Advisory Committee on Blood Safety and Availability
August 26-27, 2004
Meeting Minutes

The Executive Secretary, Dr. Jerry Holmberg, called the meeting to order shortly after 9:00 AM. After reminding Committee members and speakers to declare any actual or perceived conflicts of interest at appropriate times during the meeting, he called the roll (see attached member attendee list). The meeting was then turned over to Dr. Mark Brecher, the Committee Chairman, who commented on the meeting agenda and noted that the Committee Charter was in the process of being submitted for a two year renewal. Dr. Holmberg was then called on to review the status of the Committee's recommendations.

1. Dr. Holmberg then reviewed in reverse order the status of Committee recommendations made back to the January 2001 meeting.

   a. <u>April 2004:</u>

      i. **Reimbursement:** The Committee reiterated its January 2004 recommendation that "new" funds be found to reimburse for improvements in blood safety and availability, e.g., new tests and increased deferral of at-risk donors.

         (1) It endorsed the House-Senate Conference Report for the Medicare Modernization Act (MMA) with particular regard for reimbursement for the use of blood components and products.
         (2) It requested the Secretary to clarify and compile blood and blood costs billing and policy procedures in the in- and out-patient settings as well as the blood deductible.
         (3) The Secretary was asked to use MMA authority to exclude blood clotting factors, blood products and transfusion medicine services from the establishment of quality standards and competitive acquisition provisions of the act.
         (4) Action: The Acting Assistant Secretary for Health (aASH, Dr. Christina Beato) has been asked to work with CMS to address this recommendation.

      ii. **Bacterial contamination of platelets:** The Committee encouraged dialogue between HHS Agencies, blood programs and manufacturers to ensure:

         (1) prompt development of technologies,
         (2) design and completion of feasible studies,
         (3) licensing to permit both pre-storage pooling of whole blood derived platelet and extension of platelet dating,

(4) **Action:** DHHS representatives participated fully in a face-to-face meeting of the Task Force (June 2, 2004) and in periodic conference calls on the topic.

b. January 2004

i. **National Blood Policy:** The Committee found the goals of supply, quality, accessibility and efficiency of the National Blood Policy, first published in 1974, were still applicable today. Specifically, they recommended:

(1) An awareness campaign to support a 5-7 day inventory,
(2) DHHS should fully fund the FDA (now DHHS) Blood Action Plan's private and governmental supply monitoring and increasing blood supply,
(3) Full funding for creating and maintaining a National Blood Reserve,
(4) **Action:** A new awareness campaign is being coordinating in the private sector (AABB, ABC and ARC),
(5) **Action:** Emergency blood management is vested in the ASH, DHHS, in cooperation with the Department of Homeland Security. Funding for a National Blood Reserve missed the Administration's for 2004. Blood reserves will be available at an Armed Forces Processing Laboratory to support the Republican Convention, should the need arise.

ii. **Reimbursement:** The Committee urged the Secretary to address funding needs at all levels of the blood system to support product safety, quality, availability and access by adding resources and reforming the CMS reimbursement system for blood and blood products, including plasma-derived therapeutics and their recombinant analogues.

(1) **Action:** The ASH (Dr. Beato) and the CMS Director (Dr. McClellan) will address together reimbursement issues.

c. August 2003:

i. **Reimbursement:** Adequate reimbursement for improved blood safety and availability was stressed, and it was recommended that "validated cost data" from transfusion services or regional blood centers be used to determine reimbursement levels.

(1) **Action:** The recent (February 2004) reimbursement levels for outpatient Ambulatory Procedure Codes used blood bank community data to model needs.

d. May 2003:

i. **Reimbursement:** Adequate reimbursement must be provided to support needed improvements in safety (testing and at-risk donor deferral) and availability (donor recruitment).

(1) CMS should consolidate, simplify and review policies for paying for all blood and blood products. They should develop timely and adequate mechanisms to assure that improvements in blood safety can be concurrently implemented, including the identification of contingency funds for initiatives that require immediate implementation.

(2) CMS should amend the definition of blood and blood products to include all plasma-derived products to provide continuing access to therapy for chronic diseases and life-threatening conditions, specifically including IGIV.

(3) **Action:** Secretary Thompson directed Drs. Beato and McClellan to discuss these issues.

e. January 2003:

i. **Current leading causes of transfusion-related fatalities:** The Committee found that bacterial contamination of blood components (e.g., platelets), medical errors (mis-identification of patients and the administration of blood to the wrong person) and transfusion-associated acute lung injury (TRALI) were the "most significant" causes for transfusion fatalities.

(1) **Action:** FDA has approved and blood collectors are beginning to use pouches to divert for testing the first 30-50 ml of blood collected during a donation (including most of the potentially contaminating skin flora). The private sector is using improved skin preparation for venipuncture. The transfusion industry is mostly in compliance with a new AABB Standard (April 2004) to decrease and monitor bacterial contamination of platelets.. Pre-storage pooling and extending permissible storage beyond 5 days are considered important issues in addressing bacterial contamination. Machine readable identification of blood components will be required by 2006; improved patients identifiers using various technologies are to be encouraged. Dr. Holmberg's experience in developing and implementing ISBT-128 bar-coding for blood and blood components supports its value in reducing identification errors. FDA (Dr. Epstein) expects to remove all barriers to the implementation of ISBT-128. Technology exists to read multiple bar codes, so that all-hospital standardization is not needed.

ii. **Subcommittee formation:** The possibility of appointing subcommittees to deal with special subject areas in depth was raised but never carried forward (There can be subcommittees, but they can only educate and recommend actions to the parent committee, where open discussion can take place and recommendations formulated for the Secretary, as needed).

iii. **Reimbursement:** The ACBSA reaffirmed previous recommendations for improved reimbursement for recombinant clotting factors to facilitate and encourage their use, improving safety. CMS should promptly revise the Carrier Manual to remove insurance barriers to recombinant technology.

iv. **No action** noted.

f. <u>September 2002:</u>

i. **Reimbursement:** The Secretary should direct CMS that plasma derived therapies and their recombinant analogues be reimbursed based upon current year acquisition and actual total cost of providing such products and services both in hospitals and in non-hospital settings to ensure patient access to care.

(1) **Action:** DHHS rejected any further increase in blood reimbursements, noting that they were part of DRGs and the changes in hospital payments might or might not be reflected in transfusion services budgets. For plasma therapies, a claims-based system has been abandoned; GAO has been mandated by the Medicare Modernization Act to do a hospital acquisition cost survey, due in early 2005 to set rates for 2006.

ii. **Public awareness:** The Secretary should promote public awareness of the ongoing need for routine blood donation via:

(1) PSAs and visible blood donations by top officials and paid advertising campaigns,
(2) Funding of demonstration projects,

(3) Support specific initiatives encouraging donations by young people and minorities,
(4) Lead in increasing participation of federal employees,
(5) **Action:** DHHS pioneered the "Give Thanks, Give Life, Give Twice" Campaign. Secretary Thompson donated blood and provided press releases. It is a problem the campaigns are finite in time. Dr. Beato (ASH) asks that the viability of a frozen blood reserve be readdressed. Ms Lipton offered for the Task Force to prepare a "White Paper" on this issue.

iii. **Monitoring:** The Secretary should support blood supply monitoring to address:

(1) Long term trends in blood collection and use,
(2) Data on daily nationally distributed blood inventories,
(3) Indications of blood shortages and excesses,
(4) Predictive models to identify trigger points for coordinated national donation campaign,
(5) Coordination of governmental and non-governmental initiatives,
(6) **Action:** Analysis of an improved monitoring system was initiated in 2003. Monitoring is supported by the Secretary's Command Center.

g. <u>January 2002:</u>

i. **Response to Disasters:** Transfusion Medicine's response to 9/11and other past civilian or military disasters was reviewed and recommendations were made:

(1) Promote and coordinate a single consistent public message on blood issues,
(2) Review ESF #8 of the Federal Response Plan to incorporate the recommendations and organizational members of the AABB Task Force,
(3) The AABB Task Force to coordinate the national response of the blood community,
(4) Fund the evaluation and potentially the development of a National Blood Reserve,
(5) **Action:** ASH is responsible for the nation's blood supply; in time of disaster a coordinated message will be prepared through the ASH office. ESF#8 has be revised re coordination with the AABB Task Force. A National Blood Reserve is being evaluated.

ii. **Donor Awareness:** The Secretary should recognize and incorporate the FDA's Office of Blood Research and Review strategic plan into the DHHS response plan for counter terrorism and disaster preparedness.

