Advisory Committee on Blood Safety and Availability
Department of Health and Human Services
25th Meeting Minutes
January 25-26, 2005

The meeting was called to order at 9:05 AM after a closed session on ethical principles governing the Committee. Executive Secretary, Dr. Jerry Holmberg reported that outgoing Secretary Thompson did not sign appointing letters for new Committee members. Therefore, in accordance with the Charter, retiring members were asked to rejoin for this meeting.

I. Administrative
   a. Roll Call: Dr. Gomperts, former Committee member was asked to remain on the Committee, making a quorum, which enabled the Committee to conduct its business
   b. Minutes were posted on the web site. No corrections were made to the posted minutes.
   c. Charter
      i. The new Committee charter has been posted on the web, and Dr. Holmberg highlighted a few of the changes.
         1. The make-up of the Committee was made less prescriptive.
         2. Funding sources were expanded to include CMS as well as NIH, FDA and CDC
         3. Retiring Committee members after September 30, 2005 were listed (Drs Angelbeck, Bianco, Brecher, Haas, Heaton, Linden, Sandler, and Sayers, and Mr.s Healey and Skinner) and a request made for nominations for their replacements. A Federal Register notice to this effect is expected in May and nominations will close in June.
   d. **Recommendations the Committee made at its last meeting** (August 2004) and the Secretary's response were reviewed by Dr. Brecher.
      i. These recommendations concerned TRALI (transfusion-related acute lung injury), accelerated development and approval for therapies for rare bleeding disorders and rapid approval for platelet storage up to 7 days to help cope with delivery delays from the need for bacterial detection in concentrates (this included approval for pre-storage pooling). The Committee recommended funding expanded hepatitis B immunization programs as more cost-effective than encouraging mini-pool NAT for blood for transfusion.
      ii. Secretary Thompson's response was distributed at the meeting, as it had been unavailable in time to go out with the briefing packet. He accepted the recommendations and said that they were in various stages of moving toward implementation.

II. Follow-Up on previous Committee Discussion and Recommendations:

a. **Dr Traci Mondoro (NHLBI)** noted that investigator-initiated research projects are always welcome, including those relating to **TRALI**. Investigators are encouraged to discuss their project with the NHLBI in advance of submission to help ensure the best proposals and the most appropriate reviews. In addition, there are two initiatives with set aside funds that have developed TRALI-related proposals: REDS-II and a SCCOR programs (Specialized Centers of Clinical Research). A third is being prepared for presentation to the Board of Extramural Advisors. In 2002, the NHLBI convened a working group for TRALI issues, including developing a clear definition. The product of this group is in press in the journal, *Critical Care Medicine*, and formed a basis for a Canadian conference on TRALI in 2004. These activities in the Blood Division of NHLBI are being coordinated with the Lung Division, which also has an interest in supporting research in acute lung injury.

b. **Dr. Paul Mied (FDA)** described the **Critical Pathways Initiatives** for the review and approval of therapies as they progress from inception through basic, applied and clinical trial research. The purpose is to maximize the efficiency of the process. Major steps include safety assessment, proof of efficacy and the management of industrialization or scale up to manufacture and distribute the drug to appropriate users. It is a challenge to enhance safety, purity and potency while avoiding shortages and major unneeded increases in cost. He reported recommendations of a workshop on therapy development. These include setting standards and objectives for approval, using preexisting data, finding alternative measures for validating findings and providing more guidance on the structure of clinical trials. There was discussion that FDA should encourage technology development for areas where market forces might be limited. The discussion emphasized the importance of this initiative.

c. **Dr. Mark Weinstein (FDA)** reported a planned workshop (June 13-14, Lister Hill Auditorium on the NIH campus) as follow-up to an Advisory Committee recommendation to promote the **development of products to treat rare bleeding disorders**. Examples include deficiencies of factors V, XI and fibrinogen. This is expected to help with clinical trial design and improve harmonization with Europe and other major medical markets in the world. There may be a need for global patient directories and continuing post-market surveillance.

d. **Mr. Hal Baker (Senior Vice President Pall Biomedical)** reported on increased **hemolysis from using the Pall BPF4 leukoreduction filter**. Of the 14 million units of blood collected annually in the US, 75% are filtered prior to storage to remove leukocytes, one third of them using the BPF4 filter.

    i. In December 2004, several US centers reported hemolysis in a limited number of units so filtered. There were no patient-adverse events associated and the episodes have not recurred. Despite the

limited recall (24 lots), the supply of filters was not compromised, nor was the ability to provide leukopoor blood.

ii. A working hypothesis was developed that variable wetting during filter priming changed the effective filter area and the subsequent increased flow-rate lysed red cells with an increased shear rate. Older red cells may be more fragile. Pall kept the blood banking community informed and equipped their field staff with point-of-care hemoglobinometers (HemaCue) to help define "excess hemolysis." Although the filters had been used at any point in the 42 day storage period for red cells, Pall now recommends that blood be leukoreduced within 5 days of collection.

iii. They recommend that the AABB Standards Committee define "excess hemolysis" in stored red cells and determine how it might best be handled. Current visual inspection may not be adequate.

iv. Committee Discussion:

1. Dr. Heaton recommended that this be treated as an international problem and that the BEST Committee (International Society of Blood Transfusion) be the proper forum.
2. Dr. Sandler said that the increased plasma hemoglobin was considerably less important that the extracellular potassium level in the blood to be transfused, especially if it were to be large quantities for a child.
3. Dr. Heaton added that complement activation by red cell fragments could be a serious problem.
4. In response to a query from Dr Kuehnert, Mr. Baker said that their communications have been with blood centers, relying on them to provide information for clinicians via hospital transfusion services.
5. Dr. Bianco thanked Mr Baker for the information, but expressed concern that Pall did not send a scientist who could discuss the studies and the data that were being used to define the problem and lead to preventative measures for the future.

III. **Current Status of Bacterial Detection in Platelet Concentrates, Availability and Progress toward Seven Day Platelets**

a. Dr. Brecher recused himself as Chairman, yielding to Mr. Skinner.

b. **Ms Marianne Silva (Chairperson, 23rd Edition, AABB Standards and Member, Bacterial Contamination Task Force)** reported a platelet use and availability survey conducted in the Fall 2004. Surveyed were use, supply and availability of platelets, bacterial detection methods used, follow-up of positive results, procedures for notifying physicians and donors about positive results, the rates of initial and confirmed positives and the overall impact on quality assurance activities. Nine hundred surveys were distributed; 350 were returned, 38%. This included 33 blood centers plus one collective response each from Red Cross and Blood

Systems each submitted one collective response (33 additional centers, so that more than 50% of the US collections are represented. There were 47 hospital blood banks (collect, process and transfuse) and 262 transfusion services in the sample. From Survey data (2003) and the most recent National Blood Data Resource Center (NBDRC – AABB), the sample represents about 44% of the national production of whole blood-derived platelet concentrates (WBDPC) and 66% of apheresis platelets.

i. Platelet Production (From Survey)

	WBDPC	Apheresis Platelets
May – Aug 2003	166012	93478
May – Aug 2004	147273	98753

ii. After initiating platelet bacteriological testing, 91% of blood centers, 64% of hospital blood banks and 68% of transfusion services reported no difference in their ability to provide platelets for transfusion. The length of time that a platelet unit was available for transfusion was decreased. Most made no changes in inventory management procedures, but a number of centers found that individual day (for most, 1-4 days per month) presented greater challenges and stimulated some managerial changes.

iii. Many institutions reported no changes in outdating, but some found an increase (Table).

