and Rh typing and compatibility testing in her disaster scenario? In response, they plan to run it through their blood bank to run it through their normal process. It is recognized that they might not have that kind of surge capacity at present. Dr. Holmberg compared the disaster scenario to the organ transplant situation where the treating physician has considerable leeway in determining how much testing the donor needs and is also dealing with a life-saving situation. Dr. Duffell asked about decision-making to waive certain safety oriented procedures. Dr. Holmberg replied that there has been considerable thought and discussion but no procedure has been developed yet. Dr Williams will be discussing potential regulatory accommodations under disaster circumstances.

Alan Williams, PhD, Associate Director for Regulatory Affairs, Office of Blood Research and Review, OBRR, CBER, FDA, proceeded to discuss Regulatory Perspectives on Disaster Response. He began by summarizing salient features of the US blood supply. Unlike other developed nations, the US doesn't have a national blood

system. Ninety percent of our blood is collected by two organizations, while the remaining 10% is collected in hospital-based centers and by the Department of Defense. Most of the blood is stored in hospital transfusion services; the sum of those units and those in regional blood centers is the national blood supply. The two major collecting organizations, Red Cross and America's Blood Centers, assert that they can assess shortages and provide supply coverage in an emergency. It has been estimated that about half of the US red cell supply is life-sustaining; the remainder of the red cell transfusions are elective: some uses are not well characterized at the hospital level. The triage of available blood could be a powerful blood shortage intervention, but efforts to organize emergency triage beyond the local have not been very successful.

Another factor is the growing importance of apheresis, both for red cells (increasingly double units from one donor, nearing 30% in some centers) and for platelets. This permits more control over production: e.g., double red cells from group O donors, a combination of red cells and platelets when needed, and group plasma and/or platelets from AB donors whose red cells are not needed. These trends affect the inventory management comments noted yesterday. Platelet supply is a special case: it is especially vulnerable to collection shortages because of their short shelf life (5 or 7 days, depending on the protocols used). Platelet apheresis now supplies 85% and it continues to increase. Reverting to whole blood-derived platelets wouldn't be easy, and increasing the hours at apheresis rooms may be the only way to boost production in case of need.

Supplying safe and available blood requires a complex network of donor recruitment, product collection and needed supplies, processing labs including test kits and reagents, storage facilities, transportation and computer systems. There are such interdependencies that a break anywhere can rapidly affect the entire system. A local blood shortage, even if some is available 50 miles away, can quickly become a safety issue.

FDA has limited ability to influence the overall supply or movement of blood supplies. When an intervention is under consideration, we can try to target that intervention to preserve critical supplies, but cannot control production volume or distribution. Should a test kit manufacturer decide to discontinue an unprofitable product, FDA may try to work out an accommodation, but has no control over manufacturing. FDA maintains liaisons with most of the AABB groups/ FDA has developed, and presented to this Committee, a blood shortage monitoring program, TRANS-Net. There is also a Blood Establishment Registration Database, which can supply potential response capabilities to the Secretary's Operation Center. FDA has just added a GIS system, using Google Earth Professional, that pin-points the locations of various blood operation sites. They are about ready to share this program. It uses a "KML programming language" which allows a central facility to update information at any selected interval and transmit the data via E-Mail.

FDA participates with the AABB Interorganizational Task Force and has been involved with it in "Top Off" exercises for disaster planning and response. Others have discussed the role of this task force and its operation.

Pandemic response planning has differences and similarities to that for acute disasters. The AABB Pandemic Task Force provided a list of accommodations to maintain the blood supply during a pandemic. They included reduced interdonation intervals for red cells, modified hemoglobin requirements, reduced travel deferrals,

changed weight limits and staff activities such as cross training flexibility, modified testing requirements for tests of lower impact (WNV NAT, HIV/HCV NAT). The Task Force has urged FDA transparency about its intentions. On the other hand, FDA has suggested enhanced anticipation of pandemic-related disruptions and preparation of back-up plans for key manufacturing steps. Surge collections early in a recognized pandemic would help maintain red cell supplies for 6-8 weeks (pandemics are unlikely to strike without warning, contrary to natural and man-made disasters). Practice guidelines would be useful for triage of blood components to facilitate optimal use of available blood supplies.

FDA is committed to following its own statutes, regulations, guidances and SOPs. There is limited “flexibility.” Statutes (laws) are not flexible. Permitted exceptions and alternatives to regulations are set forth in the Federal Register (640.120). Guidance procedures are not required, but when widely adopted may be part of cGMP. Voluntary industry standards are not FDA required. Emergency and Pandemic Response Issues are FDA-wide. Adherence to standards in place is a critical foundation of the current blood collection system. FDA is not totally opposed to some relaxation, but it would depend on the recognition of shortages as an imminent Public Health threat in and of itself. Supporting data must be provided to assess the risk-benefit to the greatest extent possible. FDA is actively seeking mechanisms that will help to preserve critical blood supplies in a pandemic or other disaster. FDA did show flexibility on 9/11 through the guidance process.

