Summary:
Advisory Committee on Blood Safety and Availability
Department of Health and Human Services
33rd Meeting, January 9 & 10, 2008

At 9:00 AM, January 9, 2008, the Chairman, Dr. Arthur W. Bracey, called the meeting to order, welcomed Committee members and wished them a healthy new year. He reminded the Committee that it was composed to allow input from diverse prospective about blood safety and availability and includes representation from patients, prescribing physicians, blood banks and government agencies. The Committee's role is to advise the Assistant Secretary (for Health, ASH) on matters pertinent to developing and maintaining the highest level of safety possible for blood components and tissues.

At the last meeting, the Committee made recommendations concerning insurance coverage and availability of erythropoiesis stimulating agents (ESA), which were passed through the Assistant Secretary for Health (ASH) to CMS, which appreciated the input and continues to monitor that situation. Also, as a result, FDA is reviewing additional data regarding the use of ESAs. From that same meeting, the need to assess blood inventory continuously for reoutine and emergent indications was recognized as important by ASH. The Biomedical Research Development Authority (BARDA) is modeling blood needs for disaster responses. The Committee's belief that it is important that they be increasingly involved was forwarded to the Assistant Secretary for Preparedness and Response (ASPR).

Today, continuing a discussion of a Department strategic plan for blood and tissue safety, we will review the potential role of pathogen reduction in blood therapy. Current surveillance systems try to detect new threats, but the lag between detection and action continues to place

recipients at risk. A series of questions is posed to the Committee to help guide their deliberations.

1. What are the advances and challenges facing transfusion safety?
2. Prioritize these safety issues.
3. What are the Barriers to the advancement of technology or procedures to address these problems?
4. What are the strategies to address these problems?
5. How would pathogen reduction mitigate or reduce these safety gaps?
6. Are any of these safety gaps implicated as tissue or organ transplant issues?

Dr. Bracey then called upon Dr Holmberg to introduce new members and deal witvarious administrative issues. He noted that several members have been recalled to serve for this meeting only because the administrative action to appoint new members was slower than had been anticipated. One new member has been seated: Dr. Richard Benjamin, a "representative member" for the American Red Cross, to complete the term of Mr. Jack McGuire. Present were: Dr. Bracey, Dr Benjamin, Ms. Bensinger, Ms Birkofer, Dr. Duffell, Ms Finley, Dr. Kouides, Mr. Matyas, Dr. Ramsey. Dr. Sandler, Dr. Triulzi, Dr. Kuehnert, Dr. Epstein, Dr. Klein, CDR Libby, Dr. Bowman, Dr. Celia Witten (from FDA), Dr Burdick (HRSA). The last individuals, replacements, represent the government and are non-voting. Both Committee members and speakers were cautioned to mention any conflicts of interest they might have for today's topics.

Dr. Bracey then introduced Martin Ruta, PhD, JD, Regulatory Counsel, Office of Blood Research and Review, CBER, FDA to discuss a Proposed Rule: "Requirements for Human Blood and Blood Components intended for Transfusion or for Further Manufacturing Use," published in November. The comment period has been extended to August 4, 2008), Docket No. 2006N-0221 through http://www.fda.gov/dockets/ecomments . This is part of the FDA Blood Action Plan to revise and update existing regulations to be consistent with current industry practices and put recommendations into regulations. It's based on comments from IOM, GAO,

previous comments on earlier versions, workshops, Congressional Committees and even this Committee (ACBSA). It applies to establishments that collect and process blood and blood components, requiring them, among other things, to determine if a donor is eligible (in good health at the time of donation and is free of factors that could adversely affect the safety, purity or potency of the blood. The blood must be tested for relevant transfusion transmitted infections (RTTI).

RTTI are defined in two parts: a list of specific agents (e.g., HIV 1* & 2*, Hepatitis B* and C* viruses, HTLV I* & II*, syphilis*, CJD & vCJD and malaria – the * denotes those where testing is required); other transfusion transmitted infections for which there is a significant health risk, there may be transmission by blood transfusion, appropriate screening measures are developed and/or a screening test is licensed, approved or cleared, which have sufficient incidence and/or prevalence in the potential donor population or accidentally or intentionally released in a manner that could place donors at risk of infection. The intention is to have public discussion and issue guidance under GGP. Although FDA has recommended HIV educational material for prospective donors since 1992 or before, it now becomes a requirement to do so, if it carries through from the proposed rule to the final one.

Donor eligibility is determined with a questionnaire, a limited physical assessment and a check about previous deferral status. New in this iteration is a proposal that all facilities operating under a single license share a common list of donors who are deferred for various reasons (usually related to disease transmission) to prevent the collection and distribution of unsuitable units. One question is the feasibility of a national donor deferral registry, as is the case now with source plasma. Risk factors for RRTI include 1) certain social behaviors (a new term), 2) medical treatments and procedure associated with exposure to RRTI, 3) signs or

symptoms of such diseases, 4) institutionalization in a corrective facility, 5) intimate contact with someone at increased risk for exposure to or infected with an RRTI spread by such contact and 6) nonsterile percutaneous inoculation. Other factors to be assessed include evidence for a recent illness or procedure (e.g., dentistry, major surgery within 12 months), medication (new in regulation, but a long-standing practice), travel to an area endemic for a relevant infection, xenotransplantation, exposure to a possible release of a disease agent, pregnancy – current or within the previous six weeks (new to regs, but common practice) and unreliable answers to medical history questions from the apparent influence of drugs, alcohol, etc. (in source plasma regs for several decades). For the physical assessment, definitions for "normal" are proposed (e.g., upper temperature limit, upper and lower blood pressure limits, hemoglobin or hematocrit for allogeneic donation); comments on the need for such and the ranges proposed are requested. The hemoglobin/hematocrit levels are proposed both to protect the donor and to ensure the potency of the product for the intended use, transfusion. Other requirements include a "normal pulse" (defined)(to harmonize whole blood and source plasma regs), donor weight (minimum 110 lbs) and skin examination for freedom from signs of infection or drug abuse.

Blood must be tested for RRTI and if reactive an appropriate supplemental test (draft guidance expected) must be used. There is a requirement for testing platelets for bacterial contamination prior to release. Prior to release of the blood, a check should be made to ensure that all requirements have been met.

Some other provisions in the proposed regulations can be mentioned. The signed informed consent should include that the donor reviewed the educational material and understand not to donate if they are "at risk," that they agree to testing including supplemental testing, that they understand the risks of the donation process and that they may be deferred if needed.

Acceptable donation frequency is specified. Necessary modification of labeling requirement are set out for therapeutic phlebotomy for hereditary hemochromatosis. There are specific requirements for plasma apheresis and for source plasma.

In the discussion, it was noted that several organizations have requested an additional six months to allow time for adequate review and response and to permit the compilation and review of the significant amount of data needed for the FDA to move forward. These requests for an extension are considered reasonable, but the extension is not yet official. Some infectious agents were listed specifically because there were specifically licensed and/or recommended tests for those agents. Others were lumped together generically to allow flexibility as conditions and increased knowledge would permit. On behalf of patient organizations, it was urged that the final rule be issued with all deliberate speed. After comments are received and reviewed, there are administrative procedures and other factors which make finalization and determination of an effective date difficult to predict. Once a test was licensed, approved or cleared for any RTTI, implementation by blood collection organizations is not automatic and might still be delayed pending further review (e.g., BPAC or possibly time for public comment).

Dr. Bracey then introduced Roger Dodd, PhD (American Red Cross) to discuss the Residual Risk for Transfusion Transmitted Infections. Blood safety is of considerable public, regulatory and political concern even though blood transfusion appears to be one of the safest therapeutic measures available. The residual risk for key infections may be lower than 1:2 million units transfused. The core issues for him are: is there a framework for appropriate decision-making and is it appropriate to continue to seek a zero-risk blood supply? And will the current system of healthcare funding support such an approach?

Current interventions include donor questions plus testing (HBV, HCV, HIV, HTLV and syphilis), testing only (WNV, T cruzi, CMV and bacteria), questions only (CJD, vCJD, HAV, malaria, babesia and leishmaniasis) and questions assumed to have an effect (HHV-8, tropical infections, emergent situations – e.g., SARS). Questions are often based upon travel or exposure. Recently, a more formal approach to hemovigilance has been added, along with approval and limited application of HBV DNA testing, the adoption of Chagas testing by most blood collectors, bacterial testing by various means and individual donor testing for WNV.

Residual risk stems from a failure in the donor selection process, the lack of tests, insensitive tests, laboratory failure, mutant or variant organisms and window period infections (perhaps the major source for residual risk). In the past it has been possible to measure residual risk directly (post-transfusion patient follow-up), as a number of studies attest. Now, however, most infections are too infrequent to measure this way. Slide #8, adapted from studies by H.J. Alter, illustrates this for transfusion-associated hepatitis. The risk may be estimated from calculations from the window period and the incidence rate (new infections per person per unit time in repeat donors). The window period can be estimated by extrapolating back to zero from two or more samples the ramp-up period of HIV or HCV RNA concentration (slide #11, from Dodd, Notari, Stramer Transfusion 2002; 42: 975-979).

The sequence of events surrounding the discovery that WNV infection can be transmitted by blood is a tremendous example of a reaction to an emergent infection. Twenty-three cases of transfusion-transmission of WNV occurred in 2002. Since then, after testing was initiated, there have been a total of nine, but there have been only three of these since the use of selective individual donation testing (instead of testing in mini-pools).

Parvovirus B-19 is definitely transmissible by transfusion, but there are few clinical cases. Transmissibility of HHV-8 is established outside of the US; two potential examples reported in the US. CMV residual risk is unknown, but probably occurs, even with leukocyte reduction and antibody testing. Dengue, HEV, HAV and Colorado Tick Fever Virus blood transmission have occasionally been reported, but not necessarily in the US.

Before bacterial testing of platelets, begun in 2004, septic reactions occurred about 1:40,000, with 1:240,000 fatalities. After testing, the figures were 1:75,000 and 1:500,000 respectively. There have been further reductions attributable to diversion of the first few ml from the donor to an isolated pouch for testing.

Risks from parasites include malaria (<1 case per year, with about 100,000 geographic deferrals), Chagas' disease (pre-test <1:300,000; testing implemented 2007) and babesia (about 60 reported cases in last 20 years; risk may be as high as 1:1,000 in areas of high endemicity; no currently effective intervention).

How many actual cases get reported or identified? Without "lookback" or active hemovigilance, the efficacy of reporting transmissions is probably not good.

For emerging infections, there is a public health concern about how much of a clinical problem there is and a political problem about how many people are troubled by them. Public perceptions of risk are not straight forward. Slide 26 places a number of transfusion risks on the Paling logarithmic scale, with benefit on the horizontal axis and concern on the vertical. The greater the benefit and/or the greater the concern, the more that action of some sort is favored. One in a million is generally thought to be relatively innocuous and the level used by USA/FDA

below which any risk from a food additive is considered too small to be of concern. Infectious risks from transfusion fall on the lower side of the risk equation.