Platelet outdating

	Blood Centers	Hosp Blood Banks	Transfusion Serv
No change, pre-post	66%	68%	66%
1-5% increase	17	11	11
6-10% increase	6	2	4
10-15% increase	0	2	1
16-20% increase	0	6	4
Unknown	11	11	9

iv. The site of outdating is governed in part by the return credit policy of the supplying source. Blood centers that don't accept returns for credit won't outdate many, although their hospital customers may. Anecdotally, some transfusion services stopped inventorying platelets on site, ordering them as they had individual patient needs; a change in practice caused by the bacteriological testing standard. The establishment of the bacterial contamination standard may have accelerated the trend away from WBDPC to apheresis platelets, but the trend had been under way for several years.

v. Nearly all (88%) blood centers cultured platelets after a 24 hour hold (usually BacT/Alert). Four (of 34) tested glucose and/or pH

by dipstick (occasionally using meters) and one made a "visual check." Blood centers that cultured held the cultures for 5-7 days; 85% (27) only did aerobic cultures; 15% did both aerobic and anaerobic cultures. Eight of 10 hospital blood banks cultured platelets if their supplier did not; 38 of 43 cultured platelets harvested in-house. About half of the hospital blood banks did both aerobic and anaerobic cultures; the remainder used aerobic bottles only. A few transfusion services cultured platelets; most used glucose, pH or Gram stain for detecting bacteria.

vi. In blood centers, 1:930 platelet cultures (n = 429,827) were initially positive; true positives were 1:4,723. For hospital blood banks, initial positives were 1:328 (45,531) with 1:1686 true positives. For non-culture techniques, initial positives were 1:158-244; true positives were 0 – 1:17,986. The cut-off values for non-culture techniques was quite variable, one facility to another. Correlations were very difficult. When a non-culture technique was positive (WBDPC), the unit was usually discarded with no further follow-up except for the confirmatory culture. When possible, co-components were quarantined and not used. If a confirmed positive was detected after transfusion, all facilities instituted recipient follow-up. Donor management depended on the organism involved. Most emphasized training for the test procedure and the sampling protocol; very few investigated the source of bacteria detected (e.g., arm prep, venipuncture technique).

vii. Pertinent AABB Association Bulletins are: 02-08 (12/10/02), 03-10 (8/29/03, provided implementation trigger), 03-12 (10/1/03) and 04-07 (10/1/04). Bulletin 05-XX was issued yesterday (1/24/05).

viii. Committee Discussion:

1. Dr. Epstein observed that non-culture techniques seemed to be inferior as to sensitivity and specificity. Ms. Silva responded that it might help if the non-culture techniques were standardized.
2. Dr. Heaton asked if centers performing the most expeditious screening procedure suffered less outdates; Ms Silva reported that the survey instrument did not permit correlation between parts or questions.
3. Dr. Sandler reinterpreted some of the data that 36% of hospitals reported that patients were "at risk" of hemorrhage because of lack of platelets.
4. Dr. Kuehnert complemented the survey, but suggested that it would be important to resurvey from time to time to note changes. The apparent higher frequency of positive cultures at hospital blood banks may relate to the volume cultured; when both anaerobic and aerobic cultures are

done, the effective sample size is double that when only one bottle is used.

c. **Dr. Arjun Srinivasan (CDC)** said a "handful" of infected units escaped detection and came to CDC's attention. He described 3 of these in detail. The first 2 were elderly patients, one with leukemia and the other transfused immediately after by-pass surgery. The first received a pool of contaminated whole-blood-derived platelet units screened with dipsticks as pass/fail at ph 6.4. The post-bypass transfusion used an apheresis unit, screened by culture after a 24 hour hold, and stored for 5 days prior to administration. The BacTAlert culture (4 ml) was still negative at 5 days. The 3rd patient was a premature infant given 2 doses, 24 hours apart, from an apheresis unit (3 and 4 days storage) that was screened by a solid agar culture (0.1 ml sample) after an initial 24 hour hold. Potential causes in these cases were clerical errors, post-sampling contamination as the units were manipulated, insufficient sensitivity of the testing systems.
    i. Statistically, 100 true positive platelet concentrates per year would be anticipated. Not only are these important for potential recipients, but they also might be helpful for donors. For example, one donor's platelets culture strep bovis; evaluation led to an unexpected colon cancer.
    ii. Committee Discussion:
        1. Dr. Brecher asked if any of the centers involved changed procedures as a result. The incidents are still under investigation and there have been no changes yet.
        2. Dr. Bianco asked if any of the organisms would be detected if the anaerobic bottle were also used. The answer was probably not, although culturing the added volume may enhance sensitivity (Dr. Brecher alluded to some data he planned to present later in the meeting).

d. **Dr. Jaroslav Vostal (FDA)** discussed FDA current considerations about detecting contaminated units and interdicting their transfusion, pre-storage pooling of whole blood derived platelets and extending permissible platelet storage from 5 to 7 days.
    i. Two apheresis platelet bags and 1 whole blood derived platelet bag have been approved for 7 day storage, but implementation depends on bacterial detection as a *release* test.
    ii. Three devices have been cleared for QC purposes (BioMerieux BacT/Alert, Pall eBDS and Hemosystem Scansystem).
    iii. Other non-approved, non-validated methods are being used to meet the AABB Standard (dipstick glucose and pH, visual swirling).
    iv. As *release* tests, the performance characteristics of these tests are unknown, none of the methods are standardized (including culture), and the potential for false positive or negative tests is not clear. The technology applied to whole-blood-derived platelets is less reliable than that used for apheresis units, leading to a 2-tiered

safety system. To validate a procedure as a *release* test, the FDA-AABB Bacterial Contamination Task Force proposed a study involving 50,000 units, tested after a standardized hold (12-24 hours) and retested after 7 days of storage. The logistics and funding of such a study posed insurmountable obstacles so that it won't be done. FDA has modified the requirements to approve 7 day platelet storage, provided already approved bags are used, a standardized procedure is developed and used and there is a commitment to post-market surveillance.

v. Pre-storage pooling could be approved if bacteriological testing had equivalent sensitivity to that being used for apheresis units. Validation must show that the test sensitivity is sufficient to overcome a dilution affect. Container validation for extended storage should include corrected counts in thrombocytopenic patients, comparing pre-storage units with post storage ones. Estimated sample size is about 50 patients per arm. Pre-storage pooled platelets are considered a new product, and new quality assurance standards are necessary.

e. **Dr. Mark Brecher (UNC, Chair, ACBSA) briefly reviewed the history of the AABB Platelet Contamination Task Force.** It was formed to address DHHS' concerns that premature implementation of the AABB Standard for preventing platelet transfusion-associated sepsis would result in compromising the availability of platelets for thrombocytopenic patients.