At a very productive meeting June 26, the discussion narrowed to several potential interventions that appeared to have the most favorable cost-benefit relationship. These were targets for future discussion and consideration. The first was consideration of a reduction in the 56 day red cell interdonation interval, which seemed likely to provide the biggest “bang for the buck.” The second was a minor reduction in the weight requirements for double red cell apheresis (e.g., 5 lbs). The blood community emphasized relaxing travel deferrals, especially visits to malarial areas and deferrals related to possible vCJD or BSE exposure. These would apply to incoming donors, rather than previously deferred ones, but might reduce self-deferrals by donors who would not attend blood-mobiles. Further discussion is warranted as well as consideration as to what organizational entity, government or community, would declare the need and accept responsibility for the intervention. If it be the FDA, what mechanism would provide the most efficient pathway to the more than 1,000 blood collection establishments? Individual variance requests might not be it.

CBER met in mid-June with the Boston Fresh Whole Blood Group to consider a “Walking Donor” program, a concept that is not new. Dr. Brinsfield presented some of the characteristics of such a program (my slide #17). The first step is to determine if this type of program has a potentially unique niche in an emergency response. If so, discussions can proceed regarding some of the regulatory and logistic hurdles, which are huge. Currently, FDA neither endorses nor dismisses the potential value of Walking Donor programs. There is considerable regulatory concern about who would collect the blood and how they are trained and supervised. Ideally, collections would be made under GMP by experienced blood collectors, best by someone who is part of a licensed or registered blood collection entity. With sufficient walking donors combined with comprehensive planning, such a system could be very powerful. It is possible that those

interested in being Walking Donors would be more likely to donate more frequently to retain their walking donor status. There might be a behavioral bridge between these two considerations of an elite donor group and the general finding that it takes 6 requests to get a donor to come in. The current regulatory paradigm for blood precludes many aspects of a Walking Donor Program so that a lot of discussion would be needed to set it up.

He summarized four different scenarios that he had discussed for disasters and blood shortages: 1) a large scale extended shortage (e.g., severe seasonal shortages); 2) a local crisis that is short-lived (e.g., severe trauma or terrorist event, local supplies exhausted; expected on 9/11, but did not materialize; FDA responded with same day guidance, revised after 3 days as no longer needed); 3) a large scale crisis that short-lived (multifocal terrorist events); and 4) a large scale crisis that is extended in time (e.g., severe pandemic). The 9/11 experience identified the need for consistent public messaging regarding the safety and adequacy of the blood supply and the need for interested donors to schedule future donations rather than line the sidewalk trying to help shortly after an event.

Regulatory approaches to preventing blood shortage crises were summarized. 1) Define candidate interventions, including risk/benefit assessments (incorporated into collaborative pandemic influenza planning). 2) Define appropriate triggers (?FDA TRANS-Net program defining the effect of local shortages – cancelled elective surgery, Rh+ plod to Rh- patients, transfusion triage, imminent patient morbidity/mortality). 3) consider FDA regulatory pathways appropriate to the situation. 4) plan realistically (plan for the worst, hope for the best).

Dr. Bracey commented favorably on the notion of donor management, including the walking donor program. Dr. Williams replied by urging that behavioral research be funded to get at the large portion of the general population that are eligible to donate, but don't. He has been struck by the gap between the donors lined up to give blood in response to an event and the difficulty in recruiting in normal times.

Dr. Holmberg was then introduced to discuss the BASIS system. Before starting, he announced that Dr. Lelkens (Netherlands) was scheduled to speak about frozen blood, but was stuck on the tarmac in Amsterdam for many hours and was unable to travel. He is involved in a total frozen blood bank, with frozen red cells, platelets and plasma. Dr. Holmberg's presentation is in response to discussions yesterday concerning BASIS. He'll try to put it in perspective with TRANS-Net, mentioned by Dr. Williams, looking at the capabilities of each.

Referring to a graphic presentation of red cell collections, blood available after processing and transfused units, he reiterated that the gap between available units and those transfused is narrowing. This may be due in part to better inventory management, but, as Dr. Epstein had noted, other countries transfuse fewer units per population size that we do in the US. He also reviewed ESF #8, with DHHS the primary agency, but many others are also involved with supporting functions. When activated, ESF #8 is coordinated by the Assistant Secretary for Preparedness and Response (ASPR). Blood support is the responsibility of ASH, but is managed with the assistance of the AABB Task Force. Red Cross is listed as disaster support, but is part of the AABB Task Force for blood. *"HHS monitors blood availability and maintains contact with the American Association of Blood Banks Interorganizational Task Force on Domestic Disasters and*

*Acts of Terrorism and, as necessary, its individual members to determine: The need for blood, blood products, and supplies used in their manufacture, testing, and storage; the ability of existing supply chain resources to meet these needs; and any emergency measures needed to augment or replenish existing supplies.”*

BASIS is a database that monitors both supply and demand and provides the ability to determine shortages daily when they occur, and when an event happens, we already know the status of the blood supply. When an event occurs, affected hospitals and blood centers are activated, as is the Secretary’s Operation Center. Activities are coordinated with FDA, CEC, NIH, HRSA, CMS and the critical infrastructure (e.g., supplies, electricity, communication, water, fuel) is reviewed. DoD and the Department of Veterans Affairs are also involved. In some instances, the AATB (tissue banks), medical device people, American Hospital Association, CAP and PPTA are also involved. Regarding blood, it is important that one consistent message is delivered to the public and the ASH works through the Secretary to deliver that message.