The drivers of safety include ethical imperatives, advocacy, accreditation, public and political pressures, competition, examples from other countries, available technologies, fear of litigation and regulation. Safety requirements to be considered include zero risk, all the safety we can afford (who decides), acceptable risk (?definition), an arbitrary value (similar to that for food additives), as low as reasonably achievable (define "reasonably"), continuous improvement with no specific target and potentially different for different agents. Can we (should we) moderate the escalations of current interventions? Dr. Dodd recommended that the risk should be as low as reasonably achievable and that there be continuous improvement with no specific target, as the de facto standards currently being used. Alternate funding mechanisms may be needed and innovative ways to pay for enhanced safety.

Pathogen reduction has many potential advantages. Among these are reduction of infectivity to enhance blood safety, reduction of bacterial contamination, reduction of immunologic effects, elimination of many new testing requirements and increased public confidence. Potential disadvantages include added cost and complexity, staff safety, reduced therapeutic efficacy, uncertainty about product safety, the possibility of creating neoantigens, not true inactivation, not approvable for non-validated conditions and the lack of a single method for all components. A major barrier to the adoption of pathogen reduction technology in the US is the decision structure (or "indecision" structure) and the absence of a consistent coherent approach (there are no models to deal with blood safety). The economics of health care do not favor the adoption of safety measures in the absence of regulatory requirements or cost savings.

He summarized by saying that infectious outcomes of transfusion have been reduced to very low levels (0.2 – 5 per million units) for agents of major concern. Other infections occur at fewer than one per year in the US. Further reductions could be achieved by extending current testing approaches in response to a perceived need and as a means to combat emerging infections. There is a lack of clarity on market prospects for further safety improvements for blood, and the approaches for tissues and organs are less well efined.

In the discussion, clarification was requested for the near zero disease transmission in the last five to eight years. Many, perhaps most, recipient infections are detected by lookback. Recent Red Cross data showed that septic reactions from platelets were passively reported at a rate of 1:175,000, with a fatality rate of 1:700,000. Contamination may be as high as 1:1,000 or 1:2,000 apheresis platelets. Achieving sterility of platelet products may be reasonable to expect, but perhaps unrealistic with current technology. Dr. Dodd commented that prioritizing risks was an unsolved problem, but it's important to have some sort of a rational mechanism to achieve it. The problem is that the levels of public and political concern and public health risk don't necessarily coincide. It is a task for this Committee to find a way of working through this issue. The Chairman was asked to address availability along with safety in the future . Anecdotal evidence was described where availability of blood support was critical to permitting several liver transplants to procede and that delays in resupply from a regional center compromised patient safety. Another issue that usually lurks in the background is that of compliance. Fifty percent of the blood in the US is collected under a consent decree. How does this fit into the picture? Dr. Dodd agreed that compliance was an issue, but the absence of compliance did not necessarily translate directly and specifically to a determination of risk level. There is great

effort to take the human aspect out as much as possible, using automation mostly. Nevertheless, there are humans involved at every step, from the donation to testing and administration.

After a short break, Dr. Bracey introduced the next speaker, Marc K. Roberts, PhD, Professor of Political Economy and Health Policy, Harvard School of Public Health, to speak about "Ethical Considerations of Transfusion and Transplantation Safety." He has taught economics, statistics, public health, ethics, management and environmental policy at the Kennedy School of Government, Harvard Law School and the Harvard School of Public Health. He initiated the first course on the Philosophical Basis of Public Health Policy to be taught at a school of Public Health in the US. He is the author or coauthor of many publications and his research has focused on environmental policy, health sector reform and the ethical aspects of these decisions.

The term, ethics, is widely misused as a polemical marker for things that people want to advocate for. Broadly speaking, ethics refers to ideas in society about what's the right thing to do. In a diverse society like the US, there is no general agreement about what is the right thing to do. Instead, there are a number of basic, albeit conflicting, goals that are widely believed to be important for policy. In clinical bioethics mid-range principles for guiding interaction between doctors and patients have been emphasized. They're neither fundamental philosophical ideas nor specific policy guidelines, but somewhere in between (e.g., maxims like advancing patient's interests, autonomy, beneficence) Such mid-range principles call for elaboration in two directions: 1) where do they come from and how do we know that they are worthy of respect and 2) what are their implications?

In public health policymaking, there is no similar agreement about mid-range principles. Nevertheless, he offered some mid-range principles for the Committee's consideration. He suggested five broad philosophical ideas: 1) a good policy increases the aggregate well-being of a country's citizens ("consequentialism" – judge a policy by its consequences; "utilitarianism" – the greatest good for the greatest number). Cost-benefit or cost-effective analysis are efforts to apply this principle. 2) With the first principle, there is the risk of sacrificing some people for others, leading to the principles of equity and fairness (e.g., what differences in access to health care are acceptable, based on differences in people's economic and social status?). Different countries have quite different answers to this question. 3) The principle of "choice," respecting the capacity and opportunity for choice, both by individuals and by society (collective choice). This may get bundled in political rhetoric as the notion of "rights" (e.g., right to make my own decision, right to refuse care, right to this or that). The "right" to smoke, drink or act in other various ways that can injure their health status or injure other people. It is important to consider seriously collective and civic choices as well as individual choices. 4) A fourth idea deals with respect for a community's views and traditions about social arrangements. Americans will pay more to decrease a death from cancer than they will to decrease a death from any other disease of equivalent pain and suffering. Deciding who is the community and who speaks for the community can be very controversial in this fourth notion. 5) The last idea in this group is the need to deal with individuals with compassion. This runs the risk of nonuniform decision-making, but in the long run may improve consequences.

In every system he has investigated, some 28 different countries, the society spends "too much on treating people who are acutely ill and facing death." Analysis of acute care always indicates that it is much less cost-effective than our favorite public health measures like

immunization, prevention and primary care. Alternatively, people are on to something that cost-effective calculations are missing, such as an unwillingness to die, or to let "Grandma" die. Hence, they are willing to do a lot to avoid that result. Sensible policy-making must understand the potential conflicts between individual compassion and logical planning.

There are five principles that can help move from these broad ideas to inform the decision-making of the Committee. 1) When another policy is considered, the costs as well as the benefits must be taken into account to maximize the benefit for society. It's unethical not to consider costs because they must come from somewhere, scarce resources raised from citizens, thus decreasing their opportunity and well-being and decreasing the capacity to pursue other programs. This is politically difficult because beneficiaries always focus on benefits, not costs, and concentrated benefits with diffuse costs produces a pattern to over-provide for potential beneficiaries. This extends well beyond the health area. A classic example is the subsidy for mohair goat raising put in place in 1917; mohair was then a major ingredient in the winter trench coats. That subsidy remained for 65 years because nobody cared except the mohair goat producers, who lobbied for it at the Agriculture Committee every year; for everyone else, it was a penny apiece.

2) It is appropriate to accept imperfect or risky policies if justified by the benefits. It's really a benefit-benefit calculation; the effect of increased safety on the availability of blood is a good example of this principle. An example if the adoption of fast-track approvals for cancer and HIV drugs, even with somewhat lower standards because the costs of delaying approval were considered along with the costs of rapid approval. There are bureaucratic problems with this principle because false negatives (delayed approval) do not produce bad cases for which you are held responsible.

3) The third principle is to prefer information, influence and incentives to coercion when doing so produces reasonable benefits at reasonable costs, a result from the "rights" and "respect" ideas. Coercive policies are most defensible when avoiding large harms to others because information alone seldom changes behavior. Regulations to limit options work best when no one really wants the eliminated options. Restricting options can be an issue concerning unlicensed medical practitioners in poorer countries or the role of traditional medicine in Hong Kong.

4) The fourth ethical principle is: "protect citizens against both health and economic risks," based upon the equity argument, and ensure access to prevention and care to some appropriate minimum level. When people are forced to pay for things, the first things they don't do are those that are most important from a public health point of view (i.e., stop immunizations, stop prevention and stop annual exams).

5) Finally, policies must be based upon transparent, accountable processes, based upon explicit reasoning. Given that the substantive criteria conflict, that maximum benefit and equity might conflict or maximum benefit and equity might conflict or maximum benefit and respect for the individual might conflict, there's a great premium in making the decisions openly where the reasons are made explicit and the decision-making body holds itself accountable for increasing its own accountability and transparency. Deliberation protects against partiality and pressure/

Part of the responsibility of a democratic government is to improve the capacity of citizens for their own self-government, telling people honestly what the choices are. Nevertheless, even open processes are not completely fair, disadvantaging less sophisticated, less well-funded groups who may not have the fundamental information needed. Putting lower

income individuals at significantly higher risk than higher income individuals is not ethical. In a mass casualty situation, if we're not prepared to lower standards to get the benefit of having enough blood, we're not abiding by the principle of appropriate balancing by allowing policy to be overly influenced by narrow advocacy groups and economic interests. Being provocative rather than critical, he suggested that in comparing risks for the population, the risk per transfusion event may not be the right denominator. It would be interesting and not particularly difficult to recalculate risks on a lifetime basis. It is also useful to have a comparison rather than deal with absolute numbers.

Applying those principles to specific situations requires skill and judgment that can only be developed through an explicit consideration of the problems themselves, a bit like case studies in management decision-making, grand rounds in hospitals or arguing about Supreme Court decisions in law school. Different countries, which may be more or less egalitarian, more or less willing to pay for safety and more or less sympathetic to whales (e.g., the Norwegians and Japanese don't take whales very seriously). Hence, different countries may strike the balance in different ways.

During the discussion, it was pointed out that the Committee was composed of representatives of groups or entities that may need components, but perhaps not representative of the broad US population. Is the Committee's diversity sufficient to engage the US citizenship adequately. Dr. Roberts replied that he has insufficient information on which to base a judgment in this regard. The organized tend to have louder voices than the unorganized, even though the views of the unorganized are important. Nevertheless, it is difficult to involve the unorganized.

Should cost consideration come predominantly from the perspective of the hospital or healthcare institution or from the societal perspective, or both? Two of Dr. Robert's obsessions are: 1) healthcare cost data are somewhere between imaginary and terrible. Most of the data are based on charges, and charges have a limited relationship to costs. and 2) the data relate to fully allocated averaged costs, which often have nothing to do with actual incremental costs for expanding the service. If you try to include death or disability to many vs death to a few, you must rank health outcomes on a comparative scale (e.g., how bad is it not to have an eye vs to be dead?). WHO has developed this measurement called DALY (Disability Adjusted Life Years). He urges care in applying these analytical techniques because the available data are poor and our estimating ability is limited, especially in making close calls. The range of uncertainty around the estimates is wide.