i. The group recommended that the question of using only the BacTAlert aerobic culture bottle or both that and the anaerobic bottle be separated from validating the culture technique for prolonged (up to 7 day) storage.

ii. Committee Discussion:

1. Dr. Epstein asked if doubling the volume cultured by using both bottles was important.
2. Dr. Brecher responded that it might help detect low levels of contamination, and was probably worth doubling the cost.

f. **Dr. Joseph Sweeney (Lifespan Blood Center and Brown University, Providence Rhode Island)** reported that the country-wide shift from whole blood-derived platelets to apheresis platelets has not happened in Rhode Island. There, 80% of platelet transfusions are whole blood-derived. The major advantage of apheresis products is HLA matching capability. In his center, he estimated that reduced donor exposure from using apheresis units might prevent 1 viral transmission in 15-20 years. All platelets in Rhode Island are leukoreduced and cultured pre-storage, so that bacterial contamination risks are equivalent. Since complying with the standard, the effective shelf life of platelets has been reduced and the outdating increased, especially at hospitals. Much of the outdating resulted from pools being ordered and prepared, but not used. In response

to a query from Dr. Sandler, he reported the hospital cost for an apheresis unit was $450-475; five whole blood-derived concentrates were about $400.

g. **Dr. Mark Brecher** then presented data to indicate that the BacTAlert aerobic plus anaerobic culture system would detect 10 bacterial CFU in a single whole blood-derived platelet unit after it had been diluted with 5 other sterile units. In a number of instances, the anaerobic bottle tested positive before the aerobic, even for bacteria that were aerobic. Dr. Sandler asked whether UNC would use apheresis platelets or whole blood-derived platelets if both were cultured according to his protocol. UNC converted to apheresis platelets some time ago and expects to continue with few or no whole blood-derived units.

h. **Dr. Stein Holme (Pall Biomedical)** reported the results of a field trial that form the basis for a planned (March 2005) submission to the FDA for approval of the eBDS culture system and previously approved bags for up to 7 day storage. Studies were done at 23 blood centers in the US and Canada, culturing 118,067 units, of which 118 "failed." There were 23 true positives, 76 false positives, 1 false negative (patient sepsis, bacteria in mother bag) and 18 unproved "false" positives. These figures are similar to those reported in multiple studies. He also presented a protocol for pre-storage pooling and a 5 day dating period. The pools were held for 24 hours prior to sampling. The submission will include post-market surveillance. Similar studies are planned for the hear future to extend storage to 7 days.

    i. Committee Discussion:

        1. Dr Klein said he was more comfortable now that suitable studies were under way that would lead to prestorage pooling of whole blood-derived platelets and extension of dating to 7 days.
        2. Several members emphasized the need for collecting data after the changes have been implemented and the importance of establishing a mechanism and accountability for summarizing and interpreting the data.

IV. Report from the Subcommittee on Reimbursement

a. After lunch, Dr. Mark Brecher re-assumed the chair and called upon Dr. Gerald Sandler for a report from the Subcommittee on Reimbursement. The Subcommittee met by conference call once (Nov 29) and recommended that they develop 2 lists for presentation to the Advisory Committee and ultimately to the Secretary:

    i. specific plasma therapies including the estimated numbers of patients, the number of treatment events per patient and the cost per treatment, all aggregated into expected annul costs;
    ii. a similar list of new products or procedures (e.g., hemoglobin-based oxygen carriers, pathogen inactivation, bar code or RFID identification systems, prevention of bacterial contamination of

platelets, additional infectious disease tests) with estimated annual costs.

iii. The group perceived that lack of "new money" in the past has been an impediment to the implementation of new safety measures.

b. **Dr. James Bowman, III (CMS)** summarized the 2005 payment rules for Part B. In 1984, the prospective payment system based upon DRGs was introduced for hospital in-patient care. Subsequently, the prospective payment system was extended so that only physician payments, as a class, are paid as fees for service (Part A – inpatient hospital; B – physician fees; C –"Medicare Advantage – managed care; and D – drugs). The prospective payment system was set up to foster innovation and the introduction of new technologies. Nevertheless, several therapies (blood products and whole blood in certain settings, plasma-derived products and clotting factors) have been "carved out" into a different payment system. For example, IVIG is covered in 4 settings: in-patient – DRG; outpatient – outpatient prospective payment system (OPPS); physicians' offices, part B; and, for primary immune deficiencies only, home infusions ("Plus"). Clotting factors have been billable with complicated calculations based on selling price plus 6% and wholesale acquisition costs.

   i. Allowable costs have been ratcheted down for 2005.
   ii. For 2006, competitive bidding will be introduced for some products, to be phased in beginning January 1.
   iii. Statutory exclusions from competitive bidding included blood and blood products, DME infusion drugs and certain vaccines.
   iv. In addition, the Secretary has some discretionary authority to exclude treatment classes if competitive bidding won't save money or will have an adverse affect on patient care.
   v. Committee Discussion:
      1. Dr. Epstein asked how quickly the system could adjust to new technologies, especially new blood standards. CMS has recognized this issue and is working on speeding the process within the existing statutes.
      2. Dr. Holmberg reported that the departing Secretary just signed a document addressing innovation. It has been posted on the Department's web site and discusses how different parts of HHS should work together to speed the introduction of innovative science.

c. Issues Facing the Core Plasma Therapies were presented by **Ms Elena Bostick** (Hemophilia Association of New Jersey).

   i. Payment sources for hemophilia care are 60% private (including insurance), 35% Medicaid and 8% Medicare. Health insurance is often unavailable or very expensive. NJ has a "guaranteed purchase" law requiring the sale of health care insurance to anyone who wants it, regardless of any pre-existing chronic condition. Insurance with $500 deductible costs $79,200 annually. Many insurance executives are paid more than $1 M per year and some

companies have amassed a large surplus (e.g., NJ Blue Cross has a $1 billion surplus). Some states have high risk pools for patients with chronic illnesses; Florida has such a pool, but has not accepted any new patients since 1991 because of costs involved. Many states' Medicaid programs have 20% co-pay requirements, but when the annual costs are $100,000-150,000, the co-pay of $20,000-30,000 is often unaffordable.

ii. Attempts to control costs by restricting product access (treatment products are not interchangeable) are not acceptable. Although few hemophilia patients are eligible for Medicare (high death rate from HIV and HCV infections), this Federal system is a leader in reimbursement policies often followed by private and Medicaid insurers.

d. **Dr. Richard Metz (Advocacy Chair, National Hemophilia Foundation** and parent of a patient with hemophilia A) reemphasized the points made by the previous speaker, adding examples from his personal and professional experience. He reported that on the day before the Advisory Committee meeting, a number of groups involved with hemophilia care met to devise some solutions to their financial and therapy problems. They decided to push for legislation to mandate 100% reimbursement for clotting factor costs, using as a model Medicare coverage for end-stage renal disease. Before going ahead, they plan to collect and analyze data on the effect of this on individual patient and in total costs.