(1) **Action:** FDA strategic plan has been incorporated into the Department's plan.

h. <u>April 2001:</u>

i. **Global Blood Safety:** The Secretary should:

(1) Foster research, training and standard-setting activities in

international blood safety, including development and transfer of appropriate technologies for the developing world,

(2) Support the establishment of a mechanism to identify priorities and coordinate the exchange of information and activities among government and non-government agencies in the US and international community,

(3) **Action:** ASH Senior Advisor for Blood Policy is involved with Global Collaboration for Blood Safety. Professional organizations, AABB, PPTA and WHF are involved.

ii. **Blood Monitoring and Data Collection:**

(1) Establish an office responsible for facilitating the gathering and dissemination of national blood collection, distribution and utilization data, the development of analytic models to predict shortages.

(2) Provide Federal funds to support collection, analysis and distribution of these critical public health data.

(3) Support programs for public and physician education.

(4) **Action:** Blood monitoring with statistical modeling has been proposed and will work with the Secretary's Operation Center. Historical blood data collection will be used as needed to validate the monitoring program. Education programs neither developed nor funded.

i. January 2001:

i. **Universal Leukocyte Reduction (ULR):**

(1) Strive to minimize the impact on supply, assure adequate funding for ULR and issue a regulation to implement ULR that addresses these concerns.

(2) Support research to investigate unresolved scientific issues in ULR.

(3) Appoint to the Advisory Committee a non-voting member from CMS

(4) No formal decision on ULR has been made. Research is on-going. An CMS Committee member was appointed in August 2003.

2. **PHS Emergency Management System**: Mr Dean Ross (Director, Secretary's Operation Center - new name for Command Center) discussed the PHS emergency management system. The system interfaces with the Hospital Asset Reporting and Tracking System (HARTS), the Blood Availability and Safety Inventory System (BASIS) and a database for medical material and supplies. Some data are reported daily (BASIS); other information is reported as needed for emergency purposes (HARTS). Analysis includes geographic information systems to localize problems and solutions. The focus is on planning prospectively, preparedness, as well as on reactive responses to events.

a. The discussion focused on how the data would be publicized in a "lessons-learned" format to help with future planning. Drs. Sandler and Fitzpatrick commented on potential use of data the locals level.

b. The current "sentinel transfusion service" reporting system at DHHS was designed as a macro system; it should detect a national shortage but wouldn't be expected to detect a purely local problem. The FDA Transnet system, a web-based voluntary system, would detect local shortages if a hospital makes a report. Elements of the Transnet system will be incorporated into BASIS.

c. Dr Kuehnert (CDC) called attention to the National Nosocomial Infection Surveillance System which has collected data for more than 30 years about hospital-acquired infection and uses the anonymous information for bench-marking. This could be a model for the blood and disaster databases under discussion.

3. The Committee then revisited an earlier discussion about setting up subcommittees on emerging transfusion-transmitted diseases and on reimbursement to report to each

meeting of the parent Committee with recommendations.

a. **Transfusion transmitted diseases subcommittee:**

To identify potential threats to transfusion safety and to provide lead time to develop countermeasures, e.g. tests, procedures. Subcommittee members were identified as Drs. Kuehnert, Heaton, Linden and Epstein; Ms Lipton, and Mr Skinner.

b. **Reimbursement/Finance Subcommittee:**

To clarify reimbursement issues for thorough presentations to the Committee. Subcommittee members were identified as Drs Sayers (Chair), Sandler, Angelbeck, Penner, and Bowman; Mr Walsh and Mr. Healy.

c. **Agenda Subcommittee:**

This group meet sporadically, but now should be prepared to react to suggestions by the other subcommittees. The Committee made a commitment to discuss reimbursement issues for at least half day during the next meeting.

4. **National Response Plan and Executive Response Function #8**

a. Captain McMurtry discussed the evolution of ESF #8 since September 11, 2001.

i. Communications problems: were identified in the first contingency exercise following Sept 11.

ii. In January 2002, the Advisory Committee made recommendations to the Secretary about the interaction between the Task Force and the Federal Government (see above). An initial attempt to contact FEMA about cooperation with the Federal Government (April 2002) produced no response.

iii. In July 2003, the President of the AABB (Dr. Roger Dodd) wrote the Secretary about the functions of the Task Force in time of emergency.

b. The “final draft” of a revised overall Emergency Response Plan (June 2004) includes 15 “Annexes,” one of which is ESF #8 (public health and medical services. DHHS is the lead agency for this function, although multiple parts of the Federal and private sectors have a supporting role.

i. Information about disasters comes from multiple source, including media.

ii. Section D(1)(8) describes how the Secretary’s Operation Center (SOC) and the ASH make decisions about managing the blood supply.

iii. The Federal Charter of the Red Cross identifies their broad role in disaster management. However, blood issues will be coordinated through the AABB Task Force.

iv. Dr. Holmberg stated that the ASH and SOC would work through the Task Force in matters of the blood supply, taking due note of the prime importance of the local blood center.

5. Mr. Jamie Blietz reported on the activities of the AABB Interorganizational Task Force National Special Security Event planning (examples from past year).

a. Primary planning is at the local level. The Task Force supplements that by bringing a national perspective.

b. National Blood Reserve

c. A Disaster Operations Handbook (March 2003) is available (PDF) at www.aabb.org. A major revision is due in early 2005; revisions may be on-going.

d. Dr. Linden noted that the planning process for the Republican National Convention did not involve state agencies. In NY, there is a state agency with regulatory responsibility for blood; it should have been involved. Both Dr. Linden's agency and the NYC Health Department collected much of the same information as did the Task Force. Mr. Blietz and Dr. Holmberg reported that the Federal Government is usually involved only after a state request. In a stepwise process, if local facilities are overwhelmed by a disaster, they seek state help. In turn, the state goes to the Federal Government if their capabilities are stretched.

e. Dr. Kuehnert suggested that a representative of the Council of State and Territorial Epidemiologist be a member of the Task Force.