The Congress perceives that blood is a national resource that is needed for a strong healthcare system and is expected to be ever ready. In the past, when decisions were being made about critical issues in hepatitis and HIV, individuals (patients) who had a strong interest were not at the table. The Institute of Medicine and the Department agreed that such was a mistake and shouldn't happen again. The cost of a transfusion-transmitted disease is on the patient and his insurer, whatever that might be. There are blood shield laws in 48 of the 50 states that limit the ability to take action against blood banks. There is no national compensation program for blood injuries the way we have for vaccine injuries. There is a greater imperative to test out, if possible, the risks involved. A half billion dollars has been paid in the Ricky Ray compensation fund as a result of how the transmission of HIV was handled. The hepatitis C issue is still out there and patients are continuing to work on compensation for that. How should the Committee, as a group address, these issues knowing the level of compensation? Dr. Roberts began by

suggesting that the liability of the blood suppliers not be increased. Finding a way to protect the people at risk is a complicated subject, particularly in the middle of an election season, because determining why people should be protected against that risk as opposed to all other risks in the healthcare system (e.g., 100,000 deaths due to preventable medical error in the country every year – IOM "To Err is Human" report). Nevertheless, protecting some people against risks is better than not protecting them, even if there are other comparable risks left unprotected (the great should not be the enemy of the good). Risk compensation often becomes very political in who is compensated and under what conditions. Compensation for risk may increase public acceptance of an imperfect system. One of the obligations of this Committee is not only to react to public perception but to try to open a public dialogue about which of the current attitudes among the public is it appropriate to respond to and which it is less appropriate to respond to. There is an obligation to help people calibrate their expectations in an appropriate and interactive way.

The next speaker was Celso Bianco, MD, Executive Vice President of America's Blood Centers since 2000 and previously Vice President for Medical Affairs, New York Blood Center. The original title of his talk was, "Current Landscape of Blood Diagnostics," but he focused on "Donor Screening Assays." In the context of safety, each of the layers of protection, described by Dr. Ruta, actually contribute very little individually to the safety of the final product. For example, in 1997, an anonymous post-donation survey found that 1.9% of donors reported deferrable risks. More recently, donor deferral lists were found to have limited efficacy, based on transfusion transmitted disease markers (2008). Two confirmed positive units (out of 20 million products distributed) that should have been quarantined were released by error (Callaghan 2003-2006), examples of non-compliance. On the other hand, most licensed

screening assays have sensitivity and specificity about 99% and NAT reduced the estimated risk for HIV and HCV to nearly 1 in 2 million. Hence, testing for communicable diseases is the major contributor to blood safety (more than 90 %).

In the US, donor screening tests are reviewed and licensed by CBER after extensive trials. In many cases, each lot of a product has a lot release procedure. On the other hand, diagnostic assays are reviewed by CDRH, often under a simplified process, 510 (k). The rationale is that donor screening assays qualify a unit for transfusion in the absence of clinical data, while diagnostic assays can be repeated if the results aren't consistent with the patient's clinical picture.

The provision of blood is a mature industry: blood donor collections have been flat at an annual collection of about 15 million units for the past half dozen years. There about two million apheresis platelet units collected in 2004 (the last year for which we have data) and they increased about 5% between 2001 and 2004. A new survey, sponsored by DHHS through AABB will provide more recent data, but there is little prospect for further growth. Less than 1% (perhaps as little as 0.1%) of the revenue for the manufacturers that make our assays comes from blood. The profit margins from blood screening assays are way below those of pharmaceuticals produced by the same companies, so their interest is limited. The hospitals have somewhat limited health care resources. About 5-15% of patients are transfused and less than 1% of hospital expenses is for blood, but blood is the highest single expense in the laboratory budget. Blood centers, National Red Cross or ABC members, are all not-for-profit and work under low margins. They have limited reserves and limited ability to finance research and development. Slide #10 shows how the price of a unit of red blood cells has changed over the years, adjusted for inflation (published annually in the ABC Newsletter). Each addition (e.g.,

West Nile Virus, NAT, bacterial detection) increases the price a little bit to what it is today – a bit over $200 for a red cell. The next slide (#11) shows the average margin for all ABC blood centers over the past 5 years, now between 4.5-5.0%, enough to reinvest but not enough to introduce safety enhancements, e.g., tests, more automation, computerized donor histories.

There are two available platforms commonly used for blood testing by all blood centers in the US: one is from Ortho (Johnson & Johnson) and the other from Abbott. In the past, most centers adopted a single platform, but now there is a tendency to diversify to ensure assay availability. For each manufacturer, newer assays are replacing old ones, partly because the FDA sets stricter standards for sensitivity (e.g., HB_sAg). In some instances, the new assays are in process of being licensed, with no clear indication of when this will happen. There are two NAT platforms and each manufacturer can provide for each of the viruses for which we test. There are not enough supplemental assays to be used for confirmation of positive screening tests, and some (e.g., Western Blot) are less sensitive than the screening assays and are, or should be, obsolescent. The manufacturers have no interest in developing supplemental assays because the market for them is too small to justify the expenses in obtaining a license.

As for testing organ and tissue donors, not all assays are cleared for that and, if used, are used "off label." Those that are cleared are for individual donor testing, rather than testing in mini-pools as is done for blood donors. There are apparent inconsistencies. For example, in the case of NAT, the rationale of requiring individual testing for a bone marrow donor is not clear when the recipient will receive many units of blood and platelets, all tested in minipools. He questioned the need for a clinical trial before licensing an assay for use with cord blood, suggesting that blood from a baby was not that different from blood from an adult. Not testing cord blood donors would be unthinkable.

Dr. Leiby will discuss tests for parasites later, but it is worth mentioning here that we don't have confirmatory tests. We don't have screening tests for malaria. There is no *product release* assay for bacterial contamination of platelets. Currently used assays have not been validated for product release, but only for *quality control*. The available bacterial detection assays are not appropriate for whole blood-derived platelets, but only for apheresis products. The only point-of-use tests, Virax, tests platelets a few hours before transfusion, but it has been cleared only for use with apheresis platlets (already tested by culture and found negative). The manufacturers say that the requirements for licensing the products are so great that they are not willing to devote the resources to it (at least $10 million). The requirements for informed consent are stringent enough that donors often (>20%) opt out of trials using an unlicensed test, making them difficult to perform. The history of oxygen carriers and pathogen inactivation is instructive; for 15-20 years these approaches have been investigated, but not a single one has been brought to market. Devices aren't marketed in the US for 5-10 years after they were introduced in Europe and other countries.

He has no answer for many of these problems. Perhaps there should be alternate pathways for the approval or licensure of assays with a very limited market, e.g., confirmatory assays. Blood centers themselves should expand their activity beyond collecting red cells and do other things that may increase their value to their communities and organizations. Transfusion medicine needs to be made more attractive to manufacturers of needed products. We need public discussion and emphasize the benefits of transfusion (he's "alive because of blood transfusions.") and its important role in healthcare. The introduction of new safety measures does not necessarily mean that blood had been unsafe. TRALI has not made the blood unsafe; it

has always been there. Measures to address its prevention are a victory. We need to focus on evidence-based policies.

There was no time for questions or discussion of this presentation.

After lunch, Dr. Bracey introduced a special guest, Don Wright, MD, MPH, newly appointed Principal Deputy Secretary for Health and Acting Assistant Secretary for Health. He is the primary advisor to the HHS Secretary on matters involving the nation's public health and science. He is also responsible for oversight of the US Public Health Service including planning and execution of public health policy as it relates to disease prevention, health promotion, women's and minority health, the reduction of health disparities, the fight against HIV-AIDS, blood safety and pandemic influenza planning. Before his current appointment, he served as the Director of the Office of Occupational Medicine for OSHA. His training was in Texas.

After a few general remarks about the work of the Committee, he invited questions from the members. He was asked for his perspective on role of the Assistant Secretary for Health as the "Blood Tzar," the singular voice in the US for the long term issues of safety and availability of the blood supply. The Principal Deputy Secretary for Health is a career Civil Service position and not a political appointee, like the Assistant Secretary for Health. This allows for consistency between Administrations in the Office of Public Health and Science.

The next speaker, David Leiby, PhD, the Chief of Parasitology at the Biomedical Research and Development Center, American Red Cross, to discuss "Unmet Needs on the Horizon (malaria, Babesia, Dengue and Others?)."

There are five species of plasmodia that cause malaria: P, falciparum, P. vivax, P. malariae, P. ovale and more recently described P. knowlesi (probably the cause of cases previously ascribed to P. malariae). Malaria is transmitted by mosquitoes, primarily in tropical and subtropical areas and worldwide is a major health issue causing considerable morbidity and mortality. Malaria is limited as a blood safety issue in the US, with only five cases of transfusion-transmitted malaria in the nearly 10 years since 1998. Instead, it has become more of a blood availability issue than a safety one; the Red Cross is losing almost 100,000 donors annually because of malaria exposure deferrals. To address the issue of efficacy of the malaria-risk questions asked of donors, the Red Cross compared deferred donors with acceptable ones using an EIA antibody test procedure. Supplemental testing with PCR and RT-PCR techniques were found to be not very effective, more because of the biology of the organisms than because of assay sensitivity. They repeated the risk-factor questions aimed at screening out malaria risks. Of 3,229 non-deferred donors (controls), 11 were repeat reactive, eight of which had geographic risks that were not detected at the time blood was donated. Of nearly 1,500 deferred donors tested, 20 were repeat reactive. One had been deferred for having had malaria; all the rest were travel-related deferrals with multiple possible exposures and periods of residence. Hence, donors most at risk for transmitting malaria have been residents in malarial areas and/or had one or more bouts of disease.

Babesia, parasitizes red cells and may be mistaken for malaria because of similar morphology. In the US, the primary agent is babesia microti, while in Europe it is babesia divergens. It is transmitted by Ixodes (deer) ticks, the same ticks that transmit Lyme disease and several other agents. Babesiosis causes a flu/malaria-like illness, but can be fatal in elderly, immunocompromised or asplenic individuals. If recognized, it can usually be treated with

antibiotics. More than 70 transfusion-associated (both red cells and platelets) cases have been reported worldwide since 1979, most of them (about 10 per year) in the US. The organism remains viable in stored red cells for 21 days experimentally and 35 days in some transfusion-associated cases. There are no licensed tests and no effective interventions. However, it is very geographically limited agent, found primarily in the US in the northeast, upper Midwest and perhaps the far west. The Red Cross has studied about 2,000 donors annually in the Connecticut blood region since 1999, finding about 1% each year are seropositive for B. microti. Testing seropositive donors with a PCR procedure finds seasonally variable positives. Up to 50% of transmitting donors are positive with the PCR procedure; many, but not all transmit babesia to hamsters on inoculation.

Dengue virus is a single-stranded RNA arbovirus that is responsible for Dengue fever (50-100 million cases annually) and Dengue Hemorrhagic fever (several hundred thousand cases per year) worldwide, a huge burden. It is transmitted by the Aedes aegypti mosquito and there have been transfusion cases reported. Slide 19 shows the distribution of Dengue, through Northern Africa, Asia, South America in increasingly up through Mexico and even into the US. It pretty much mirrors the distribution of the A. aegypti mosquito. Clinical characteristics include fever, headache, myalgias, arthralgias and hemorrhagic manifestations. The case fatality rate is about 5% and it's considered to be a resurgent disease. About 100-200 cases are introduced into the US annually, mostly by people who already have had Dengue, although there has now been some localized transmission here, first reappeared in 1995. It could spread through the country much like West Nile has. There was a dramatic increase in US cases in the 1990s. All Red Cross blood donations in Puerto Rico, where there is plenty of Dengue, were studied with a NAT procedure during September-December 2005, immediately after the peak

transmission season. Twelve of more than 16,000 tested were positive, about 1:1,300. Three of them lacked IgG, suggesting a recent or acute infection.