e. **Ms Julie Birkhofer (Executive Director, North American Plasma Products Therapeutics Association)** presented their priorities for reimbursement. For 2005, a major question will be the affect of the average sale price plus 6% and will it be enough to sustain the market.

i. She requested CMS to clarify with carriers how these reimbursement issues should be handled for various therapies. The GAO is collecting data for use in setting 2006 rates. The effect of Part D (drugs) on reimbursement practices is unknown. The multiple unknowns make it difficult to plan from year to year.

ii. Various cost-containment strategies, mentioned by previous speakers, have different effects on various fragile, often "orphan" patient populations. PPTA is working with multiple organizations at the state and national level to get acceptable solutions for these multiple problems.

f. **Ms Michelle Vogel (Director, Government Affairs, Immune Deficiency Foundation)** reported that changes in reimbursement policies, January 1, 2005, wreaked havoc with the use of IVIG by many patients with primary immune deficiency. For example, payment for IVIG in hospitals was $80/gm, while in doctors' offices it was $40/gm. Medicare determined that hospital admission was not medically necessary. In many instances, the result was that patients had no place to go for their infusions and many delayed or discontinued therapy. CMS was very helpful in generating a "fix," but more permanent solutions are needed. There seems

to be little difference in the efficacy of different products (some patients disagree), there can be large differences in tolerability, based on osmolality, volume, pH, IgA content, sugar content and format (lyophilized or liquid). She recommended that because of these differences in tolerability, patients should have similar reimbursement policies to allow them access to any or all products on the market.

i. The IDF recommends: separate codes for each brand of IVIG; adjustments to provide similar reimbursements for lyophilized or liquid products; consider the distributor's role in providing products (few patients obtain them directly from the producer); increase the administration fee (similar to that used for the chemotherapy administration code); and cover IVIG administration in the home care setting.

ii. Dr. Holmberg asked about the difference between average wholesale price and average sale price. Apparently because of the calculations and assumptions involved, using the AWP provides a more appropriate reimbursement than does the ASP + 6%. In response to a question from Mr Healy, Ms Vogel reaffirmed the recommendation for using separate codes for each manufacturer's product.

g. **Drs. James Bowman and Carol Bazell (CMS)** then fielded questions from the Committee.

i. Dr. Wong asked that reimbursement for treating hemophilia patients with inhibitors using Novo-7 be treated as a special case. Nono-7 is crucial for treating high-titer patients, but it is 900 times more expensive than any of the factor VIII preparations. Her Hemophilia Treatment Center went $3 million over budget last year because of this product and cannot afford to do necessary surgery on such patients without better coverage. After discussion, Drs Bowman and Bazell thought that most of these patients, being children, were covered under Medicaid (MediCal), which is state run; CMS has limited influence on state-run programs. The codes used for various products and services are generated by CMS and are not part of statute; CMS will work with various communities to generate codes that are most useful without being too cumbersome. Congress mandated the use of average sale price + 6% in setting levels of reimbursement. Although it is not clear if they considered distributor costs, CMS has little latitude to change the numbers. Some of the complexity in the system comes from administrative decisions, but the majority is congressionally mandated. CMS is willing to work with various constituencies to simplify and make more rational the system within the constraints of statutes.

ii. Ms Lipton observed that data were necessary to approach solutions to many of these problems and the multiple facets of the blood industry need to collect and analyze those data.

iii. In response to Dr. Haas, Dr. Bowman noted that CMS has no discretion about the 20% co-payment or the Average Sale Price + 6%. Nevertheless, when the Medicare Modernization Act drastically reduced reimbursement for office drug infusions, the oncology community worked with Congress and CMS to address infusions of biological response modifiers and chemotherapeutic drugs. On the other hand, product and service codes are within the purview of CMS and are under review.

iv. Mr. Skinner noted that under discussion are rare diseases and there is limited ability to collect other than anecdotal data. He asked if CMS accept anecdotal data. Dr. Bazell replied that CMS welcomed data, but needed to look at its multiple facets in interpretation and use. They can act on specific patient need information.

v. Dr. Holmberg asked for clarification of what was included and what was exempt from the coming competitive bid requirement. Dr. Bazell responded that blood products and IVIG are exempt in the statute. The Secretary has discretion to exempt some others. It is expected that there will be proposals for comment as the competitive bidding process is phased in beginning in January 2006.

vi. Responding to Dr. Sandler, CMS uses resources at the FDA, NIH, HRSA, AHRQ and the VA as needed to help decision-making. There is no in-house research on which to draw. The current CMS Administrator is fostering interaction with other agencies, mostly DHHS but also government wide. Dr. Heaton asked how the introduction of new technology in the provision of blood and blood products was being handled to avoid reimbursement slowing implementation. Dr. Bazell reported that the CMS actuary office was working on this. She would check into its status and report back.

vii. Dr. Bowman added that Dr. Holmberg had begun proactive meetings several months ago with the Chief Actuary to address the whole blood/blood component issues.

h. Public Comments:

i. **Ms Jan Hamilton (Advocacy Director, Hemophilia Federation of America)** reported that her organization had met with Dr Mark McClellan (CMS Administrator) to discuss “standards of care” issues. They found him very receptive; HFA recommends that others engage in similar discussions.

ii. **Mr. Cory Dubin (Committee of Ten Thousand)** reiterated some of the issues of access and choice of medication. As one who is infected by both HIV and HCV, he has great concern about changing products and possibly further disrupting his immune system.

iii. **Ms Mary Modell (Alpha-One Foundation)** shared concerns about access, cost, competitive bidding, etc. There are only 3 products available for them and 2 sites for infusion (physicians' offices and hospital outpatient departments).

i. Committee Recommendation:
   i. After a brief recess, the Committee returned to the issue of bacterial contamination of platelet products.
   ii. As introduction, Ms Karen Lipton indicated that the AABB Bacterial Contamination Task Force would continue to be active, ensuring continuous progress and collecting data. The AABB has a "sole source" 1 year contract from the ACBSA to collect annual data for 2003 and expects to incorporate some platelet contamination into the data base.
   iii. Dr. Heaton proposed a resolution that was discussed, amended and passed unanimously by the Committee.
      1. The committee found that current reimbursement schedules for plasma derived products and their recombinant analogues for treatment of chronic conditions are not adequate to support optimal care of individual patients. Additionally, shortages in supply of these needed therapeutics have impacted the health care of these lifelong disorders. The committee, therefore, recommends that the Secretary take steps to augment reimbursement of plasma derived products and recombinant analogues.
      2. The committee endorses the following principles to guide such efforts:
         a. Plasma derived products and their recombinant analogues should be reimbursed at rates consistent with their true costs, including costs of distribution and administration;
         b. Reimbursement should be sufficient to ensure an adequate supply of these therapies;
         c. Individual products within product classes should be recognized as therapeutically unique;
         d. Equivalent reimbursement should be provided in different care settings;
         e. The lifelong cost of treatment to the individual patient should be addressed in any pricing structure, including the extraordinary impact of co-payments.