Dr. Holmberg emphasized that BASIS was developed as a monitoring tool, not a blood management tool. It uses weighted values and statistical sampling to ensure that it is representative and is being validated with the HHS-funded national survey tool. In addition to certain quantitative data, it collected qualitative or semi-quantitative information about delay or cancellation of surgery, incomplete filling of orders, use of a supplier alternative to the usual source, use of a non-standard protocol because of shortage and was routine transfusion practice ignored. Each center’s data are secure and protected, available to the center providing the data, but not visible to other centers, protectable under the Critical Infrastructure Information Act. Blood centers and hospitals are still being recruited and added to the database to improve the generalizability of the information in the database.

The Chair opened the discussion, noting that the transfusion service usually, but not always knows when surgery is delayed or postponed. Are there other sources than the transfusion service for hospital data? In reply, there is no set way of handling this potential problem; in general, it is expected that the transfusion director will be informed or otherwise be aware of the problems. There are still hospitals and their blood banks that are managing blood inventories manually, with index cards, rather than by computer. Dr. Epstein asked if the blood centers enrolled were the “right” ones, so that data would be generalizable. Dr. Holmberg replied that they have used two random selection processes: 1) a random selection of 300 facilities through all 10 Public Health Regions; 2) currently working on the second sampling to get additional facilities to participate. They are weighted by size and geographic location.

The Chair then opened the Public Comments section of the meeting. The first was Ms. Lori Williams, Faculty Member and Neuroscientist, Department of Symptom Research, MD Anderson, Houston. She spoke on behalf of the Scientific Advisory Board of the National Patient Advocate Foundation, addressing their concerns about CMS’ National Coverage Determination for erythropoiesis-stimulating agents. We worry that maintaining a patient’s hemoglobin above 8 gm/dl and disallowing therapy over 10 gm/dl will increase blood usage and lead to a shortage for cancer patients of packed red cells because of the increased demand. The FDA approval for ESAs allows continued therapy in the 10-12 gm/dl range. Her work in symptom research has made her aware of the importance of hemoglobin and how its level affects symptoms in patients with cancer. A



study by her colleague, Dr. Shelley Wang, directly correlated fatigue with hemoglobin level in over 200 patients with leukemia and lymphoma. Self-reporting fatigue on a scale of 0-10 (0 = no fatigue; 10 = as bad as could be imagined) is a well established, reliable and valid method of measuring symptom severity in patients with cancer and other chronic illnesses. MD Anderson experience is that levels of 7 or higher is “severe” and interferes with the ability to work, perform general activities, enjoy life, maintain a normal mood, relate to other people normally, walk and even think. About 65% of patients with a hemoglobin of 8 will report severe fatigue. At 9, it is 55%; 10, just over 50%; 11, 40%; and finally at 12, it drops to 24% with severe fatigue. At hemoglobin levels of 15 Gm/dl, no patient reported severe fatigue. Blood bankers at MD Anderson have estimated that they might see up to a 25% increase in demand for blood products, which is about 1,000 units a month. Increased use of blood components may mean increased side effects from blood, e.g., transfusion-related lung injuries, iron overload and fluid overload.

After a short break, the Committee continued with general discussion, working on a recommendation for the Secretary resulting from today’s deliberations. Important parts of the discussion dealt with how much data (how big a sample) was needed and why the government needed data from blood centers and hospitals and what would they do with it. The blood establishment (Dr. Bianco, ABC) believed that they had a system that would deal adequately with emergencies and disasters. Ms. Finley pointed out that the AABB Task Force had depended on data from previous disasters and emergencies (including 9/11) during which very little blood (several hundred units) was the most that was used, but natural disasters and terrorist activities could occur on a much larger scale and might overwhelm what is now in place.

The Committee voted unanimously to make the following recommendation to the Secretary:

“Whereas the blood supply is a critical part of the Nation’s healthcare infrastructure, the HHS ACBSA believes that knowledge of real-time national blood and blood product inventory and its dynamics is essential for emergency preparedness and response. The committee finds that blood center data are extensive, but not comprehensively aggregated nor available to HHS; hospital data reporting is essential, but limited. Although the blood supply is elastic, it is unclear whether it is sufficiently elastic to address potential disasters.

“The Committee recommends that:

1. HHS establish sufficient hospital and blood center participation in inventory reporting to allow accurate determination of national blood and blood product inventory as a trigger for efficient local, state, and federal responses.
2. HHS develop comprehensive models to address and respond to needs for blood and related critical materials in a variety of surge, donor depletion and other threat conditions to accurately cover blood needs.
3. HHS work with the blood community to define shortage scenarios that would require implementation of alternative strategies for blood collection, distribution, and use.

4. HHS support operations research to characterize and recruit potential donors who do not now routinely donate.”

A motion was made, seconded and passed to adjourn the meeting.