The chikungunya virus ("chik-v) was first identified in Tanzania in 1953, but has not yet made it to the US. It's a zoonosis, primarily transmitted between primates and humans. It is mostly localized in developing countries in Africa and Asia, transmitted by Aedes aegypti mosquitos, and less commonly Aedes albopictus (the Asian Tiger mosquito growing more numerous in the US). The incubation period of chik fever is 3-7 days; acute fever is days to weeks and an infection confers lifelong immunity. The perspective of chik fever changed in 2005 (an outbreak on La Réunion with 40% of the population ill) and 2007 (outbreak in Italy). The disease was more severe and there were some fatalities from respiratory failure and brain infections. The transmitting vector in Italy was the Asian tiger mosquito and the trigger was an infected immigrant who infected the mosquitos. Slide 27 shows the current distribution of the Asian Tiger mosquito in the US, mostly in the Southeastern part of the country, but it is spreading.

There are some chinks in the blood safety armor. Some of our approaches, e.g., malaria, are misquided. Unmet challenges include babesiosis, which is quite narrowly localized and raises the question of localized approaches to donor deferral. New approaches, which may include agent-specific measures are needed. Pathogen reduction and multiplexed proteomics should be considered.

In the discussion, it was noted that infectious agents may move with mosquitoes and with people (travel, etc.). "Lyme disease moved on the wings of birds and babesia on the backs of mice." (Andy Spielman) The ticks that attach to birds can contain Lyme disease and Lyme

disease moved quickly across the country. Hence, geographic approaches to donor deferral may have limited efficacy. No one had any information about the mobility of blood donors, but it is likely to be important. Blood products may also be shipped after collection well outside the region for use. Transmission of Chagas disease by platelet products (a total of seven transmissions in the US) has led to implementing screening). Despite no reported transmissions by plasma or packed cell products, Dr. Leiby believes that T cruzi is probably also transmitted by red cells. FDA is aware of many of the current limitations of our approach to malaria and has held workshops to try to circumscribe the issues, especially travel-based deferrals and whether Africa and Latin America should be treated the same.. Current policies were originally accepted as the best we could do at the time they were adopted. The geographic range of babesia is expanding beyond New England. It is likely that many cases of babesiosis are mis-diagnosed as malaria.

The next speaker was Brian McDonough, Vice President of Worldwide Marketing, Ortho Clinical Diagnostics, to address "Economic Factors of Test Development and Implementation." His comments do not necessarily reflect the opinion of his company, but he has their approval and support to express them. His presentation will be in four sections: 1) similarities and differences between blood centers and public companies; 2) perspective on market attractiveness; 3) broad subset of companies that support the transfusion medicine industry and 4) summary and suggestions how to move forward in these respective worlds with thoughts on how to change behaviors in decision-making.

The mission statements of blood systems in the US are all similar in providing blood components and related services on a very cost-effective basis. Public companies are also similar to each other to provide high value products and services that support customers'

missions to save and improve lives and help manage and perhaps reduce the overall cost of healthcare. There are underlying business drivers that set the two groups apart and separate. Blood centers strive to be self-sufficient, providing 100% of all the products required by their hospitals and communities. Public companies are driven by the need to grow consistently year after year. Blood centers operate in monopolistic fashion, like public utilities. Public companies of necessity and by design are competitive. Blood centers try to be low cost providers; companies want to sell at fair value. Blood centers, with a few exceptions, have a limited focus and expense in R&D. Public companies have a very significant focus and expense in R&D. Blood centers are accountable to a national authority or to a local board of directors, while companies are accountable to share-holders. Blood centers exist to meet needs of community hospitals and remain "financially viable"; public companies exist to meet the financial needs of shareholders and strive to remain "mission viable."

With regard to "market attractiveness," new tests grow the market; test improvements do not. For example, the P-24 antigen and the HCV antigen were dropped from the menu of offered products as a consequence of NAT. The serology market from 1990 through 2007 did not represent a very attractive business opportunity. The total cost of testing of 80 million donations worldwide is about $1.4 billion. The NAT market, only about seven years old, now represents slightly more than 50%. From the year 2000 to the present, $700 million of new expense has been met by the blood industry. About 3% of the in vitro diagnostics market, worldwide, is donor screening, and it has remained relatively constant at this percentage for the last two decades. On the other hand, this in vitro diagnostics market may nearly double to $60 billion (from $34 billion) by 2013 with a very significant increase in "biomarkers" and in the rest of the nondonor-related market ($32 billion to $42 billion). From the perspective of two other

companies (e.g., GE and Siemans), the market is likely to grow to $120 billion, when you include their current business and add the future growth in their imaging business. Adding their current and growth business in information technology (their entire diagnostics/imaging/information technology and their market looks like $185 billion. Where does that suggest that these companies look and invest for their future growth opportunities?

Many companies use a portfolio management graph (slide 18) to chart the reward vs risk or the relative probability of success in introducing a new product. Positive factors include that the health risk is well known and understood, that a standard of care would develop for implementing the new assay, that there has been regulatory, national or in some instances funding authority assurance of action and that this company believes they can be the first to market (a significant advantage). Failure of any or several of these to be realized will be negative factors, something that Brian Custer will discuss later in the meeting. The standard of care might not be persuasive, at least on the projected timeline, and the market may look for ways to minimize adoption despite the evidence of health risk reduction. Regulatory and/or funding action can be delayed. Today there's a significantly higher level of competition for investment dollars and from the point of view of diagnostic companies, the relative risk of tests for the donor screening market may be higher than was true in the 1980's. Investment in a new screening test in particular competes against four major fields of future interest, hematology and especially cardiovascular, metabolic and oncology diseases.

Hence, the market attractiveness of low growth donor screening must compete with projected high growth for new biomarkers. These new biomarkers could provide earlier disease detection which means earlier intervention and better clinical outcomes for patients. In vitro diagnostics companies are facing a shift, as with much of healthcare, from a focus on laboratory

efficiency in hospitals and blood centers more toward disease-based interventions for currently unmet medical needs, homing in on clinical outcomes driven by health economics and a more patient and physician orientation.

Many companies have undergone corporate changes in the past few years. Take-overs and mergers is a way to increase market share and permit a reduction in overhead costs and costs per unit. One may buy another company to gain access to intellectual property or to change strategic focus and become more broad-based or to gain access to channels that allow them to reach more customers. Some companies are purchased by investors who think they can manage it more effectively and then spin it off for greater profitability. On the other hand, some companies are sold to divest non-revenue or non-profit producing parts of their business ("dogs"). Some divestures are to narrow business focus and go for deeper penetration. Some may merely generate cash for debt management or investments. One example is Haemonetics, which went from a bag and plastic bowl manufacturer to a more diversified one by acquiring three different software companies (IBM, Infonale and 5-D) and a small firm with a medical device. Another example is Siemens, now probably the largest diagnostic company in the world, especially immunodiagnostics through the acquisition of Bayer, Dade-Behring and DPE. Only one of these has any assays in the donor screening market with less than 1% market share. It is his judgment that Siemens is unlikely to invest much money in infectious disease for the donor screening market although they may not exit it entirely.

Ortho is not exiting the donor screening market, although they will be dropping an assay from their menu. More broadly, suppliers to remain interested in the transfusion medicine market, although there is greater competition for R&D funds and ambiguity on what technology is needed or the industry wants to adopt. It is important that a consensus be developed on

requirements and that this be communicated to suppliers, e.g., the management of West Nile and bacteria screening in the US. Conversely, the CJD and pathogen reduction issues have been badly managed or could be good examples on nonconsensus. The expectations for implementation in the market should be defined, e.g., all donors or a subset. In the past, implementation has been delayed until both manufacturers have the product, generating more risk for the companies.

He forecasts some increased supplier consolidation and a shift of R&D dollars to other growth areas than transfusion medicine. There likely will be less or fewer new technologies devoted to transfusion medicine. Higher prices may be expected. There are some start-up companies that find the transfusion medicine and blood bank market attractive, e.g., RFID, point-of-care tests, micro-array. Market consolidation can increase stability; fewer competitors in a non-growth market is better from a company's viewpoint, and probably from the perspective of a blood center. The small customer base of donor centers throughout the world (about 1,000, with about 200 representing 70% of the purchasing power) is attractive, compared to customers numbering in the thousands.

The discussion began with the message that too much money is spent on sickness and treating people in the last years of their life and the health care dollars should be applied to preventative medicine and public health. The tests done on donated blood prevent transfusion-transmitted disease. How does that fit into the model Dr. McDonough presented? The diagnostic companies today focus on new unmet needs. The infectious disease testing is essentially a commodity and, with a few exceptions, not new business. To the major companies in the diagnostics world, unmet needs are opportunities for growth; the tests as commodities are not. To what extent does the picture looks different to a small company. Why aren't there small

start-ups for niche markets? There are small startups, for example, microarray testing, the ability to do multiple assays on a single computer chip. This is a fascinating technology that is likely to have widespread application in the future world of diagnostics, although probably not in the donor screening environment in our professional lifetime. A major reason is that the art of finding an assay with exquisite sensitivity and specificity is not easy in a micro-aliquot of blood. In addition, there is a very complex array of licenses and patents that these startup companies must go through to get clearance to put a particular assay on their technology. Further, the cost in the US for a complete donor screening system to the market requires more capital to invest in a field that is not growing. Hence, these companies with a good idea must find a parent who can marshal it through the regulatory process and who reaches into the markets throughout the world and produce a good return. You can count the number of companies in donor screening to serve that purpose on one hand. Nevertheless, there are some great opportunities. A number of companies have jumped into bacteria screening because it is a well-defined, well-articulate opportunity for bacterial screening of platelets; the growth opportunity is to expand to bacteria screening all of the red cells. Do companies look at the ripple effect of confirmatory tests and others related to treatment for the infected donor. For example, there's increased recognition of Chagas' disease in the US stemming from increased awareness feeding the desire for further testing. Chagas' is a good example. Bringing a test to market as quickly as possible may target 95-99% of the need with the first generation assay, leaving it for subsequent claims for 5-10k approval for cadaveric and/or confirmatory assays on the second generation procedure. The timeline, however, for additional generations and applications does not always meet the original plan.

The next speaker was Mark Brecher, MD who has a bachelor's degree in chemistry, an MD from the University of Chicago and had specialty training in transfusion medicine at the Mayo Clinic. He is Vice Chair and Professor of Pathology at the University of North Carolina. His topic is "Innovation in Bacterial Testing" ("past, present and future" of testing for bacteria in platelets.

There has been a large reduction in the risk of virus transmission by blood transfusion through the years, but bacterial contamination has remained constant at 1:1,000 to 1:2,000 units. Until recently, this contamination was largely ignored, becoming of great interest in the blood banking industry only for the last couple of years. The sources of contamination of platelets are the donor's skin surface and appendages (preparation reduces but does not eliminate the bacterial load; the hollow needle may punch out a core which is collected with the blood), a transient bacteremia in the donor (e.g., from the gut, the bacteria most likely to produce a fatal reaction) or possibly contamination through the bag surface (suggested, but not well understood). During the early part of this decade, about 4 million bags of platelets were transfused annually, of which 1 million were apheresis-derived and 3 million were whole blood-derived. With 1 in every 1-2,000 bacterially contaminated, 2,000 to 4,000 contaminated platelets were transfused per year. Clinical sepsis occurred from 10% - 40% of these few as 1:10 of these. Whether or not the sepsis was fatal depended on the organism; Gram negative bacteria are much more dangerous than Gram positives. Estimates vary, but there have been probably 40-533 deaths annually from platelet-induced sepsis, a fatality rate of 1:7500 to 1:100,000 per unit of platelets.