V. Topic III: Current and Emerging Infectious Pathogens: Sharpening our Approach for the 21st Century to Reduce the Risk of Transfusion Transmitted Diseases. (2nd Day)

a. In the absence of Dr. Jeanne Linden (Chair), Dr. Epstein reported for the Emerging Transfusion Transmitted Diseases Subcommittee (Mark Skinner, Matt Kuehnert, Jerry Holmberg, Andy Heaton, Karen Lipton and

Jay Epstein). Instead of focusing on individual diseases and pathogens, they viewed the public health system as a whole to identify gaps and establish priorities to deal with known and emerging transmissible diseases.

b. Today's understanding of existing threats and their potential for transfusion transmission, describe existing frameworks for dealing with them and finish with case studies as examples of strengths and weakness in the current system.

c. **Dr. Mark Smolinski (Vice President for Biological Programs, NTI and formerly Study Director for an Institute of Medicine Report, *Microbial Threats to Health: Emergence and Response*)** presented an overview by telephone. Protection against biological threats needs to be 100% effective, whether natural or purposeful. A recent IOM Report carried a 1993 report forward with a more global emphasis. Microbes know no borders. The best defense is a robust public health system with excellent science, full capacity and collaboration with clinical and veterinary medicine in academy, industry and other public/private partners. The spectrum of threats includes newly recognized or newly spread pathogens, resurgence of endemic or antimicrobial resistant infections, discovery of the infectious etiology of chronic diseases and intentional use of biological agents. Respiratory infections, HIV/AIDS, diarrheal diseases, tuberculosis and malaria are the leading infectious causes of death world-wide, each responsible for more than a million deaths per year. In the US, infectious diseases have been edging upward in prevalence, even when HIV/AIDS is excluded. He quoted Dr Fauci (NIAID, NIH) that we've seen 2 new infectious diseases per year over the past 20 years. Factors fostering emergence include changes in demographics and behavior, developing technology and industry, economic development and changing land use, international travel and commerce, microbial adaptation and change, breakdown of public health measures, changing human susceptibility to infection with an aging population and more chronic disease, changes in climate, weather and ecosystems, poverty and social inequality, war and famine, lack of political will and intent to harm. He listed the 10 recommendations of the report.

    i. In response to a question from Dr. Bowman, he reported that NTI has developed the Global Response Fund ($0.5 million) or WHO to respond to an outbreak anywhere in the world, with the expectation that donor countries would replenish it. This fund has been used more than 20 times, including working with SARS and has been replenished each time. NTI has invested heavily in the Department of Communicable Diseases at WHO and urged making this a priority there and at the United Nations. NTI has helped develop WHO's Global Public Health Intelligence Network, as formulated by Health Canada. It is responsible for more than half of WHO's detection of the outbreaks around the world.

ii. Dr. Smolinski replied to Dr. Bianco that blood donor testing could be a good source of surveillance, if the logistics and ethics can be worked out. He noted that stored blood specimens had been very useful in studying the hanta virus outbreak in SW US.
iii. In reply to Dr. Gomperts, Dr. Smolinski noted that relatively few countries have effective surveillance systems so that the estimated frequency of newly emerging diseases (2 per year) is probably low. Further, the factors leading to the emergence have not been well studied because of limited resources. For example, it is not clear how West Nile virus got to the US, but our mosquitoes were able to spread it well. Virus mutations or genetic manipulations have not been detected as yet.
iv. Dr. Holmberg asked him to expand on what resources were necessary. First, is the education and training of existing public health personnel. More people are needed to enter the field, and this will require increased salary resources.

d. **Dr. Roger Dodd (VP for Research, Holland Laboratories, American Red Cross)** provided a factual background on newly recognized transfusion transmissible agents, starting with parasitic agents and moving on to bacterial agents, viral agents, TSEs and, finally, bioterrorism.
i. Malaria is globally widespread, classically re-emergent and may be the most frequent transfusion-transmitted disease. There are 2-4 cases annually in the US, mostly from unexpectedly long asymptomatic infections in individuals with prolonged stays in western sub-Saharan Africa. Incomplete or poorly interpreted donor health histories been faulted in some instances.
ii. Babesiosis is the most common blood borne parasite in the US and is endemic in Northeaster and Upper Midwestern US. None of the currently available measures are effective in preventing transmission.
iii. Chagas disease is endemic in much of Latin America, although in some areas public health measures have begun to reduce its prevalence. Serological (antibody) tests can potentially reduce its spread by transfusion.
iv. Leishmaniasis is vector-borne and endemic in Iraq and Afghanistan. No transfusion-related transmissions have occurred in the US yet. Most of these agents survive during blood bank storage and are more likely to produce severe disease in elderly, debilitated or immunocompromised patients. Splenectomy also renders a patient at greater risk.
v. Bacterial contamination, especially of platelets, has been covered well elsewhere. Separate mention might be made of the agent of human granulocytic ehrlichiosis, which is tick-borne and tracks Lyme disease and babesia. Rickettsia and Chlamydia appear to have the potential for blood transmission, but has not been reported.

vi. West Nile virus has been reported transmitted by blood; testing of pooled donor samples with a nucleic acid-based procedure prevents many, but not all cases. Human herpes virus 8 is the most recently described herpes virus, although it has been around for some time. It has the potential for transfusion transmission, but no case has been proven yet.

vii. The same is true about SARS and Simian foamy virus, although the latter is not clearly associated with pathology.

viii. Dengue seems to be reemerging; a few cases have been seen in border areas of the US, e.g., Texas, Hawaii.

ix. Variant Creutzfeldt-Jakob disease (vCJD), the human version of "mad cow disease," has apparently been transmitted twice by transfusion. There may be an element of host sensitivity; all human vCJD (not transfusion associated) has occurred in subject homozygous for methionine at codon 129. One of the two transfusion-associated cases (without clinical symptoms) was heterozygous, which could change susceptibility, incubation period or both. The human epidemic seems to be on the wane in Britain where it has been the most widespread.

x. Bioterrorism agents in the top tier (class A) include anthrax, plague, smallpox, tularemia and various viral hemorrhagic fevers. Many are primarily transmitted by inhalation. Some have short incubation periods before clinical illness. The preclinical asymptomatic viremia is likely to be short. Initial plans to close down blood collections in affected areas, supplying them with blood collected elsewhere was brought into question by instances where the extent of potential contamination was not known.

xi. Committee Discussion:

1. Dr. Sandler asked about the potential role of pathogen inactivation. Dr. Dodd noted that it would certainly be helpful, but in instances when the pathogen load is high (e.g., B-19 parvo virus, sometime HCV), the inactivation process may not be robust enough by itself and testing would be required.
2. Responding to Ms Lipton, he noted that formal hemovigilance would be useful, but all current systems are primarily voluntary. Furthermore, we have a small amount of clinical vigilance for transfusion transmitted diseases now.
3. Dr. Kuehnert asked about prioritizing the threats. Dr. Dodd said he doubted that there would be explosive outbursts of parasitic transfusion-associated diseases. One can consider 2 axes of concern: one is the threat to public health, how much disease, how serious is it and how readily can one intervene; the other is the level of political/public concern. For example, both were high for HIV, while vCJD seems to

have a low public health threat level but a high degree of public concern. Some diseases have been explosive, requiring intervention before much information was available (e.g., SARS), whereas West Nile provided more time to collect data and plan.