6. Commander Michael Libby described plans to prove the concept of a National Blood Reserve by an exercise during the Republican National Convention.

a. The exercise tasks the Armed Services Whole Blood Processing Laboratory (DoD) to provide coordinated blood shipments (2 of 30 RBC units each) to the NYC area.

b. Normally, the Secretary, DHHS, would request assistance through the local Homeland Defense Command (NORTHCOM, in this instance) from the Secretary of Defense (for this exercise, the request will go from HHS to the Armed Service Blood Program Office to an ASWBPL (there are 2: East, at McGuire AFB, NJ and West, Travis AFB, CA).

c. Goal was to test logistics between DoD and civilian blood centers.

d. DoD uses ISBT 128 bar coding; not all civilian centers use it.

e. ASWBPLs can ship up to 7,200 RBC units daily; can provide frozen red cells and cryoprecipitate, but not platelets.

f. DHHS reimbursed DoD for the difference in transportation and acquisition cost of blood product.

g. Dr. Richard Davy (NY Blood Center) described their efforts in preparation for the Republican National Convention. A sizable inventory of red cells and platelet will be transferred to satellite centers for temporary storage to facilitate shifting to hospitals with a need. A blood collection drive is planned at the Times Square Marriott, but security considerations prelude publicity about the event. They don't anticipate any effect of inventory shifting on outdates, but will be able to find out after the event. They have redundant communications: land lines, Nextel, AOL and the NYC Office of Emergency Management 800 MHz radio network.

7. **Report for Centers for Medicare and Medicaid Services (CMS):**

a. Dr. Edith Hambrick (Chair, CMS Advisory Panel on APC Groups) discussed the Proposed 2005 Rule for Hospital Outpatient Prospective Payment System and Medicare, Part B (Physician Fee Schedule). The comment period for the OPD

rule will be open until October 8 and for the Part B rule, September 24; final form of these rules is not yet known.

b. Blood is considered to be special; as data are collected, APCs (Ambulatory Payment Classifications) for Outpatient Transfusions are refined and changed as needed.

c. Better data is leading to a 25% increase in overall costs.

d. New codes will further refine the data for 2005.

e. Home use of blood products is being kept separate.

f. "Blood deductible" has been kept at 3 units.

g. Drugs (including biologics) are classified as sole source, innovator multiple source and non-innovator multiple source. Payments for each group differs in relation to the average wholesale price (AWP).

h. Clotting factors and IVIG are paid under Part B.

i. Questions were asked about the "blood deductible," but these were outside Dr. Hambrick's expertise and will be referred within CMS for answers (those with questions were asked to E-Mail the questions to her). Dr. Bowman (CMS) said

that the "blood deductible" was in statute, and he would review it for the committee.

j. Apparent reductions in payments for some items caused concern (e.g., recombinant Factor VIII.

k. Public Comment

i. Ms.Wiegmann, AABB, expressed concern that payment for some low volume products was being decreased (e.g., granulocyte by apheresis from $1245 to $749). AABB is working with hospitals to improve cost reporting to CMS, but would like more assistance from CMS in educating these hospitals.

ii. Ms. Michelle Vogel (Immune Deficiency Foundation) complained that the determination that a piece of durable medical equipment is not "medically necessary" precludes immune deficiency patents from using an infusion pump for their IVIG, but instead requires an IV drip, which is much slower and less efficient. The determination that a pump is not medically necessary has been translated in some areas of the country to a lack of medical necessity for the drug (IVIG).

iii. Ms Shannon Pemberthy (National Hemophilia Foundation) thanked CMS for correcting some mis-classifications of clotting factor products, and especially for the speed with which changes were sent to the field and implemented.

iv. Ms Mary Beth Savory-Taylor (American Hospital Association) pointed out that lump sum DRG payments were a disincentive for hospitals to report blood costs (or other itemized costs). The amount paid doesn't change, regardless of how complete the cost reporting is. In the past, it has been a zero sum process and "new money" was rarely added.

v. Ms Elena Bostic (Executive Director, Hemophilia Association of NJ) noted that in the past, home care companies have written off the 20% Medicare-required co-pay. With the reductions envisaged in the new rules, these companies are less able to cover that co-pay. 20% of the average $100,000 - 150,000 annual cost of hemophilia care is more than most patients can afford. They will collect and supply supporting data to CMS.

vi. Tim Hannon (Anesthesiologist from Indianapolis):

(1) The Committee has not been addressing the issue of better utilization of blood, assuring that every transfusion is truly needed.

(2) Dr Klein suggested that the figure, 20-25%, for inappropriate use of blood was an "urban legend, unsupported by hard data.

(3) "Sale price" is only part of the costs; many additional resources are used to deliver blood to the patient and these have not been addressed.

vii. Jim Romano (Hemophilia Federation) commented the new rule would likely limit access because of the co-pay issue (Dr. Hambrick suggested that the 20% co-pay was a statutory requirement over which CMS had no control).

viii. Ms Teresa Lee (Advanced Medical Technology Association) commented that about 80% of blood is given to in-patients where reimbursements are less fixed, being part of the DRG system.

ix. Dr. Wong (Committee Member) asked about reimbursement for treatment with Novo 7. Dr. Hambrick was unfamiliar with its use and asked for an E-Mail so she could refer it to someone in CMS to address the issue.

x. Dr. Bianco (Committee Member) reiterated that with DRGs, there was little incentive for hospitals to code individual therapies, since it would make no difference in what they were paid.

8. **Ad Council Public Awareness Initiatives**

a. Mr. Scott Caswell (ABC) opened the discussion by describing the challenges addressed.

i. Increasing blood awareness and move away from crisis appeals
ii. It's the blood on the shelf that saves lives
iii. The traditional blood donor:

(1) We have become reliant on "baby boomers" which are white, professional, middle aged male

iv. Rise in donor deferrals has also impacted blood availability.

v. Young adults, 18-24, are the largest demographic group since the "baby boomers."

(1) Good donors in high school; lost to follow-up afterwards.

(2) High school donations in fall and spring behind these seasonal inventory highs.

vi. Partnership with the Ad Council (long history of successful slogans)

(1) 2003 reached $1.3 billion in donated media.
(2) Average teen/young adult campaign gets $26.3 million, more than 50% in radio.
(3) Results

(a) Seat belt education: use increased from 21% to 73% since 1982.

(b) United Negro Fund raised nearly $1.9 billion since 1972 to help more than 300,000 young people to go to college.

b. Mr. Ryland Dodge (ARC) described how partnering with Euro RSCG Worldwide (Messner Ad Agency, NY) developed the program.

i. Develop a comprehensive outreach plan to leverage media support using Ad Council outreach capabilities and AABB, ABC and ARC as local and national partners, focusing on target audience.

ii. Use non-traditional media: e.g., Internet, health clubs, stores, and co-branded messages.

iii. Target audience relates to issues that directly affect them rather than larger social issues on which they can have relatively little direct impact.

iv. Self-absorbed and unwilling to be inconvenienced by something not perceived to have a direct affect on them or their peers. More responsive to major catastrophes.

v. Need education about blood donation.

c. Mr. Marc Pearce (AABB) described some media messages that are ready to go

i. Two approaches:

(1) You can't save the world, but you can save three lives by donating blood.

(a) Ad Council to distribute to 20 million media outlets (Top-down)
(b) Blood community must manage bottom-up distribution.

(2) "Al Blood" is a puppet that oozes blood and provides information about blood donation and use. Intended for Internet distribution.

(3) Web-site: www.bloodsaves.com

Dr. Sandler expressed doubts that "One donation can save 3 lives" was evidence-based, although it has been in wide use for years. There could be a credibility gap for knowledgeable people.

d. Other members of the Committee spoke to the importance of donor recruitment at the local level, wondering if national advertizing would be effective. The presenters said that the ad campaign was planned to "soften up" the targeted public to make local recruiters more efficient and effective.

e. Mr. Bart Fisher presented on behalf of the Give Life Foundation, of which he is the Co-founder and Chairman.

i. Purpose: to promote the donation of blood, blood products, organs and tissues (working with Hill & Norton, PR firm).
ii. CBS New Year's Day telethon urging a resolution to give blood on a special day, e.g., birthday.
iii. Use celebrities (model: Jerry Lewis' Muscular Dystrophy program).
iv. Work with Distributive Education Clubs of America (DECA).