FDA has sponsored several meetings to try to deal with the problem of bacterial contamination. Regulation was deemed necessary, since hvospital administrators are unlikely to back something that costs money unless it is mandated.

In 2002, several things changed: 1) BacT/ALERT automated liquid culture system was validated and cleared (by FDA) for *quality control* of platelets; 2) a second quality control system (Pall eBDS) was approved by FDA; 3) a group of speakers and moderators from a third FDA-sponsored bacterial contamination meeting issued an open letter to the blood banking community urging that something be done. This led the AABB and the CAP (College of American Pathologists) to change their accreditation standards to require methods to limit and detect bacterial contamination in all platelet components (AABB) or a system to detect the presence of bacteria in platelet components (CAP). Out of concern for an adverse effect on platelet availability, Dr. Christine Beato (Acting Assistant Secretary for Health) requested that the AABB delay implementing this requirement. After considering the issue, the AABB said "no."

Other strategies to limit bacterial contamination included studying and improving the preparation of the venipuncture site and shifting toward single donor apheresis platelets. Another strategy was diverting the first few ml of blood (most likely to be contaminated by a core contaminated skin) to a separate plastic pouch to be used for testing.

In the spring, 2004, the Inter-Organizational Task Force on Bacterial Contamination of Platelets (AABB) assessed the effect of these measures on the blood supply via a survey. The vast majority of blood centers, hospital blood banks and transfusion services reported little or no change in their ability to provide platelets for patients and found no increase or a very small increase in out-dating. Most apheresis platelets were tested by a culture technique (BacT/ALERT or Pall eBDS), but the application of such techniques to random-donor whole-blood-derived platelets was logistically difficult and expensive, so most such components were tested using non-cleared methods, e.g., pH, glucose levels. These are not very sensitive or

specific and allowing their use was a mistake, in his opinion. The Red Cross found that the true positive rate has held steady at about 1:5,000, while their septic transfusion reaction rate has dropped about 50% or more. Although fresh platelets can result in septic reactions, the majority of such reactions occur from day five platelets.

In general, attention paid to septic reactions has been successful, dropping from 1:40,000 before culturing to 1:75,000 after and further to 1:175,000 after diversion had been properly implemented (ARC data). Only one fatality was reported between October 2006 and October 2007, which is 1:700,000 (passive reporting probably is under-reporting). A report from Hema-Quebec showed a decrease in septic transfusion reports, as did results from Blood Systems.

Most blood services using the BacT/ALERT system are using one aerobic bottle without the recommended (for blood cultures) anaerobic bottle. Many of the true positives are Gram negative bacteria, which are likely to produce severe or fatal septic reactions. In a small study of (2,400) apheresis units that were recultured on issue or at outdating, none were found positive, suggestiong that few are missed. For eBDS, 118,000 apheresis and whole blood-derived plastelets from 23 blood centers, the positive rate was also about 1:5,000 and one example of staph epi caused a septic transfusion reaction (this organism grows slowly and it is likely that other similar slow growers will occasionally be missed.

One of the initiatives stimulated by these studies and discussed in this Committee was to collect data to support extending the dating for platelets back to seven days, where it had been before septic reactions directed the reduction back to five. A postmarket surveillance study (Passport) was initiated in 2005 and involved both Gambro and Fenwal platelets. The hypothesis to be tested was that tested 7-day single donor platelets were no more dangerous than 5-day

untested platelets. Fifty-thousand outdated platelets were to be tested in 29 organizations and 47 centers. Accrual has been slow, and two of 2,600 tested at outdate were positive, suggesting that they had been missed initially, a worrisome rate of1:1300. At UNC, going back to 7-day platelets would add about 320 platelets annually to those available for transfusion. On the other hand, only 8% of their platelets are transfused on days 6 or 7, so there isn't a lot of inventory older than day 5. Many report a drop in outdate of about 50% when they moved from 5 to 7 days of platelet storage. This gain in platelets will likely pay for the cost of testing. Safety is improved and money is saved, an unusual combination.

One unanswered question is the need for anaerobic cultures. Reactions from platelets contaminated with anaerobic bacteria are very rare. It may be that the different culture media make a difference. Currently platelets are released after cultures 13-21 hours; a few slow-growing streptococci grow faster to detectability in anaerobic bottles than in aerobic (21 vs 43 hrs), although this is of unknown clinical importance. Errors, human and from equipment, can occur and rarely cause patient problems.

Pall Corporation has introduced the "Acrodos" pooling system so that random, whole-blood derived platelets can be cultured and stored for five days. The market penetration of this system has not been great.

The Virax Pangera bacterial detection system will pick up 10^4 to 10^5 bacteria per ml with a rapid test that can be done at the time of release to the patient. It has been approved for use as an adjunct to early culture for apheresis platelets, which is probably not where it is needed. Marketing forces probably governed what the manufacturer requested. It is marketed by Abbott.

Outside of the US, many countries have gone to 100% hacterial screening with seven day dating. A very few use BacT/ALERT for quality control only and not for release. A smaller portion of the total platelet use is apheresis rather than whole-blood derived, compared to the US. Some have decided on a gradual implementation of pathogen reduction. Pathogen reduction has been implemented in La Réunion Island because of the Chikungunya virus, and France has decided to implement it slowly in the entire French system (starting with Guadeloupe and Martinique in the Caribbean). Japan stores platelets for up to 72 hours and "has no problem" (at least 2 fatalities from septic platelets in the past seven years). Some septic conditions can be delayed (e.g., heparin flush catheter contamination with pseudomonas fluorescens causes sepsis that was detected by look-back from 84-421 days after the contaminated flush).

Opening the discussion, how is it known when false positives were really false positives. In response, this assumption merits more discussion. Is the a possible increased risk for recipients receiving 5-7 days platelets without informed consent and without IRB approval an ethical problem? Personally, Dr. Brecher doesn't, since this is a post-marketing surveillance study similar to other such studies for drugs. The UNC IRB did review the study and agreed that informed consent was not needed.

The next speaker was David Asher, MD, from CBER, FDA to discuss the Development of Tests for variant Creutzfeldt-Jacob Disease (vCJD). Dr. Asher is a graduate of Harvard College and Medical School, a Diplomate of the American Board of Pediatrics and the Chief and Supervisory Medical Officer of the Laboratory of Bacterial, Parasitic and Unconventional Agents, FDA. His topic is "Development of Tests for variant Creutzfeldt-Jakob Disease (vCJD)." His presentation has not been officially FDA-cleared, but everything in it is available in the public domain and primary sources should be cited, if a citation is needed . The CBER

web site and WHO guidelines can provide official information and primary sources. Transmissible Spongiform Encephalopathies (TSEs) are characterized by a sponge-like appearance of brain tissue and the formation in brain tissue, and sometimes other tissues, of amorphous-stained material – "amyloid plaques." There are four or five TSEs of animals, depending on how you want to split them (scrapie in sheep or goats, transmissible mink encephalopathy, chronic wasting disease of deer, elk and moose and bovine spongiform encephalopathy – BSE – in cattle, other ungulates and cats), of which all except feline spongiform encephalopathy (which may or may not be separate from BSE in felines) have been seen in the US. The BSE agent (prion) causes variant Creutzfeld-Jakob disease (vCJD) in man which, because of its demonstrated blood risk, is the most important to us. Except for BSE, none of the animal disorders have been implicated in human infection, although monkeys are succeptible experimentally to all. There are three to eight human TSEs, depending on how they are split. Kuru provides a lesson in public health and demonstrates that the incubation period for infection can approach 50 years. Creutzfeldt-Jakob disease (CJD) has been known since the 1920s; the first case of vCJD became known in 1984 and was described in 1996. The last two (Gerstmann-Straussler-Scheinker syndrome and fatal insomnia syndromes) are extremely rare and won't be further discussed. All are transmitted by food or by products, some of which are in classes regulated by the FDA (e.g., surgical instruments, corneas, dura mater grafts and human cadaveric pituitary hormones, which is no longer approved in the US). There have been four transfusion-transmitted cases of vCJD in the UK, the first new class of medical products implicated during the past 10 years.

Kuru merits special mention. In 1957, kuru was the leading cause of death among women of the Fore language group in Okapa, New Guines. In 1957, for esthetic rather than

medical reasons (it violated Australian and Queensland law, the occupying governments) the practice of ritual cannibalism was prohibited. Over the next 20 years, the cases of kuru fell to almost nothing, so that in 1999, there were no cases and then none til 2003. Simply preventing contact with contaminated tissue seemed to have eliminated completely an epidemic of the spongiform encephalopathy.

Slide 13-16 summarize what is known about tissue infectivity for TSEs. Neural tissue, tissues closely associated with the nervous system and some lymphoid tissues are infectious. Epidemiological studies in man have failed to implicate blood as a risk factor. Experimental studies in laboratory animals have not been reassuring. Four cases in the UK have demonstrated without much doubt that blood could transmit vCJD. In a hamster model, infectivity appeared about half-way through the incubation period and continued to increase into clinical disease. Infectivity was found in all components, but there is some evidence that it is restricted to nucleated cells and to plasma, but no component can be processed to complete purity.

BSE has been found in three cattle in the US, one of them from Canada. Canada has had at least 12 recognized cases of BSE, 11 native and one imported from the UK in 1993. The UK has had the great majority of cases worldwide. Cases peaked there in 1992 with just under 40,000 diagnosed cases. No one knows how many truly infected cattle there were, but the exposure of the UK population to contaminated beef products must have been considerable. BSE has been reported in native cattle of 25 other countries since feed bans and other protections were put in place in UK. The number of diagnosed cases in UK has fallen sharply since these procedures were adopted, 114 in 2006 and only 49 cases through September 30 of last year. Unfortunately, there is another risk of BSE in the world, the widespread export of contaminated meat and bone meal from the UK, including to the US and Canada. Although there are no record

of imports, there are records of the exports. Hence, there are worldwide risks of unknown magnitude, although we hope it is low.

There is very little reason to doubt that BSE is the cause of vCJD because of its unique clinical presentation, unique pathology and striking accumulation of prion protein in lymphoid tissues, not seen in other forms of CJD. Through December of last year, there had been 204 cases reported, 166 of them in UK and 38 nonUK cases, of which at least seven were probably infected in the UK (six had lived there for more than six months, including two in the US and one in Canada). vCJD cases peaked in the UK in the year 2000 (7-8 years after the peak of BSE). Nevertheless, in 2003 the first of four reported transfusion-transmitted cases were reported. Donors later recognized to have vCJD are followed through the transfusion medicine epidemiological review. There have been 18 "vCJD donors" whose 66 labile components were distributed to 66 recipients. Twenty-three of those recipients are still alive and a very small number have survived five years; four of them have evidence of infection with vCJD. These four seemed to have come from three donors; the red cells were not leukoreduced. Nevertheless, it is too early to conclude that leukoreduction was protective. Reassuringly, 174 batches of implicated plasma derivatives have not resulted in infection. The recipients have been warned and are being followed for evidence of vCJD.