4. Dr. Klein observed that we don't seem to have a consistent approach to these agents. There is still limited information about SARS presence in the blood prior to symptoms or data about silent cases, if any. Seroprevalence studies suggested the presence of more asymptomatic infections than was first thought. It is not known how many of these were viremic and for how long.
5. Dr. Kuehnert confirmed the lack of information and pointed out that post illness viremia was longer than originally realized. These studies often take a back seat to more pressing issues of epidemiology and pathogenesis.

e. After a brief recess, Ms Karen Lipton (CEO, AABB and a Committee member) summarized the blood organizations' approach to emerging pathogens. A key part of this process is the Transfusion Transmitted Diseases Committee. A Standing Committee of the AABB, its charges include monitoring existing and emergent infectious issues, proposing position statements, making recommendations to AABB Board and other committees on discrete issues and establishing priorities for dealing with arising issues. The Committee includes liaisons from ABC, ARC, CDC, FDA and CAP. They interact with the Clinical Transfusion Committee and the Blood Bank and Transfusion Services Standards Committee on many issues.
    i. Sometimes interorganizational task forces are convened to address specific problems; they may be disbanded when the problem is under control. AABB provides staff support for these activities.
    ii. AABB communicates with members and interested parties with Association Bulletins that advise members on AABB policy and guidance, provides information updates, announces interim standards and reviews issues annually for relevance.
        1. Pulse Points provides rapid communication to subscribers.
        2. Standards are requirements for accreditation and are republished every 18 months.
    iii. ABC has a Scientific, Medical and Technical Department that monitors events and distributes relevant information to ABC members and staff. They liaison with the relevant AABB committees. In situations considered urgent, ABC SMT staff develops and propose a policy to their officers and a preliminary position can be disseminated within 24-48 hours.
    iv. ARC operates under a single FDA license and covers the issues by using scientists, many of who are based at the Holland Laboratories. They are establishing a permanent Medical

Scientific Advisory Committee of experts who are external to the Red Cross. ARC maintains liaison with suitable AABB Committees. Hence, all three organizations have similar, but not always formal processes.

v. Committee Discussion:
    1. Dr. Kuehnert asked about the role of local public health departments in this schema. There is an attempt to involve local public health personnel, but both blood banks and local health departments need education on how best to do this.
    2. Dr. Epstein asked about the blood organizations contribute proactively to a research agenda. This is one of the priorities of the TTD Committee, which sends the results to the Board and to the NHLBI with recommendations for research funding. The Clinical Transfusion Committee participates in this exercise also.

f. **Ms Mary Gustafson (Director of Worldwide Regulatory Policy, PPTA)** presented the Plasma Protein Therapeutics Association's approach to current and emerging infectious pathogens. Each plasma therapeutic is unique with differing manufacturing processes and different pathogen clearance steps. Hence, product safety is primarily the responsibility of individual manufacturers. Nevertheless, there are some issues that are common throughout the PPTA, which is a worldwide organization. They have a Pathogen Safety Steering Committee that is scientifically driven, managed from the European Office and chaired by Dr. Thomas Kreil (Baxter). It is their most active committee with 4-6 face-to-face meetings annually plus numerous conference calls. They are charged with monitoring and assessing emerging pathogens, supporting liaison with national authorities of standard-setting or regulatory agencies and creating temporary issue-specific task forces as needed. PPTA also has a Regional Regulatory Committee and a group that establishes voluntary standards. They have established a patient notification system. Recent problems they have dealt with include Parvovirus B-19 (voluntary standard for viral load), inactivation or removal of West Nile Virus and the clearance during the manufacturing process pf prions of transmissible spongiform encephalopathies. A "round table" may be convened to help coordinate efforts and deal with problems. A similar group convened about 1 year ago and considered case studies for vCJD, West Nile Virus, parvovirus B-19 and SARS. Key issues are risk assessment, testing the manufacturing process and pathogen clearance, communication with donors and recipients, donor management and encouraging appropriate product use.

g. **Ms Shannon Penberthy (MARC Associates, representing the National Hemophilia Foundation)** presented views of consumers, with collaboration from the Alpha One Association (Ms Miriam O'Day), the Immune Deficiency Foundation (Ms Michelle Vogel) and the World Federation of Hemophilia (Mr. Mark Booker). Each organization

monitors multiple sources (e.g., US Health Agencies, manufacturers, news reports, consumer information, physicians and foreign governments) for possible safety concerns. They investigate these using task forces and committees, consultation with Federal Agencies such as FDA and CDC, and with multiple foreign sources. They play a major role in communicating results of investigations through medical advisories, web-sites, published articles and chapter/medical provider contacts. Advocacy activities include addressing specific concerns, participating in the development of Federal blood safety policy and educating consumers about the risks and frequency of specific problems. Their major concerns involve the apparent informality of the process using relationships rather than regulation, the lack of a structure to respond rapidly to emergency situations, stark limitations on post-market surveillance and the lack of international collaboration. They recommend help in increasing consumer literacy, dissemination of disease and incident specific information, guidance for consumers and health care professionals, increased post-market surveillance with enforcement, better patient notification and multidisciplinary approaches to risk assessment, including bioethics. (Dr. Holmberg commented that the last recommendation was recognized and being addressed)

h. Dr. Kuehnert (CDC) opened the discussion of HHS strategies for addressing emerging infectious pathogens, focusing on CDC's role and suggesting how blood banks, transfusion services, industry, clinicians and transfusion recipients ("the blood community") might work with them to improve transfusion safety. He reminded the Committee of many of the points made by Dr. Smolinski from the IOM reviews. When an infection surfaces, questions to be asked include:
    i. Is it transmitted person-to-person, is it transmitted through use of donated biological tissues including blood or blood products?
    ii. Is it endemic, epidemic, globally imported or from a bioterrorism threat?
    iii. Is there a reliable diagnostic test and does it cause recipient disease?

i. Some recent examples were given. CDC has a patchwork of programs to address many of the concerns about blood safety, but there is no central research activity for blood safety. More needs to be done.
    i. In-progress CDC reorganization follows principles of strategy and goals development from a population health assessment. Goals management will drive public health priorities and allocations, emphasizing research, innovation, health protection marketing to the public and consolidation when feasible.
    ii. Blood donor screening for West Nile Virus has been the first indication that human infection with that virus is present in a locality, preceding the detection of neuroinvasive disease. In the reverse direction, a Georgia statewide epidemiological survey by CDC and local health departments suggested that the discovery of

white particulate matter in some units of leukodepleted blood did not have major clinical significance. This also highlighted the importance of having such a surveillance system in place, should other potential problems surface, improved biovigilance.

iii. Committee Discussion:
    1. During the discussion, Dr Bianco noted that CDC had to work through local health departments and that this was an impediment during some of the response to West Nile Virus. Dr Kuehnert regards the local health departments as partners rather than conduits from the CDC.
    2. Dr Gomperts asked about surveillance for common pathogen markers as an approach to detecting new agents before they become problems. Dr Kuehnert replied that astute clinicians questioning unexpected outcomes have been one of the most effective harbingers of a new problem.