(1) Marketing counterpart (marketing students) of Future Farmers of America.
(2) 300,000 clubs in US high schools and colleges.

v. Dance marathons for promotion.

iv. Give Life Foundation is also lobbying to establish and fund the National Blood Reserve.

(1) FY 05 Appropriations (or at least report language) in support.
(2) Concerned about fragmentation in the blood community.
(3) Has a sense of urgency and has submitted an unsolicited proposal to the Department of Homeland Security to fund the NBR with FY 04 Appropriations ($17 M).

9. **Transfusion-related Acute Lung Injury (TRALI):**

a. Dr Mark Popovsky summarized the current status of TRAIL, including the activities of the NHLBI Working Group.

i. Pulmonary complications of blood transfusion include anaphylactic and allergic reaction, circulatory overload, hemolytic transfusion reactions (infrequent), bacterial contamination (rare), and TRAIL.

(1) Leading cause of transfusion-related death (mortality rate 1-23%)

(2) True incidence unknown
(3) First case reported in 1951; probably had occurred before

ii. TRALI: Presenting symptoms - respiratory distress (76%), hypotension or hypertension (15% each).

(1) >90% within 1-2 hours of transfusion (100% within 6 hours).
(2) responsible transfusions always contain plasma.

iii. Pathogenesis not clear

(1) HLA or granulocyte (HNA) antibodies common in donor and/or recipient.
(2) Implicated often multiparous women (some implicated in >1 case).
(3) Implicated units often contain biologic response modifiers (BRM).

iv. Recommendations

(1) Identify patients at risk
(2) Identify donors at risk
(3) Screen multiparous donors for HLA/granulocyte antibodies
(4) Screen transfused donors
(5) Develop a product management scheme

(a) Defer implicated donors
(b) Divert plasma from females or antibody positives
(c) Wash/freeze RBC from implicated donors
(d) UK Serious Hazards of Transfusion (SHOT) program may help determine the effect of such measures on the frequency of TRALI

(i) Outsourcing all plasma to US/male donors only
(ii) Estimated to decrease TRAIL by 90%

b. Dr. Steven Kleinman reviewed a recent TRALI meeting in Canada, modeled after the US NIH Consensus Development Conferences. He was Chairman of the Consensus Panel

i. Consensus definition of TRALI (based upon NHLBI TRALI Working Group)

(1) New acute lung injury during or within 6 hours after transfusion

(2) Hypoxemia (clinical and/or laboratory evidence)

(3) Bilateral lung infiltrates on chest x-ray

(4) No other temporally associated acute lung injury risk factors

(5) "Possible TRALI" if there are one or more temporally associated risk factors

(6) Acute Lung Injury risk factors: Aspiration, pneumonia, toxic inhalation, lung contusion, near drowning, severe sepsis, shock, multiple trauma, burn injury, acute pancreatitis, cardio-pulmonary bypass and drug overdose

(7) Exclude

(a) Mild TRALI (criteria not well defined)
(b) Coexistence with circulatory overload
(c) Worsening lung injury with preexisting acute lung injury

ii. Donor management to protect recipients of future or co-component donations

(1) Associated donor - blood transfused within 6 hours of TRALI.

(2) Panel preferred HLA (class I and II) or HNA antibody studies to exonerate or implicate each associated donor; a donor-recipient cross match could detect, but not identify antibodies

(3) Deferring all implicated donors is recommended because past look-back studies have shown frequent repeats

(4) Flagging an "associated" donor to permit a change in his designation to "implicated" if he is associated with a second case raises ethical issues for both the donor and the potential recipient

(5) Not sure how to manage a donor with antibodies that are not specific for the patient's antigen

iii. Primary prevention possibilities in order of preference.

(1) Don't use for transfusion plasma from multiparous women or transfused men.

(2) Avoid plasma from all females.

(3) Test all females and defer those with HLA/HNA antibodies; Tests are complex and expensive

iv. Local policy should be based upon availability of tests and effect on blood availability of deferring donors with possible, but unknown risk for producing TRALI.

c. Panel made no firm recommendations for donor management

i What additional research in needed?

(1) Epidemiological/Clinical.

(2) Predisposing clinical or genetic factors (donor or recipient).

(3) Epidemiology viz components implicated.

ii. Pathophysiology

(1) Animal mode

(2) Does neutropenia protect? If so, how and why?

(3) Mechanism(s) for fever and hypotension

d. Discussion:

i. UK has stopped using locally collected plasma, contracting outside the country for plasma only from males. Recent stepped up passive surveillance for TRALI has implicated only female donors. Estimates based upon components involved suggest that the new plasma policy (put in place out of concern for vCJD transmission) will prevent up to 90% of TRALI cases. However, it is too soon to detect that change in the surveillance program (SHOT).

ii. Could the US adopt and male-only plasma policy? None of the blood bank software in use in the US permits segregation of blood by gender. Opinion varied if the US could satisfy plasma-for-transfusion demand only from male donors. In the US, much of the plasma transfused is with apheresis-collected platelet. To derive full benefit, would it be necessary to collect apheresis platelet only, or mostly, from males?

10. **Therapeutic plasma issues: Economics and the role of reimbursement.**

a. Mr. Jan Bult, President, PPTA, discussed Industry economics.

i. In 1998, there were serious shortages of IVIG; a few years ago, there was a shortage of Factor VIII. What has changed since then?

(1) Monitoring systems are in place to assess changes in supply dynamics. Information public available on the Web.

(2) Industry is better positioned to meet consumer demand.

(3) Industry economics has become increasingly important.

ii. As a concentrated industry, it is tightly subject to anti-trust law.

(1) Certain discussions and agreements are illegal, e.g., limit production, reduce inventories, coordinate output, allocate capacity, set quotas, discontinue particular products and limit supply of particular products.

(2) No facilitation of information exchange among members.

iii. Industry changes

(1) Consolidations and divestitures have led to closure of plasma centers and fractionation facilities leading to a reduced volume of fractionated plasma and staffing reductions.

(2) New companies entered the market; new products approved; facilities upgraded and expanded; enhanced technologies and use of both source and recovered plasma led to higher yields.

(3) Recombinant technology applied to Factors VIII and IX reduced the demand for plasma-derived material.

(4) Multiple products are needed to support the costs of fractionation.

(a) With off-label use, the demand for IVIG approaches infinity; most other products may be in surplus and fail to support the manufacturing process.

(b) Economics of plasma industry differ from those of the pharmaceutical industry, despite frequent lumping of them together.

(i) e.g., Raw material (plasma) costs predominate for plasma biologics compared to the dominant cost of

marketing drugs.

(ii Plasma therapeutics' patient base is small.

(iii) Plasma therapeutics are non-generic proprietary products.

(iv) Capital, plant and equipments investments high; long delay between collecting raw material (plasma) and the final product.

(v) Emerging requirements for clinical trial are very difficult to meet, limiting the number of new plasma protein therapeutics.