There is some evidence that the incubation period for the food-borne cases was between nine and 21 years. The Japanese case became apparent 12 years after a 24-day stay in the UK, as close to a point exposure as can be expected. The other cases in Japan appeared much later than those in the UK. For the transfusion-transmitted cases, incubations can be set and varied from just over six years to eight and a half years. The UK case with evidence of infection but no

clinical disease died of an aneurysm five years after the transfusion, suggesting that the incubation period is not much shorter than for food-borne vCJD.

More than one hundred long-term survivors of transfusions of blood from donors who later came down with sporadic CJD have been followed. None of these recipients have evidence or ever had evidence of CJD. Hence, the risk is currently unmeasurable for sporadic CJD, but substantial from red cells, from donors with vCJD (see above). We still believe there is some theoretical risk because finding the agent in blood is so consistent with animals that it is hard to believe that with the human pathogenesis of sporadic CJD there can be that much difference. The risks can be managed to a degree by limiting the sources of raw materials to the safest possible donors by history (in place), screening (about to be discussed), using manufacturing processes to reduce the risk (likely in play for plasma derivative; less likely for labile blood components) or restrict product use (probably not feasible beyond good medical practice). The three most important determinants of risk are clearance during manufacture, quantity of product used by the patient and the prevalence of vCJD in US donors. Based on a prion protein tissue survey in the UK, as many as 237 people per million might be infected. The absence of a second wave of vCJD in UK is reassuring, considering the long incubation periods of other TSEs. It has been suggested that UK Public Health policies about BSE/vCJD have been based on "ignorance and fear." We might prefer to describe them as prudent respect for uncertainty and the precautionary approach. At this time, US protection for recipients is based entirely on deferral policies. Unfortunately, most of the deferred donors are not infected and not all potentially infected donors are deferred.

Two possible solutions are introducing a process that would remove infectivity (some ligands combined with filter technology might do this) or using a valid screening test on donated blood.

The gold standard for TSEs is the detection of infectivity. Among a number of animal assays, testing for infection in transgenic mice seems the most accessible. The greatest problem is spontaneous disease in mice that over-express either mutant or wild-type prion proteins, leading to misinterpretation of acceleration of disease as an infectious process. False negatives also occur. All of these assays are based on the demonstration the TSE amyloid; the workhorse technique is the Western blot demonstration of proteinase K resistance material. The prion protein is PPI-anchored to the cell surface. Pruisner's belief that this is the infectious agent is not universally accepted. With regard to tissue donors for whom autopsy tissues can be retained, there are many tests licensed for animal use (9 in the European Union) that could be used on human post-mortem tissues if desired.

All of the rapid tests for animal (and possibly human) testing are based on the detection of the abnormal forms of the prion protein. Many variables affect detection sensitivity: amounts present, proteolytic treatment, denaturation of the protein, the affinities and specificities of the primary antibodies, antibody labels and the amplification techniques used. The use of robotics produces more consistent results than do manual techniques. FDA has been encouraging test development, but progress has been slow.

There are surrogate assays that have been reported. One is protein 14-3-3, released into the cerebrospinal fluid, but this is neither specific nor feasible for antemortem testing. The abnormal protein has been sought in blood, but the results are no longer promising.

One problem has been obtaining and standardizing biological reference materials. The UK NIBSC is working on this, including quantities of infected sheep blood. There is no US reference material, although FDA and others have worked with WHO and Swiss reference materials. Another problem is the lack of confirmatory tests, once a positive result has been obtained. Testing for prevention of prion disease has a long way to go.

The next speaker was Harvey Alter, MD, Chief, Infectious Disease Section and Associate Director of Research, Clinical Center Department of Transfusion Medicine, NIH, to speak on "A Reductionist's View of Pathogen Reduction." Dr. Alter was a co-investigator on the original discovery of the Australia Antigen test.

The "Precautionary Principle" has been endorsed by FDA and the US Blood Establishment in the wake of the HIV tragedy states:

> "For situations of scientific uncertainty, the possibility of risk should be taken into account in the absence of proof to the contrary
> Corollary: The precautionary principle asserts that measures need to be taken to face potential serious risks."
>
> Alter's Corollary: Pathogen reduction is the ultimate precautionary principle by eradicating almost all potential for infectious disease transmission even before risk has been conclusively established, and possibly, even before the agent has been recognized"

Many view the decline of post-transfusion hepatitis from 30% in the 1970s to near zero by 1997 as a major accomplishment of blood transfusion medicine, but he suggests it to be a glaring example of a failure. Decades passed before agents were recognized, the extent of the hepatitis risk accurately defined and proper testing strategies implemented so that hundreds of thousands of cases of post-transfusion hepatitis occurred between 1970 and 1990. For hepatitis B, the interval was from 1940 to the first Australia antigen test in 1970, 30 years. For non-A, non-B (hepatitis C), the interval was 15 years. For HIV, it was three years and for West Nile

virus it was much better, under one year (although there were warnings that WNV was transmitted by transfusion in 1999; hence, it was really four years). The list goes on. In fact, any agent that even transiently traverses the circulation of man during an asymptomatic phase of infection is a threat to be transfusion-transmitted. The likelihood of that transmission is highly dependent on the duration of 'viremia' and the level of concern is dependent upon the severity of the ensuring disease." This reactive strategy to pathogen risk has an inherent problem of an inevitable delay between recognition of risk and the prevention of risk.

He suggested a new paradigm in transfusion safety that may initially add costs but ultimately will both provide maximum safety and turn out to be cost neutral, and probably cost saving. Nearly all of infectious agents can be reduced to nonpathogenic levels by treatment with nucleic acid intercolating agents such as psoralens and riboflavin in the presence of ultraviolet light. They inactivate most clinically relevant viruses (RNA, DNA, single- or double-stranded, enveloped or not, intra- or extra-cellular), all clinically relevant Gram-positive or negative bacteria thus far tests, spirochetes, protozoa of known transfusion relevance and lymphocytes (to prevent graft-vs-host disease). Disadvantages include a decrease in effective platelet yield and limited inactivation of some high titre agents such as HAV and Parvo B-19, but the recipient population is likely to have antibodies at levels to be usually protective. There is no toxicity known for riboflavin. The risk from psoralens is mainly theoretical at the low residual doses that would actually be transfused. There may be some concern in pediatric cases, but the safety margin even here should be wide. None of these processes have been proven to work for red cells, a current disadvantage.

There are offsets to the estimates of high costs. With a process useful for red cells, it should be possible to eliminate some of our current assays, e.g., syphilis, anti-

hepatitis B core, Chagas' disease, WNV and possible others. The need for new tests such as for babesia, Dengue, malaria and HHV-8 would not be needed. Bacterial testing could be eliminated, as could radiation, both major cost-savers. Donor exclusion based on geography could be eliminated.

Evangelistically, he suggested that the precautionary principle and the moral imperative dictate that we implement what is available, even if it is less than perfect. Solvent-detergent treatment of plasma products has obviated concern about transmission of WNV and dengue by those modalities. If it had been available in the early 1980s, the vast majority of cases of HIV and HCV in the hemophilia population would not have occurred. He urged the blood bank establishment, NIH, FDA and industry to make pathogen reduction a priority and work in concert to make it happen. He recalled around 1996 that David Kessler (FDA Commissioner) urged blood banks to develop NAT testing for routine donor screening, a suggestion that was greeted with huge skepticism and even derision. Nevertheless, there followed a government-industry collaboration which resulted in a remarkably rapid development of NAT testing that has been of immeasurable benefit to blood safety. He urged the Committee to say that pathogen reduction is the right thing to do and we need to find a way to do it.

In the discussion, the current status of the review of psoralens was requested. There have been clinical trials to permit many European countries to introduce routine pathogen reduction for platelets. Further trials are underway to try to satisfy FDA needs for the Cerus psoralen product (The Navigant product is riboflavin). It was noted that the Department responded to the IOM report in 1995 with principles for incremental improvement and for behavior of physicians, the government, the industry, blood testing

facilities, etc that were clear about how we respond to infectious agents. Would you like to comment on the role of incremental testing in view of the Department's sworn testimony to the Congress, which is still where we stand in this country regarding blood safety issues? Dr. Alter replied that they have been quite vigorous in the precautionary principle since the late start with HIV. Nevertheless, there is the inherent problem of reacting to something that has already occurred. There are a lot of agents out there to develop and implement new tests for, while pathogen reduction is more proactive.

The next speaker was John Chapman, PhD, Vice President of Research and Development and Scientific Affairs for Thermogenesis Corp, to discuss "Toxicology Related Issues of Pathogen Reduction." He was actively involved in the development of pathogen inactivation (Inactine) from1988-2004, when he disengaged.

There are two scenarios with regard to infectious disease risk and transfusion: for one, a small population of infected donors may transmit virus to a large population at risk; in the other, a large proportion of the population (donors and recipients) are infected and you wish to protect the few uninfected persons from being infected (e.g., CMV and EBV).

Pathogen reduction processes involved treating the blood or blood product (now usually a chemical plus photoactivation) and then removing the products of the chemical reaction. Nucleic acid targets provide the chemical basis for selective toxicity (infectious agent, but not the component – plasma derivatives, platelets or red cells). Toxicity is not totally selective, however, the basis for potential problems. As development work proceeds, it is very important that there be a continuous interchange with FDA. The

amount of added risk tolerated from a process is determined by the level of benefits. . The purpose of the program is to reduce risk, not substitute one risk for another.

Risk assessment has two parts: exposure assessment (dose, frequency, magnitude) and hazard assessment (hazard of chemical, its nature, what kind of infection is produced and outcome). As with drugs, there are standard batteries of tests to characterize the toxicity of a compound. Since these chemicals target nucleic acids, a battery of genotoxic and mutagenic assays are needed. Absorption, distribution, metabolism and excretion affect the general health effect. Finally, there is the important carcinogenicity bioassay. In vivo toxicity can be approached by giving maximum doses of treated components (e.g., platelets), often limited by the volume tolerated. Another approach is to give the active ingredient to the toxic level.

In general, for pathogen reduction agents studied, toxicity has been apparent between 1 and 100 mg/kg, like most biologically active drugs. The actual exposure with proposed use is much lower, leading to a more than thousand-fold safety margin. Animal testing is imperfect and one prefers a safety factor of at least 10-fold for extrapolating from animals to humans, another 10-fold to overcome person-to-person variation and yet another 10-fold to cover toxicology end-point variation. These together are 1,000-fold. Neverthelss, there may remain a theoretical risk, even if it is not measureable.

It is also unlikely that there is any long-term toxicity. The agents being used are water soluble and would be rapidly excreted without accumulation. Reaction products

are generally less biologically active than the parent compound, so that the safety margin is unlikely to be compromised by side products.

Slide 15 summarizes the findings for amotosalen (the Cerus product for use in non-red cell components). There are very good safety margins for all of the end-points studied. Genotoxicity studies support that this compound plus ultraviolet A light does not cause a relevant risk for mutagenicity or carcinogenicity, with at least a 40,000-fold safety factor (no effect at this level).