j. **Dr. Edward Tabor (FDA)** then summarized the FDA role and approach. Travel is one of the key factors in the global spread of an infectious agent. The goal is to anticipate potential threats, monitor them for degree of risk and focus funding and laboratory resources on dealing with them.

i. The Emerging Infectious Diseases Committee has a core membership but calls in many other individuals from various Federal Agencies for participation when their expertise is needed.
    1. This committee feeds into the monthly "Public Health Service (PHS) Blood Conference Call."
    2. The committee has overseen the creation of a working database of agents with potential for transfusion transmission. When a pathogen appears to have this potential, the committee reviews what is known about it through intramural research in progress in the various agencies or extramural research, usually funded by NHLBI.
    3. Specimen repositories are identified when possible that could provide samples for testing, of both donors and recipients as necessary.
    4. Laboratories, either in or outside of the government, are identified who can do the necessary testing.
    5. The database currently contains 29 viruses or virus groups, 11 bacteria, 8 parasites and 2 prions. The information is communicated to "PHS Blood" or elsewhere so that decisions on the next step(s) can be made.

ii. Committee Discussion:
    1. Dr. Bianco asked for more detail about "the list." Dr. Tabor replied that it was a working document containing published and unpublished material and even some that is conjectural. Before it could be made public, more verification of sources and reliability would be needed, as

provided by clearance by participating agencies. This would be possible, but also time-consuming.

2. Mr. Mark Skinner noted that differentiation between the risk of disease transmission via plasma-derived products and blood or blood components had not been part of the discussion, but was clearly important to patients who needed the former. Mr. Skinner had asked for such a listing previously and reiterated his request that clear differentiation be part of the discussion in the future. Dr. Tabor said that the EID Committee was concerned about plasma product safety, but the issues (e.g., pathogen inactivation, clearance during the manufacturing process) are different. For most of the agents discussed today, plasma safety is not a problem.
3. Dr. Heaton questioned who should be represented on the EID Committee, suggesting plasma representation, transfusionists or practicing clinicians and interests that may be involved in bringing new tests to general use. Dr. Tabor replied that there was a practicing transfusionist on the committee. Further, the group's role is to evaluate sentinel events before they mushroom into bigger problems. Enlarging the group might make it more cumbersome in its ability to respond, although the concept could be considered.
4. Dr. Gomperts pointed out that the potential for pathogens to jump species from animals to man had been little discussed; yet this was what apparently happened with HIV and AIDS. A parvovirus jumped from cat to dog. There should be prospective consideration of this possibility.
5. Dr. Haas said that all of these approaches discussed are likely to require additional resources, from market forces or from the government.

k. After lunch, Dr. Epstein assumed the chair to moderate presentations of a series of examples of past activities, including lessons learned.
    i. **Dr. Hira Nakhasi (FDA)** presented West Nile Virus as an example of a model response where the right elements came together. The first West Nile infection recognized in the US was in 1999. By 2002, CDC had evidence that it was transmitted by blood transfusion and FDA issued a series of guidances about donor management. Since about 80% of infections were asymptomatic but accompanied by viremia, clinical symptoms turned out to be of little use in deferring infected donors. Manufacturers were encouraged to develop tests for West Nile virus, and it seemed that serological (antibody) tests would not be useful. Existing platforms for nucleic acid amplification testing were rapidly adapted to West Nile Testing. Testing began under

an investigational new drug (IND) exemption in July 2003. Minipools of varying sizes were used from the beginning. FDA participated with an ad hoc AABB task force in developing and monitoring the use of this test. The nature of the virus made it likely that pathogen inactivation procedures in general use would prevent West Nile transmission through plasma therapeutics. During the first year of testing, 818 viremic donations were quarantined and not used; 6 donations (4 had low level viremia detectable with individual donor testing, in retrospect) were not detected by minipool testing and transmitted the infection. During the mosquito season 2004, 199 donations were interdicted and 1 was not (it occurred just before the geographical area switched to individual donor testing because of the expected frequency).

ii. **Dr. David Leiby (Red Cross Holland Laboratories)** discussed Chagas Disease as an illustration of an unmet challenge. It is caused by Trypanosome cruzi, a small parasite that is vector borne in nature. It can be transmitted from mother to unborn child, by organ transplant and by blood transfusion. It is endemic in Latin America and is "emerging" via immigration. Latinos are now the largest US minority. Many parasitemic individuals are asymptomatic and often the parasitemia is intermittent. There have been 5 transfusion-associated cases in the US and 2 in Canada; recipient disease was fulminant in patients who were immunocompromised. The clinical course in immuno-competent individuals is not clear; most cases are probably not recognized. In all Latin American countries, serological testing is being done. There is no test licensed for US use. Nucleic acid-based tests are not available and their utility is not clear. The likelihood of "window" period antibody negative infectious units is not high. Current approaches to pathogen inactivation seem feasible, but more study is needed. FDA presented a clear path to developing a donor screening test at BPAC in September 2002. Chagas disease is not well known among US clinicians. Work on blood screening has been interrupted by the emergence of new agents that have seemed more pressing.

iii. **Dr. Louis Katz (President, ABC, Executive VP Mississippi Valley Regional Blood Center)** described HIV as a case example of evolving challenges, interventions and donor management. In December 1982, the MMWR reported a patient with AIDS and no other risk factor than a platelet transfusion. "If the platelet transfusion contained an etiologic agent for AIDS, one must assume that the agent can be present in the blood of a donor before onset of symptomatic illness & that the incubation period for such illness can be relatively long…." In January 1983, interventions considered to prevent possible transmission included explicit donor inquiries about sexual behavior, surrogate testing (anti-HB core

antibody and T4/T8 ratios) and voluntary self-deferral by at-risk donors. All of the information that was available at that time was epidemiological. HIV had not been isolated and there were no validated tests. In the midst of scientific uncertainty, there was a distrust of CDC (swine flu "fiasco"), planned budget cuts for CDC, civil rights and ethical considerations and a perception that direct questions would increase rather than reduce the problem. There was an important weakness in the system, an inability to deal with a new threat that was characterized by substantial uncertainty. Nevertheless, progressively more stringent deferral of potential donors with at-risk behavior (primarily, males-who-had-sex-with-males; iv drug users had been excluded for years) led to a reduction in transfusion risk, even before testing began. Next steps include individual donor NAT and other improvements in testing that may help. At Dr. Katz' center, they have begun to use a touch screen, computer-assisted donor medical history, which seems to improve sensitivity and specificity of some of the questions. Pathogen inactivation will help if it can be approved. Recipient protection is paramount, transcending cost-effective standards. He ended with a plea that new technologies be adequately supported financially as they are implemented.