(6) Outside of economic factors, there is no immediate threat to supply.

b. Discussion: Dr. Penner commented that the use of IVIG to treat autoimmune disorders was "off-label," but potentially very high. Many studies are suggestive of benefit. Nevertheless, the plasma industry has not been aggressive in supporting studies that would result in addition approved uses, nor have they been successful in persuading insurance carriers to pay for off label use. Mr Skinner pointed out that the market for plasma-derived factor VIII was stable or decreasing because most developed countries are converting to recombinant factor. Developing countries are unlikely to pay US prices for plasma-derived factor. Hence, the ability of the hemophilia treatment market to carry much of the fractionation cost weight is limited. He asked if sufficient cost savings were available anywhere to take up the slack. Mr Bult responded that in the US, 70% of the factor VIII market is recombinant and 30 % plasma-derived. Europe and Japan are about 50-50. Of the world hemophilia patients, 70-75% has no treatment at all. PPTA is working with WHO to address the issue that affordability is the major problem, much bigger than supply. Mr Walsh asked if the industry was addressing distribution channels, in which middlemen seem to be responsible for considerable cost. Mr Bult replied that individual companies were addressing this issue, but the industry as a whole was not. Dr. Haas commented that some economic theory separates need from demand, especially of cost prevents demand from satisfying need, hence, the global need for factor VIII can not be afforded, holding down demand.

c. Ms Julie A. Birkhofer (PPTA) discussed the Role of Reimbursement in Therapeutic Plasma Treatment.

i. Reimbursement drives access, availability and innovation.

ii Ensure patient/physician choice in therapies.

iii The Medicare Modernization Act (MMA) has put in place a variety of new reimbursement methods, most of which rely on the private market but are theoretical and unproven. This subjects fragile patient populations to such unproven approaches.

iv Changes in reimbursement policy seemed certain to extract a price for access. Examples were provided of patients with hemophilia, alpha-1 protease inhibitor deficiency and with immune deficiency.

v. Goals are to control cost, reduce spending and control utilization. Federal programs are immensely important because they usually set the process used by private insurers.

vi Discussion: Ms. Lopes asked how the fractionation process could take so long to a final product. Ms. Birkhofer referred to Mr. Bult's presentation and to a min-disc that describes the process. Copies of the disc to be provided to Committee members.

d. Ms Michelle Vogel (Immune Deficiency Foundation) discussed consumer access, using the immune deficiency diseases and the IDF as an example.

i. IDF Goals focus on patient advocacy.

ii. Access to state-of-the-art medical care.

iii. Early diagnosis

(1) WHO recognizes more than 140 primary (genetic) ID diseases.

(2) B-cell, T-cell and leukocyte abnormalities.

(3) In US, first symptoms to diagnosis takes 9.2 years (average). There are approximately 50,000 patients with Immune Deficiency in the United States

iv. Innovative life-management programs

(1) 67% of patients take IVIG, usually every 3-4 weeks

(2) IV infusion pump takes 3-8 hrs; IV drip double that time
1. Adverse impact of designating pump "not medically necessary."
2. 64% have insurance coverage problems: e.g., denial, exceed life-time cap, delays for prior authorization, formularies.

3. Adverse impact of considering IVIG as a "drug" rather than biologic; "generic" requirement.

(3) Allowance fails to cover costs; providers can't lose money; reduces patient access to care.

e. Dr. Donna DiMichele (Medical and Scientific Advisory Council - MASAC - for the National Hemophilia Foundation) spoke about licensure issues for New Advances in Replacement Products for Rare Bleeding Disorders. (other than hemophilia).

i Available care for hemophilia is better than that for rare bleeding disorders
(1) Rare disease affects less than 200,000 in US.

(2) Hemophilia = 1:10,000; Others = 1:500,000-1 million

ii. For rare disorders, access to care depends on product availability and the expertise to use it properly.

(1) Available market can't support development costs, including cost for adding a label-approved use.

(2) e.g., Factor VII concentrates approved to treat hemophilia with inhibitors, but not Factor VII deficiency.

(3) Licensure required for reimbursement would mean equal access
(4) Few patients for well designed clinical trials.

iii. Coalition of organizations concerned about affected patients, including working groups of the International Society of Thrombosis and Hemostasis and the World Federation for Hemophilia. (National Organization of Rare Disorders to be invited).

(1) Add licensed indications

(2) Harmonize license requirements and encourage "reciprocity"
(1)

(3) Develop new products to fill voids

(4) What data will be required to support these changes

iv Discussion: The FDA reacts to applications for licensure and labeling changes, and finds it difficult to be proactive. No applications pertinent to candidate products have been received by the FDA. FDA has an open mind about solving these problems and there is nothing in US law that

prohibits using data collected outside the US. It is necessary that the studies have acceptable experimental designs and appropriate controls on data collection. Interested parties should enter discussions with FDA. FDA will do what is scientifically sound, practical and reasonable. Dr. Bianco asked about government support for product development. Dr. Nemo pointed out the NHLBI is happy to meet with investigators or groups that have concepts for study and/or product development. Mr Healy recommended that CMS be included in discussions because of the importance of reimbursement to the viability of these products.

f. Public Comments: Ms Miriam O'Day (Alpha-1 Foundation) reported that her patient group has similar problems with product availability, reimbursement and access.

g. Mr David Cavenaugh's group (Committee of Ten Thousand) is concerned that the last remaining trial of gene therapy for hemophilia has been terminated. They are concerned about new infectious disease threats in plasma-derived therapies, currently variant-CJD (vCJD).

h. Other speakers spoke to the issues of reimbursement and co-pay requirements including Ms Anne Rogers (Delaware Valley Chapter and the US Chapters, National Hemophilia Foundation), Mr. Jim Romano (Hemophilia Federation of America), and Ms Sue Stringer (Mother of a 21 year old with hemophilia, whose medications cost half a million dollars per year). The burden of the 20% co-pay for hemophilia treatment was revisited toward the end of the meeting. I was suggested that the reimbursement issue for plasma-derived therapeutics and their recombinant counterparts, including patient co-pay requirements was complicated and deserved more discussion. It was referred to the Subcommittee on Reimbursement for revue and return to the Committee for possible action.

11. **Follow up on Impact and Assessment of Risk of Bacterial Contamination of Platelet Products:**

a. Jaaroslav Vostal, MD (FDA) provided FDA's current thinking on the potential design of a field study of bacterial detection in platelet products.

i Current Status

(1) Two automated bacterial detection systems approved for QC.

(2) AABB Standard 5.1.5.1 requires every unit to be Quality Control tested (100% QC)

(a Culture-based systems limited to apheresis units.

(b) Whole blood-derived platelet tests for pH/glucose by dipstick.

(c) Methods are not standardized; pH/glucose dipsticks specificity and sensitivity questionable.

ii. Improvements wanted

(1) Standardization of culture systems

(2) Application of standardized, validated procedures for Whole Blood Derived Platelets (WBDP).

(3) Allow pre-storage pooling and extended storage (from 5 to 7 days)

(4) Validate culture (or other) technology to support "release test" claim.

(5) Field test for this purpose would be large and expensive.

(6) Experimental designs under discussion.

b Steven Kleinman, MD, presented a status update from the AABB's Task Force on the detection of bacterial contamination of platelet.

i Purposes of the Task Force to serve as focal point for all issues related the AABB bacterial detection standard that was effective March 2004.

ii. Three years ago, three million WBDP concentrates at 6/dose = 500,000 doses.

iii. One million apheresis-derived platelets (1-3 transfusable doses each) Increasing apheresis platelet use accelerated by culture requirement.

iv. Since implementation of standard, no severe shortages, but some reduced availability.

(1) Reduced use of WB-platelets to supplement Apheresis platelets when demand fluctuates.