In the past, he had been involved with studies on Inactine (PEN110), an alkylating agent for pathogen reduction of red cell products. Inactine is no longer being considered because early clinical trials showed an increased propensity for patients given Inactine-treated red cells to form antibodies, a problem not yet seen with psoralen.

He recommends proceeding with psoralen technology, even if it is currently only available for platelets. From a purely business perspective, pathogen reduction is unlikely to progress without the promise of a return on investment from red cells and plasma as well as from platelets.

Ethylene oxide (ETI) which is used to inactivate pathogens in medical disposables may be compared with methylene blue, psoralen and PEN 110 for blood cells and plasma. For each, the removal step is incomplete and there is some in vivo exposure. ETO is a very hazardous highly reactive alkylating agent that is mutagenic, carcinogenic, fetotoxic, teratogenic and toxic to testicular function. The other three are mutagenic, but only PEN110 is also carcinogenic and none have reproductive toxicity. There are

regulatory limits to ETO human exposure, which compared with expected limits for the other three are 1,200 to 6,000-fold greater.

In the Discussion, it was noted that FDA considers toxicology data as preclinical information and part of the threshold for allowing clinical studies. Hence, FDA has reviewed and accepted the reasonable safety of these agents at their residual levels because they allowed clinical trials to proceed.

The first presentation in the Open Public Comment session was by Paul Cumming, MBA, PhD, President of Talisman, Ltd, to acquaint the Committee with the safety benefits gained by using an audio-visual touch-screen computer-assisted self-interviewing system for recording the donor medical history. Because 75% of errors reported to the FDA involve the donor interview and donor processing, we're concentrating on that. The Talisman QDS system is currently in use and considerable data have been collected on its performance. It can be used on mobile operations, where about 75% of all blood is collected. Although some of the benefits involve donor satisfaction, he focuses this presentation on safety benefits. Implementation of QDS in one center was followed by less variability between donation sites, a 27% reduction of initial test positives among first-time donors went down and an increase in behavior-based deferral. Post-donation information reports (information about deferrable behavior omitted in the initial interview) decreased. There was probably a time-saving of about 5 minutes per donor, although there is enough variability between interviewers to make this difficult to prove unequivocally.

Dr. Bracey opened the Committee Discussion with some general remarks on the genesis of this Committee to encourage action to prevent adverse outcomes of transfusion. There seems to be a fairly heavy weight toward pathogen reduction as, in Dr Roberts' terms, the right thing, recognizing that there are some unanswered questions. The discussion should be in the context of current challenges to transfusion safety, recognizing that viral transmission has been reduced to very low levels that are not directly measurable. TRALI (about 50% of fatality reports made to FDA), hemolytic transfusion reactions (25%) and bacterial contamination (10-12%) are looming as large continuing threats. Perhaps the largest risk is in how the products are used, e.g., blood is over-transfused, under-transfused or wrong component is transfused. Another safety issue is blood shortage (especially platelets), which is a collection problem (including deferrals). The effect of a test or deferral issue on availability should not be discussed.

The Committee could encourage a commitment by both government and the private sector (industry) to advance pathogen reduction as a priority goal. The Committee lacks the information to determine the safety and efficacy of pathogen reduction technology per se; that decision lies with the FDA. Moving pathogen reduction technology forward will take resources and a commitment, not unlike the situation was with NAT. The nay-sayers were overcome by a public-private partnership that acted on the premise that it could and would be done.

There isn't a good way to evaluate either availability or safety because comprehensive data are not available, only a series of anecdotes on either side. More presentations and more data will be available on the second day of the meeting. The meeting adjourned at 6:00 PM to reconvene the next day.

The Committee reconvened at 9:00 AM, January 10, 2008. CDR Libby was absent and Dr. Ruth Solomon (FDA) was added; otherwise the Committee attendance was unchanged.

This day focused on current systems for pathogen reduction. The Committee will also consider two draft proposals, defined by a subgroup to be presented to the group with a summary of their discussions.

The first speaker of the day was Dr. Harvey Klein, Chief of the Department of Transfusion Medicine and a Special Assistant to the Director of Science for the Clinical Center, NIH, and an Adjunct Professor of Medicine at Johns Hopkins. He is also co-editor of Mollison's Transfusion Medicine. He is to review a Canadian Censensus Conference on Pathogen Reduction.

Current procedures to reduce the risk of transfusion-transmitted infection include: donor history and examination; testing; sample diversion; leukoreduction; post-donation information; donor deferral registries; and limit recipient exposure by restricting use to appropriate indications. The whole blood sector has used a reactive strategy, developing tests to screen out pathogens as they are discovered. On the other side, the plasma derivative industry has used a strategy to inactivate agents that might be transmitted and there hasn't been any transmission of HIV, HBV or HCV since inactivation was begun.

When the West Nile virus came to the US, there were no transmissions from fractions treated to inactivate pathogens.

The initial goal of pathogen inactivation in blood components focused on eliminating the transmission of viruses, but it has been found useful in preventing the transmission of bacteria and parasites. There may also be added value in reducing the risk of graft-vs-host disease and possibly even TRALI. The Canadian Consensus Conference did not consider any particular company's technology.

The US has been slow to accept inactivation because the safety of the US volunteer donor blood supply is terrific, there is no inactivation method for all components nor for all agents and our surveillance and screening tests have dealt very well with emerging pathogens. There is also the issue of costs.

The Canadian Blood Services, Hèma-Quebec and BEST convened a Consensus Development Conference, based on the NIH model to formulate a decision when the data available are plentiful but not sufficient to support a data-driven decision. A steering committee, Chaired by Dr. Morris Blajchman, planned the conference, crafting six questions, identifying speakers to provide background information and appointed a panel to develop a consensus to address the questions. Current risks presented focused on Canadian data, but US data are similar, viz yesterday's presentations. Dr. Klein chaired the panel, which included a hematologist, a pediatric hematologist, a medical ethicist with legal training, a transfusion medicine consultant, a multiply transfused patient, an economist with cost-benefit estimation experience, an intensivist and a microbiologist.

The consensus was presented publicly for comment; comments were also solicited from persons not present. The consensus statement was further refined and published.

Question 1 was: "Is the current risk of transfusion-transmitted diseases acceptable in relation to other risks of transfusions." Based on the data alone, the Panel did not recommend introduction of pathogen inactivation with its attendant unknown risks. However, active surveillance cannot account for the risk of an emerging infectious pathogen and the reactive strategy permits an agent to disseminate before clinical disease is recognized and may undermine public confidence in the blood supply. Such risks require a proactive approach in accordance with the precautionary principle.

Question 1 a: "under what new circumstances should pathogen inactivation be implemented?" Pathogen inactivation should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available. Non-infectious hazards of transfusion can entail serious safety issues and the introduction of inactivation technology should not preclude efforts to reduce non-infectious risks.

Question 1 b: "should the criteria be the same for RBC, Platelets and FFP?" The same criteria of safety, feasibility and efficacy should apply to all blood components and a single method to inactivate pathogens in all blood components would be ideal. However, the absence of a single integrated system does not necessitate a delay until a method is proven satisfactory for all components..

Question 1 c: "should different criteria be used for certain patient populations?" The treated product should be used universally; few data are available on which to base individual risk-benefit assessment. "Vulnerable populations" (premature infants, children

and pregnant women) might be at particular risk for transfusion-transmitted pathogens and derive special benefits from pathogen inactivated components.

Question 2. "What minimum acceptable safety and efficacy criteria should be used for the pre-approval assessment of pathogen inactivated products?" a: "What criteria should govern acceptable toxicology standards and how should they be assessed?" The panel encouraged harmonization of approaches and sharing of data among the various regulatory agencies, recognizing proprietary restraint.

Question 2 b: "What post-market surveillance should be required with the implementation of pathogen inactivated blood components?" The Panel recommended specific studies, mandated by the regulatory agencies and supported by manufacturers or blood suppliers, of adverse reactions with linkage to national hemovigilance systems. Reports should be prepared and analyzed annually. Hemovigilance data should be shared across jurisdictions.

Question 3: "For pathogen inactivation technologies that have regulatory approval, what implications should be considered before widespread adoption?" A process will be needed to select the most appropriate inactivation technology, including consultation with appropriate patient and physician stakeholder groups and an educational program for blood centers, hospitals, providers and patients. Informed consent may be needed for certain decisions.

Question 4: "If pathogen inactivation were to be implemented for all components, what criteria would allow: a i) changes in donor deferral or testing, i.e., relaxing current donor deferral/exclusion policies?" Those believed to be of marginal

value should be reviewed for elimination or modification, e.g. tattooing and travel. a ii) "What criteria would allow the cessation of any currently undertaken screening tests?" To be considered might be tests for agents not readily transmissible (e.g., syphilis), agents of low infectious titer and high log-kill by inactivation techniques (e.g., West Nile Virus), agents sensitive to inactivation and for which redundant safety measures are in place (e.g., CMV, HTLV and anti-HBc) and agents sensitive to inactivation and for which current tests have poor specificity and sensitivity (e.g., bacteria). Gamma irradiation of cellular blood components could be eliminated if nucleic acid targeted inactivation technology were introduced. a iii) "What criteria would allow a decision not to implement new screening tests for agents susceptible to pathogen inactivation?" Such a candidate agent would not require testing unless of unusually high infectious titer.

Question 4 b: "Should multiple inventories be considered for each component and if yes, how should allocation be decided?" The Panel recommended universal implementation (or of a particular component, if methods for all components were not available) and were opposed to keeping multiple inventories.

Question 5: "How should the cost-benefits of pathogen inactivation be assessed?" Implementation should not be based solely on an economic analysis, since costs are unknown and benefits are difficult to quantify. Both direct and indirect costs should be considered, incrementally and for budgetary impact. Decision-making should be transparent and context specific. Estimates of the costs to reduce non-infectious hazards (e.g., patient barcode, unified on-line database for multiple hospitals and TRALI), were $14-$28 incremental cost per unit and $1.5 M per event avoided.

Question 6: "What other information, considerations and research-related questions would need to be answered to decide whether a particular pathogen inactivation procedure should be implemented?" The panel recommended consideration of robust governmental support for a large-scale investment in developing an integrated pathogen inactivation technology for all blood components. Large, adequately powered randomized clinical trials should be done to evaluate and confirm effectiveness of any new inactivation technology. There might be unanticipated consequences to the health care system, e.g., the development and availability of tests for new agents may be compromised. Prion diseases have not been addressed by current inactivation technologies. Research initiatives should be directed toward methods suitable for implementation in developing countries.

In the discussion, it was noted that pathogen reduction methods used for clotting factors had obviated transmission of HIV, HBV and HCV since 1987, but there had been transmission of HCV by a particular immunoglobulin product in 1994, demonstrating the complexity of the problem. This correction was acknowledged and there had also been some hepatitis transmission by albumin, probably a failure of the inactivation procedure. Following the conference, both Health Canada and Hema-Quebec plan to proceed with pathogen inactivation technology, using governmental funds. They expect to start with pilot projects to work out logistics and other potential problems. The extensive discussion of trading potential risks from pathogen reduction for preparedness or precaution about an emerging agent was heavily weighted by the strong likelihood that we haven't seen the last of the new or emerging agents.