iv. **Dr. Mike Cannon (CDC)** discussed human herpes virus #8 (HHV-8) as an example of an unresolved scientific question potentially affecting blood safety. HHV-8 was discovered in 1994. It is an enveloped virus related to the Epstein-Barr virus. Primary infection is often followed by a long latent period with a potential for viremia for years. It is cell associated and pretty much removed by leukodepletion. There is no approved assay. Clinically, it is associated with Kaposi's sarcoma, effusion lymphoma and multicentric Castleman's disease. The risk of Kaposi's is increased dramatically in the face of immunosuppression, such as following organ transplantation or HIV infection. Studies have shown about 3.5% of donors are seropositive, with some variability between laboratories (NHLBI-REDS). Some multitransfused blood recipients have seroconverted, but the donor-recipient has been difficult to detect. The use of repositories of samples collected in earlier studies (donors, recipients and some donor-recipient links) has been invaluable. Still, one can only say that blood transmission of HHV-8 is possible, but of low probability.

v. **Mr. Mark Skinner** then addressed the issue as to what should be done if one knows or has reason to suspect that one or more blood products had been contaminated. He described 2 examples in which donors later found to have vCJD contributed to a plasma pool. Plasma, plasma pools and subfractions of plasma pools are sold between fractionation companies so that traces of material

from an individual donor can be very widely disseminated. Notification of potential end-users can be delayed or non-existent, extending to multiple nations. Overly zealous notification and publicity (all patients in a group may be affected) can lead to patient access-to-care problems (e.g., the refusal of dentist and G.I. physicians to perform needed procedures because instrument decontamination and sterilization is difficult). Risks may be assessed in several countries or by several organizations, none of which may agree with any other.

vi. Public Comment:
    1. **Mr. Cory Dubin (Committee of Ten Thousand)** spoke for a group who are affected by hemophilia, HIV and HCV and who are part of a larger chronic disease community. They are impatient that too little has been done in follow-up of infections that have been known for years and worried that the widespread transmission of HIV in blood in the early 80s could happen again with another infectious agent (not "whether" but "when"). He noted that post-market surveillance had been discussed as early as 1994 (HCV "look-back", too), but resources have not been found to make these happen.
    2. **Mr. Hal Baker (Senior Vice President of Global Marketing and New Product Commercialization, Pall Medical)** reported that Pall expected to introduce in Europe in spring 2005 a "Leukotrap Affinity Prion Reduction Filter" for removing white cells and prions from red cell products in one step. He offered to provide more information to the Committee in the future, if desired.

vii. The last group of speakers formed a Panel for Questions and Answers.
    1. Dr. Heaton noted inconsistencies in international tracking and follow-up of plasma for fractionation and suggested better harmonization between countries.
    2. Mr. Healy said that material for fractionation in the US was required to come from licensed facilities. The material in question (Mr. Skinner) came to the US under "compassionate use" rules. PPTA has standards for tracking, but they are voluntary rather than required. (Mr. Skinner concurred; material to treat very rare disorders is often the problem.)
    3. Dr. Holmberg noted a common thread in inadequate tests, especially Chagas and HHV-8. Dr. Katz pointed out that companies were unlikely to develop tests unless they were likely to be used. The market precedes test-development.
    4. Dr. Bianco questioned the statement that most Chagas transmission in the US is vertical, i.e., mother to child. Dr.

Leiby: only 5 known vector transmitted cases in the US; 2-11% of sero-positive women infect their newborn. These are Latin America figures; there are no comparable studies in the US, but there is no reason to suspect that the probabilities differ here either.

5. Dr. Epstein reminded the Committee that a major purpose today is what determines the sense of urgency and the public health priority when the evidence and levels of risk are comparable. An unidentified attendee opined that shifting money from testing for AIDS drug assistance programs to "preventing bad outcomes" would decrease bad outcomes, an overall goal.
6. Mr. Skinner urged better understanding of the fractionation and transmission processes as a way to increase safety.
7. Dr. Bianco reiterated Dr. Dodd's earlier comments that public perception of risk was very strong driver of priorities.
8. Dr. Tabor pointed out the importance of research done in government laboratories in creating market forces in the development of tests. Fixed budgets, however, limit flexibility in adding projects.

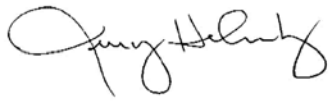
l. **Dr. Holmberg (Committee Executive Secretary)** discussed Structured Policymaking on Blood Safety, a process developed by Julius Court and Enrique Mendizabal (Overseas Development Institute, London) for WHO. The usual approach to policy is focused on writing and evaluating it, rather than on the processes involved. The life of a policy is often a chaos of purposes and accidents. One definition of "policy" is "purposeful course of action followed by and actor or set of actors." Developmental steps include planning (identify the problem and set an agenda), doing (develop the policy), checking (monitor and review) and acting (evaluate, recognize, change and communicate). Good policies are outcome oriented, forward-looking, evidence-based, innovative and flexible, developed openly and clearly with participation, partnership, effective use of resources, continuously evaluated and reviewed and based on accountability.

m. In these contexts, what are the next steps for the Committee?
    i. Ms Karen Lipton suggested that communication, transparency and research were three major problems requiring greater flexibility and activity. The FDA had problems calling ad hoc problem-solving groups due to the Public Advisory Committee Act. She suggested that the CDC might have greater flexibility. Research was also limited, be it at the FDA, CDC or contracted out. Dr. Haas put in a plug to provide resources for the entire public health system Mr. Healy commented that West Nile Virus was addressed thoroughly and with excellent communication, a model for that sort of an issue.

ii. Dr. Epstein summarized a number of "gap" areas: coordination of the public health response was a problem in itself, as well as coordination between agencies. Better means for prioritization, including the research agenda, are needed. Phase IV post market surveillance needs work. Other problems include risk communication and technical development, especially the role of government support. One approach to filling these gaps might be to establish a framework in which to operate.
iii. Dr. Kuehnert reiterated some of these points, but emphasized what was embodied in Dr. Nakhasi's last slide, the number of partners that worked together on the West Nile program.
iv. For the future, Dr. Sandler suggested that blood safety could continue to be approached as it has in the past, "only better," or another avenue could be more thoroughly explored. He recommended that the Committee take up, as a major topic, pathogen inactivation. He described pathogen inactivation as a "$2 billion gorilla" in the middle of the conference room. If pathogen inactivation was a viable alternative, there would be many changes in the way the blood supply was managed. Cost would be a major factor. Perhaps the discussion should be expanded to include emerging technologies.
v. Dr. Heaton noted that tissue was a rapidly expanding area of interest, including perhaps tissues and organs for transplantation, semen, human milk and various cellular therapies. When government funding was an issue, the role of the NHLBI (NIH) should not be minimized.
vi. Dr. Bianco commented that in 1983, much of the reaction of the blood community was denial; now he is afraid it has become overreaction. In response to Dr. Bianco's and Ms Lipton's concern about communication, Dr. Epstein noted that the FDA is involved in a great deal of communication pathways. He opined that one of the problems might be advance information on issues that are prime for discussion at one or more of the multiple approaches used by FDA, e.g., BPAC, TSEAC, workshops, guidance documents or liaison to outside groups and committee. The FDA is aware of these problems and is attempting to find fixes.

VI. In the absence of a quorum, the Committee adjourned at 3:37 PM.

Submitted by:



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