(2) Permitting pre-storage pooling would facilitate bacterial testing and allow extension of storage to 7 days and enhance availability.

v. Requirement for a clinical trial will delay these enhancements for 1-2 yrs or more.

(1) Some disagreement about the need for a clinical trial vs analytical (spiking) studies.

(2) Other countries have pooled WBDP before storage and stored them for up to 5 days. Cultures on the pools have been a pre-release criterion. Nearly all countries harvest platelets using a buffy coat technic and wind up with a leukocyte-reduced product; the US uses a platelet-rich plasma procedure and leukoreduction adds a step and cost. There are differences in the resulting platelet concentrates, but it not known if these differences are crucial to prolonged storage or to bacterial detection.

(3) If Buffy Coat (BC) platelets are equivalent to PRP-platelets or if the differences do not affect storage or bacterial detection, then much of the data obtained outside the US could be available to support approval for bacterial detection and longer storage.

(4) Absent data supporting equivalence of the two technics, switching to the BC-platelet procedure could allow the use of non-US data to support bacterial detection and longer storage. This is likely to be complicated.

(5) FDA needs data and a request for licensure before it can act. Preliminary meetings between sponsor and FDA are often useful in defining what needs to be submitted.

vi. This study falls within the mission of the NHLBI (Dr. Nemo), but the Institute needs a project and a principle investigator; preliminary meeting(s) are often very helpful and are encouraged. When supporting research about commercial products, NHLBI generally expects participation by the companies involved. Without them, the Institute might find it difficult to provide funds.

vii. DOD does not have a requirement to ship platelets to a war zone (Iraq), but is interested in avoiding bacterial contamination and extending the shelf-life of platelets.

viii. Homeland Security has not been approached for funding; nothing is likely to be available until FY95 (Lipton).

c. Ms. Nancy Heddle (McMaster University) reported a randomized block-design non-inferiority trial of whole blood-derived platelets prepared from platelet-rich plasma (WB-plts) performed in Canada on thrombocytopenic patients. Patients were randomized to receive pre-storage pooled or time-of-use pooled WB-plts that had been stored for 5 days after collection. Platelet concentrates were leuko-

reduced at the source when they were prepared. The end point was the 18-24 hr corrected count increment (CCI); patient charts were reviewed to detect reactions and changes (decrease) in amount of bleeding.

i. Block design: Every 2 transfusions formed a block. Patients were randomized to receive pre-storage pooled platelets or day-of-transfusion pooled platelets first; the alternate product was administered when the next transfusion was needed. Incomplete blocks were not included in the analysis.

ii. 23 patients, 85 complete blocks (calculated needed sample size = 73) The

iii. CCI of pre-storage pooled platelets was not inferior to that of platelets pooled shortly before being administered.

d. Committee discussion on the topic (Dr Brecher noted his potential conflict of interest and turned the Chair over to Mr. Skinner):

i. Different experimental design than contemplated by FDA. FDA has also considered double label studies in which the comparison products are labeled with different isotopes and then given together, so that each patient is his own control. This study did not specifically investigate alloimmunization, although the design has such adverse events apply equally to both arms. (Dr Epstein and others pointed out later that including patients with a CCI $\leq$ 4.5 in the analysis biases the interpretation; censoring reduces the numbers and negates the ability of the study to demonstrate non-inferiority) Study was done because European data on BC-platelets might not pertain to PRP-platelets and it was important to find this out.

ii. Dr Lopes asked if the process of approval for pre-storage pooling and for 7 day storage could be speeded up and if European data could be used in support. Dr Sandler framed the issue as pre-storage pooled 7 day platelets or nothing (he had previously reported the non-availability of platelets in the Washington area in the last day or so). He sought common ground between that situation and a 2-year delay and a large expenditure. Dr Sayers pointed out a need to “rescue” whole blood-derived platelets to provide inventory flexibility. There appears to be some limit on the capability to recruit apheresis donors to cover all platelet needs.

iii. Dr Penner asked if safety or efficacy of 7-day vs 5-day were issues. Dr. Brecher (expressing an opinion) pointed out that bags from 2 manufacturers had been approved as efficacious by FDA for 7 day storage. Severe reactions and fatalities come from contamination with Gram negative bacteria, most of which grow quite rapidly and would be detected by an early culture. Dr Penner suggested that 7-day platelet outdating be

accepted and that we proceed, recognizing the information indicating the lack of significance of risk factors.

iv. Dr Klein commented that WBDP were being tested by methods that, in his opinion and supported by data, are useless. On the other hand, apheresis platelets were being tested by approved procedures.

v. Dr Kuehnert decried the lack of commercial interest in supporting studies that were. Considerable data are now being collected, but in non-standard fashion, making interpretation difficult. He recommended including the relative risks of different bacteria in planning. For example, P. acnes poses little risk, while some Gram negative bacteria present incredible risk.

vi. Dr. Heaton worried that harvesting platelets with the buffy coat technique might compromise the quality of red cells: whole blood is held for 12-24 hours before the buffy coat with about 30 ml of red cells is harvested and used to obtain a platelet concentrate. Buffy coat platelets survive better in the circulation than to platelet-rich plasma derived platelets and are a better product. The FDA proposed trial is very expensive (probably $10-11 M) for 1.5-2.0 M doses per year. The first manufacturer has little incentive to support such a trial if a second, etc, firm can spend $200,000 plus for their product to be approved. He suggested that Federal funds be used for the trial.

(1) There is no SOP for culturing platelets.

(2) Variables include need for both aerobic and anaerobic cultures, time of sampling after collection or preparation, volume to be cultured.

12. **Public Health Impact of Implementing HBV Minipool NAT**

a. Miriam Alter, PhD (CDC) discussed the Epidemiology of hepatitis B virus (HBV) and Programs on Prevention.

i. Clinical features:

(1) Acute illness (jaundice): <5 yrs old - 10%; ≥ 5 yrs old - 30-50%

(2) Case fatality rate - 0.5-1%

(3) Chronic infection: <5 yrs old - 30-90%; ≥ 5 yrs old - 2-6%

(4) Chronic hepatitis - 66%; Premature mortality from chronic liver disease - 15-25%

ii. Screening and diagnostic markers

(1) Serological markers: HbsAg and anti-HBs; Anti-HBc (HbcAg only in liver, does not circulate and there are no tests); HbeAg and anti-HBe

(2) Presence of HbsAg is indicative of viremia; disappears with complete recovery; remains detectable with chronic infection.

(3) Anti-HBc (IgM) appears after HbsAg and remains detectable indefinitely (IgG after 6 mos). Isolated anti-HBc antibody may mean infection (HBV NAT positive in 10%) or false positive.

(4) Nucleic acid - HBV DNA precedes appearance of HbsAg, but serum levels are low; remains detectable (sometimes barely so) with chronic infection.

iii. Epidemiology

(1) 73,000 new infections per year (2003); 21,000 clinically ill (jaundice); 300 deaths; and 4,400 with chronic infection.

(2) Blood borne, sexually transmitted (percutaneous and mucous membranes).

(3) Risk factors: IV drug use, high risk sexual activity (unprotected with infected partner, multiple partners or men having sex with men). Perinatal infection is no longer an issue in US with screening, vaccination and immunotherapy.

(4) Post-transfusion hepatitis B is too rare to be measurable.

(5) No cases in Sentinel County study since 1998.

(6) Vaccine preventable: Licensed 1981; available 1982.

iv. Progress in Prevention

(1) 2003: 90% ages 19-35 months vaccinated; 60% ages 13-15 yrs vaccinated.

(2) Good infrastructure coverage and evidence-based guidelines; established

(3) High-risk adults vaccinated:

(1) Health care workers, public safety workers - 70-80%

(2) Drug users, male-male sex, STD clients, inmates - <10%

(4) Natural immunity: Adults 30-60 yrs: Caucasian approximately -4%, African American 15%, Asians 60-80%.

(5) Inadequate infrastructure; Vaccination low priority

b. Discussion: Disease reporting is a state requirement and voluntarily report to CDC. Clinical hepatitis B is reportable in all states, and positive HbsAg is reportable in most. Nevertheless, under-reporting is a problem (Alter and Linden). In the minipool NAT trials, 2 of the yield cases (positive NAT, negative for HbsAg) were in vaccinated individuals, "breakthrough" infections (Busch). This phenomenon is rare in vaccinated individuals and unlikely to be a problem in blood donors (Alter).

c. Paul Holland, MD reported on "Hepatitis B Virus Nucleic Acid Amplification Technology: Potential Uses in a Blood Center.

i. Potential of NAT

(1) Identify infectious donors during infectious part of seronegative "window"

(2) Identify donations from low level carriers.

(3) Re-enter donors with false positive serological tests.

(4) 5 US sites tested 704,902 donations using PCR-based NAT in pools of 24.

(5) 23 DNA only positive

(6) 9 probably falsely positives (follow-up limited)

(7) 2 confirmed "Window" period donations

(8) 12 false positives

(9) Yield for HBV (1:330,000) ≅that for HCV NAT testing.

ii. Discussion: In response to Dr. Angelbeck, Dr Holland reaffirmed that 10% of patients older than 60 yrs who contracted post-transfusion hepatitis B died.

d. Gerardo Kaplan, MD (FDA) reviewed the BPAC Discussion and FDA' Current Thinking on HBV Minipool NAT.

i. Application to FDA to license a nucleic acid test (NAT) for HBV for screening blood donations in pools of 24 (Mini-pool NAT - MP-NAT)(Roche COBAS AmpliScreen HBV test. Another NAT for HBV is under development).

ii. Claim: COBAS AmpliScreen in conjunction with anti-Hbc will reduce the residual risk of transfusion-transmitted HBV. FDA is currently evaluating if it can be an alternative to tests for HbsAg an if approved, should FDA recommend its use?

iii. Residual risk after serological tests (current): 1:180,000. With pooled NAT: 1:210,000. With single unit NAT: 1:410,000

iv. 581,790 donations tested: 23 DNA pos only; 21 false pos, 2 true pos (window period):

(1) 16 HbsAg pos, anti-HBc pos, MP NAT negative: 12 were positive by individual-donor NAT (ID-NAT) and 3 had 900-1200 copies per ml (quantitative NAT).

(2) Anti-HBc screening cannot be dropped now.

(3) Two probably infectious donors were detected by MP-NAT, but not by current serological tests.

(4) BPAC Questions:

(a) Do the sensitivity and specificity of the Roche COBAS AmpliScreen test in minipools of 24 samples support licensing of the assay as a donor screen? Yes - 15, No - 1, Abstentions 0.

(b) Assuming continued use of screening tests for anti-HBc, do the data support use of the Roche COBAS AmpliScreen HBV test in minipools of 24 samples to screen blood for transfusion as an equivalent alternative to the HbsAg test? No - 16, Yes - 0, Abstentions - 0

(c) If the data do not support use of the Roche COBAS AmpliScreen HBV testing minipools of 24 samples as an equivalent alternative to HbsAg to screen blood for transfusion, what additional data would be required to validate such use?

(i) Committee members emphasized the need for additional data from clinical studies due to the small number of critical samples in the Roche study.

(ii) It was suggested that ID NAT would be a better replacement for HbsAg than MP NAT.

(iii) Do the data support use of the Roche COBAS AmpliScreen HBV test on minipools of 24 samples to screen blood for transfusion as an added test in conjunction with licensed donor screening tests for HbsAg and anti-HBc?

1) The Committee declined to vote on this question

Comments included:.

a. Whereas the test may identify some additional HBV positive donations, the public health benefits of routine additive testing

are unclear.

b. If practical technology were developed, ID NAT for HBV would provide a greater benefit to blood safety than MP NAT.
c. Useful studies of HBV NAT can be done in high risk groups as well as blood donors.

(5) If FDA were to approve Roche AmpliScreen HBV test on minipools of 24 blood donor samples, the following policy option may need to be considered.

(a) Recommend routine use in conjunction with licensed HbsAg and anti-HBc

(i) Pro: adds a third test to marginally increase safety; implementation date could be set to permit development of alternate HBV NAT tests compatible with non-Roche systems

(ii) Con: imposes added costs and increases complexity; creates logistic problems for the majority of blood centers that do not presently use the Roche assay system.

(b) State that implementation of the Roche AmpliScreen HBV test is voluntary, but reserve the option for a future recommendation on routine use of HBV NAT on minipools of donor samples.

(i) Pro: Allow local decisions on test value

(ii) Con: Most likely lead to implementation of minipool NAT only in a number of blood collection establishments that currently use the Roche system for HIV and HCV NAT. Create a public perception of 2 tiers of blood safety.

(c) Regard all uses of HBV NAT on minipools as voluntary, but also encourage manufacturers to develop automated, high throughput systems to permit HBV NAT on individual donor samples.

(i) Pro: Same benefits as option b) (above) but creates an added expectation for development of a technology that FDA would be likely to recommend.

(ii) Con: Same as in option b)

e. Michael Busch MD, PhD (Blood Centers of the Pacific, Blood Systems, Inc) discussed the Yield and Cost-effectiveness of HBV DNA Screening of US Blood Donors using Minipool (MP) or Individual Donation (ID) NAT.

i. Window period reductions and yield over presently licensed tests

<u>Yield per 10 M donations</u>

Investigational HbsAg	2-9 days	3-13
Pooled sample NAT	9-11	13-15
Individual donation NAT	25-36	35-50

ii. Japan - anti-HBc and MP NAT (pools of 50, recently reduced to 10)

(1) HbsAg procedure is a particle assay that is insensitive compared to current US assays.

(2) Ten million total units screened; 181 MP NAT (50) positive, HbsAg negative (58% were positive by the currently most sensitive, investigational HbsAg test - Prism)

iii. Germany - do not test for anti-HBc, but use Prism (most sensitive HbsAg assay at present; not available in US); 20 M units screened; 42 NAT-only positive units (2/3 were anti-HBc positive)

(1) "True" yield after Prism HbsAg and anti-HBc testing = 15 in 20M

(2) Infections avoided (quality life years gained) with SD NAT compared with present testing

(3) HIV - 6.9 infections avoided (49 QALY gained); HCV - 59 (35) and HBV 37 (6)

(4) 23% of the yield for HBV SD NAT would be achieved with MP NAT

(5) Implementing MP HBV NAT would not provide sufficient sensitivity to permit dropping either HbsAg or anti-HBc testing.

(6) Data should be collected to determine if implementing ID NAT would permit dropping HbsAg testing (thinks it likely; clarified to be in the context of continued anti-HBc testing).

f. Public Comment: Sue Stramer, PhD (AABB, ABC and ARC) addressed the questions posed to the BRAAAC.

(1) Is Roche minipool HBV NAT test approvable for blood screening? It may be approvable in the currently proposed minipool context, but its efficacy should be greater if it were applied to individual donations or to significantly smaller pools may be approvable in the currently proposed minipool NAT context, but its efficacy should be greater if it were applied to individual donations or significantly smaller minipools.

(2) If approvable, should it be required? Offers only a minuscule reduction in risk over present testing for HbsAg and anti-HBc

(3) Should a claim for minipool NAT to replace HbsAg be granted? Current data are not robust enough to support elimination of either HbsAg or anti-HBc markers

g. Committee discussion:

i. Dr Holmberg posed a question for the Committee from Dr. Beato (aASH): What is the public impact of implementing HBV minipool NAT for blood donor screening?

(1) Dr Sandler pointed out that there were no vaccines for HIV and HCV, so the only protection against transfusion transmission is blood donation screening. For HBV, there is an effective vaccine; the general public should be encouraged to protect themselves against this virus by getting immunized. That would do more for public health than HBV minipool NAT tests. Dr. Brecher raised the possibility of vaccinating donors.

(2) Dr Alter said that well founded public health vaccination policy focuses on higher risk groups before such a low risk group as blood donors. Putting resources into vaccinating low-risk blood donors might result in pulling resources away from more vaccinations for high risk individuals.

(3) Dr Sandler suggested that the massive general public vaccination he was considering would have to be prioritized, with higher risk individuals first, gradually enlarging the catchment.

(4) Public health would be better served by expanding CDC's vaccination program than by adding HBV minipool NAT to blood donation screening.

(5) With current blood screening, blood recipients, even those given multiple transfusions, are not currently considered high risk. Perhaps CDC's immunization advisory committee should visit this issue.

ii. Dr Stramer indicated that AABB, ABC and ARC opposition to minipool HBV NAT testing would need reevaluation when ID NAT testing because feasible.

iii. Dr. Epstein suggested that the question was one of cost/benefit. BPAC did not address that issue and FDA is meant to focus on science and not deal with relative cost and benefit issues. Ms Lipton noted that ID NAT testing for HBV was coming and the cost-benefit equation might be quite different then.

iv. Dr Sandler made a plea that tests and procedure that incur incremental costs should be defrayed as they are incurred, not after several years, as is needed for DRGs to change.

The meeting was adjourned at 4:35 PM, August 27, 2004.

Recommendations to the Secretary
Based on Discussion of the August 26-27, 2004 meeting

Recommendation 1: Transfusion Related Acute Lung Injury (TRALI)

The Committee reviewed the transfusion related acute lung injury (TRALI) data and did not find scientific evidence to recommend an intervention at this time. The Committee recommends that the Secretary support:

- the expeditious development of a standardized definition,
- implementation of clinician education and effective surveillance,
- modeling the impact of deferral or screening intervention, and
- research into the etiology, diagnostic testing, epidemiology, treatment and prevention.

Voting:
16 in favor, 0 against (August 26, 2004)
Amended on August 27, 2004 to remove "available," "sufficient," and "specific"
9 in favor, 0 against, 1 abstention

Recommendation 2: Access to Treatment for Individuals with Rare Blood Disorders

Whereas, the Department of Health and Human Services' (DHHS) Advisory Committee on Blood Safety and Availability recognizes the lack of licensed treatments for individuals with rare blood disorders (e.g. Factors V, VII, XI, XIII and Protein C deficiencies) presents a significant health risk and a discrepant therapeutic standard from that for persons with some other blood disorders such as hemophilia; and,

The Committee notes importation for personal use and off-label use are not adequate long-term solutions or acceptable alternatives; and,

The Committee concurs that there is a need to promote the development and licensure of treatment products for these individuals; and,

It may be appropriate to adopt flexible approaches to validating therapies for rare blood disorders.

The Committee recommends that DHHS promote the development of products to treat individuals with rare blood disorders including facilitating:

1) Obtaining additional licensed indications for already licensed products; and,

2) Approval of products and their indications in the United States for European licensed products; and,
3) Developing new products.

The Committee also recognizes the importance for industry, investigators and regulators to cooperate in both pre and post market approval of potential new therapies and indications.

The Committee encourages the government to invest in research and to support adequate reimbursement to optimize treatment for rare blood disorders.

Voting on August 27: 16 in favor,0 against,1 abstention

Recommendation 3: Bacterial Detection in Platelet Concentrates and Seven Day Platelets

Whereas;

- Consistent with previous recommendations of the Committee, the Advisory Committee on Blood Safety and Availability has concluded that bacterial contamination of room temperature stored platelet components represents one of the most significant remaining infectious risks of blood transfusion; and,

- The transfusion medicine community has adopted a voluntary standard that requires the implementation of methods to limit and detect bacterial contamination in all platelet components; and,

- There is now inconsistent practice in the application of currently available bacterial screening tests and the Committee recognizes that public health would be improved by the availability of a release test approved for this purpose; and,

- Given the current inadequate supply of platelets, the Committee recognizes the need for seven day storage of platelets to meet patient needs; and,

- The currently proposed study of bacterial screening for release control of 7-day stored platelets would take at least two years to complete.

- The Committee recommends to the Secretary of Department of Health and Human Services that:

- The Department supports the use of grant or contract funding that would allow availability of funds to support applications to develop bacterial screening suitable for release testing of platelets for use in routine practice.

- The Department considers alternative strategies that could expedite licensure of seven day platelets in significantly less than two years.

Whereas, the Committee has heard evidence that:

1)
most apheresis platelets are currently tested by an approved quality control method to detect contamination by bacteria,

2) 2. individual whole blood derived platelets (WBDP) are not and can not be similarly tested by a practical validated assay for bacterial contamination,

3) this situation has resulted in a dual level of safety for platelets prepared for transfusion, and

4) a threat to platelet supply has developed as the inventory of WBDP declines.

Given the availability of;

5) In vitro data supporting the acceptable quality of pre-storage pooled WBDP.

6) European data supporting the clinical safety and efficacy of pre-storage pooled whole blood derived buffy coat platelets.

7) The data from the McMaster study of the clinical safety and efficacy of pre-storage pooled WBDP.

The Committee urges Department of Health and Human Services to adopt strategies to expedite licensure of a pre-storage pooled WBDP component for transfusion based on a critical review of the available information.

Voting on August 27, 15 in favor, 0 against, 2 in abstention

Recommendation #4: Public Health Impact of Implementing HBV Minipool NAT for Blood Donor Testing

Whereas, the hepatitis B virus (HBV) risk from transfusion now exceeds that from human immunodeficiency virus (HIV) and hepatitis C virus (HCV); and,

- HBV mini-pool nucleic acid testing (MP NAT) as currently configured has limited ability to reduce risk of transfusion transmitted HBV compared with individual donor (ID) NAT technology that is under development; and,

- The average morbidity of HBV infection is significantly less than that of HIV and HCV, but donor screening by MP NAT would incur a cost comparable to other NAT tests; and,

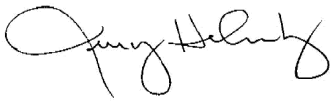
- Vaccination is an effective prevention strategy for HBV unlike HIV and HCV.

In regard to the introduction of mini-pool (as currently conceived) HBV NAT for blood donations, the Committee believes that for comparable expenditures of health care dollars the general public health would be better served by expanding the hepatitis B immunization program.

The Committee believes the Secretary should encourage the development of multiplex direct pathogen testing on individual donations.

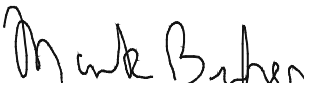
Voting on August 27, 9 in favor, 0 against,1 in abstention

Submitted by:



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

Certified by:



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