The next speaker was Margarethe Heiden, PhD, head of the Section of Transfusion Medicine, Paul Ehrlich Institute in Germany to address "European Regulatory Experience with Pathogen Reduction," There are three main Directives for the regulation of blood in Europe: Technical Directives for collection, testing, processing, storage and distribution of blood components; Directives with Standards for screening tests and in vitro diagnostics; and the Medical Device Directive with Standards for apheresis and blood bag systems. These are European standards, but implementation depends on each individual country.

She then discussed her first hand experience in Germany. The German Transfusion Act requires blood establishments to have manufacturing licenses from regional authorities and the Paul Ehrlich Institute. The Robert Koch Institute is responsible for donor epidemiology. Other cooperating parties include the German Medical Association and interested Scientific Societies. There is a National Advisory Committee for Blood composed of representatives of interested parties. Koch and Ehrlich Institute members are non-voting. "Drugs (including blood) cause concern if (according to the state of scientific knowledge) there is (reason for the) suspicion that their use (according to their determination) leads to harmful effects, which exceed a degree which would be tolerable according to the current state of (knowledge of) the medical sciences." This implies immediate, annual and continuous reevaluation for which the Paul Ehrlich Institute is key. A graduated plan for pharmaco-(hemo-)vigilance includes the collection and analysis of data, proposals for action with a public hearing and finally an order from a competent authority (for blood, Paul Ehrlich Institute) for

action. In certain circumstances, licensed establishments ("marketing authorization holders") can act on their own authority.

A second strategy for decision-making for actions promising greater safety but lacking sufficient data for immediate action involves discussion by the National Advisory Board and a non-binding recommendation. Examples include leukocyte depletion, use of sterile docking devices and pre-donation sample diversion.

A third strategy involves the introduction of a new kind of testing or manufacturing that may improve safety or other aspects, but current assessment does not necessitate immediate implementation. Examples include HBV by NAT and S/D inactivation of pooled plasma. Individual establishments may apply for a new or changed "marketing authorization" to introduce the innovative technique into their program. This third strategy was used for pathogen inactivation because the frequency of transfusion transmission of the three main viruses, HBV, HCV, and HIV, is so low from current donor management procedures that there is little more to gain. It may be needed by the presence of emerging viruses, but they are not now a problem in Germany.

Nevertheless, the frequency of bacterial contamination has compelled action, especially for platelet concentrates. One measure has been to reduce the storage period for platelets to four days, since few septic reactions occur before that time. There is still some question about the safety of pathogen inactivation and at least one (amotosalen-light treatment) does not inactivate all bacterial efficiently, especially spores. French data following the introduction of inactivation procedures are awaited. Establishments can apply for marketing authorization to introduce a new procedure, such as pathogen

inactivation and some have already done so. This is largely to protect against new viruses for which there is no test or in emergency situations when testing may be difficult.

Both S/D inactivated plasma and methylene blue inactivated plasma are in use in Germany (Europe). The failure to inactivate non-enveloped viruses has covered in the package inserts Donor plasma is screened to exclude hi-titer parvovirus B-19 donations from pools. Amotosalen-light treated platelets are contraindicated for newborns being treated with UV light (below 425) for increased plasma bilirubin because the tiny residual amotosalen could react with the UV light and produce erythema.

In the discussion it was clarified how Germany approaches economic issues. Orders for nationwide introduction of a test or procedure are independent of the government, but such support is requested. There has been no reduction of testing or radiation because pathogen inactivation of platelets has not been made universal. When it is universal, they expect no longer to require travel deferrals. It's too early to detect any change in the usage pattern for inactivated platelets. Anti-HBc testing was successful in reducing HBV transmission so that adding mini-pool NAT testing for HBV would not add safety. SD plasma is made from pools of 1,200 donors. It was noted no infant should be irradiated with light below 425, so that the prohibition for giving amotosalen-light inactivated platelets to neonates is purely a precaution. When products are licensed with restrictions and a requirement for post-market surveillance, the license must be renewed in 5 years to continue indefinitely. Annual safety reports are required and withdrawals may occur if needed. Hemovigilance in Germany is aided by the systematic donation repositories that can be used for retests and identification of low level viremic

donations. Their transmission figures are more reliable than those in the US, where resources have not been available to keep retention samples. There have been no thrombotic events from SD plasma use in Germany.

The first speaker after a lunch break was Laurence Corash, MD (Chief Medical Officer, Cerus Corporation and Professor, Laboratory Medicine, UCSF) to discuss the "INTERCEPT Blood Systems: Pathogen Inactivation of Labile Blood Components." After noting that a red cell system with S-303 is in clinical trials, he focused on their experience with the platelet and plasma systems, which have been commercialized. but he didn't include that in today's discussion. All of the information to be presented has been published and the Committee provided with the references.

The objectives of this project are to inactivate pathogens and leukocytes by a targeted nucleic acid photochemical process to prevent transfusion-transmitted diseases. Additional objectives include establishing clinical safety and efficacy, supporting therapeutic indications with randomized controlled clinical trials and expanding safety profiles with active post-market surveillance. Procedures should be operationally feasible and cost efficient. Transfusion risks are better presented per patient rather than per donation because most patients receive multiple transfusions and often multiple components.

Both INTERCEPT systems in current use (one for platelets and a slightly different one for plasma use a photochemical platform with a psoralen compound with a high safety margin by pharmaceutical standards. The pathogens inactivated (slide #6) include both cell-free and cell-associated enveloped viruses (e.g., the emerging

chikungunya virus infects megakaryocytes and is internalized into platelets). Retroviruses when sequences are integrated into host genomes are also inactivated. There is a spectrum of activity for the non-enveloped viruses (e.g., about 5 logs for parvovirus B-19; HAV is resistant to this treatment). Bacteria are inactivated (except for spores) with some variability (e.g., encapsulated bacteria are relatively resistant, notably pseudomonas). Protozoans are sensitive, both cell-free and intracellular. Leukocytes (including T-cells) are inactivated and prevented from producing cytokines.

After briefly noting several clinical trials for pathogen inactivated platelets and for inactivated plasma (warfarin reversal and other indications for FFP), he focused on the SPRINT platelet trial, which included evaluation of hemostasis (primary endpoint, preventing "grade 2 bleeding;" secondary endpoints included more severe bleeding, need for additional prophylactic platelet transfusions and mortality). Eighty percent of the patients on the SPRINT trial had hematopoietic stem cell transplants. Treated platelets and treated plasma were not inferior to standard products in this trial.

The Intercept platelet product has been approved for seven day storage of platelets in many regions of Europe. The Intercept system has been approved in France for platelets and plasma and the first marketing approval has been granted for Intercept platelets in Germany Active post-market surveillance (piggy-backed on national programs if available) has been done in 60 centers in 20 countries for more than 100,000 doses of platelets and plasma. In all cases, the adverse event rate was reduced after INTERCEPT use was started. Because of the epidemic of mosquito-borne (and blood transmitted) chikungunya fever on La Réunion island, blood collections were discontinued and all products (except platelets) imported. The introduction of the

INTERCEPT system for platelets allowed local platelet production. None of the 427 patients given 1,950 platelet components were infected by transfusion and there was a substantial reduction in acute transfusion reactions.

European experience showed a decrease in platelet out-dating (five day platelet storage) and a small in the time stored to use. When allowable platelet storage time was increased to seven days, out-dating decreased to about 1% and mean storage time to use increased slightly to near 4 days. Composite per unit monetary cost of replacing current technology with INTERCEPT was about 30€ (or $45, based on 1€ = $1.50). The days of platelet support per patient was unchanged. To offset platelet losses during INTERCEPT processing, they increased the time of platelet-pheresis by 10 minutes per donation. Processing can be completed with the same time schedule as is serology and NAT testing and one day earlier than is required for bacterial culture. With INTERCEPT keeping a separate inventory of CMV negative units was deemed unnecessary.

During the discussion there were several clarifying questions about adverse events. Except when post-market surveillance was piggy-backed on the highly structured hemovigilance system in France, Ceres put in place their own active system, with internet reporting to a centralized database using protocols established for the purpose. That model should be easily adaptable for use in the US. In the SPRINT trial, the non-hemolytic transfusion reaction rate was significantly lower in the INTERCEPT arm compared with the control. There were no septic reactions in either group. In Europe, there have been no transfusion associated septic episodes in 28,000 monitored platelet transfusions and only one case of TRALI (apheresis donor with a high titer of HLA antibodies).

The next speaker was Raymond Goodrich, PhD, Chief Science Officer for Navigant Biotechnologies, to discuss "Pathogen Reduction Technology: Challenges, Hurdles, Status and Future Direction," focused on their platelet system. In 1998-9, they began to study pathogen reduction with riboflavin because of its chemical characteristics and its widely known low toxicity. Preliminary work showed satisfactory recovery and survival of treated platelets and small clinical trials in South Africa and the US showed positive results. After an additional clinical study in Europe (France) involving 100 patients, the data were submitted and the product has been CE-marked, permitting it to be sold in Europe. A similar program with plasma (FFP) is expected to result in a CE-mark this year. A program for red cells and whole blood has been started.

Riboflavin ("Mirasol") is capable of inactivating many enveloped and non-enveloped viruses (3 - >6 log inactivation), Gram-positive and Gram-negative bacteria, and tested protozoa (slides 14-16). It inhibits WBC function in vitro and prevents GvHD in laboratory settings. In an animal model, it prevents platelet antibody development; human studies are under way. Standard toxicological studies show low toxicity.

He presented without figures or slides an interim analysis (small number of subjects) of a non-inferiority trial done in France encompassing multiple platelet transfusions over a 28 day treatment period. Overall, adverse events were reduced in the riboflavin arm by about 10% compared with the reference arm. The interim conclusion was that the treated platelets were safe and effective.

Navigant has initiated a program of hemovigilance similar to that described by Dr. Corash.

In discussion, it was noted that a hemostatic endpoint in addition to the laboratory one (CCI) will likely be required in the US, although it was not for Europe,

The next speaker was Marc Maltas, MSc, International Business Unit Manager, Intensive Care and Emergency Medicine for Octapharma to discuss "Octaplas: Product Insights." Octaplas is solvent-detergent (SD) inactivated plasma developed to prevent transmission of HIV (and other enveloped viruses), to provide a standardized, cell-free hemostaticly balanced product and to prevent sepsis from bacterial contamination from the donor or during collection. Long approved as a biopharmaceutical product by the Council of Europe, it has been granted marketing authorizations in most of the European Union, in some non-EU countries in Europe and in a number of countries world-wide. As a biopharmaceutical product, it falls under both hemovigilance and pharmacovigilance rules. It is not licensed in the US. This report is based on 15 years experience in Europe.

In the countries where Octaplas is used, it has replaced 75-100% of the FFP administered. Through pooling (here a positive advantage rather than a disease dissemination disadvantage), allergens and soluble substances and antibodies against white cells are diluted or neutralized to prevent TRALI. Approved Indications for Octaplasma are treatment of complex and isolated coagulation disorders where specific factor concentrates are not available and of thrombotic thrombocytopenic purpura, usually in conjunction with plasma exchange.

All enveloped viruses tested to date are rapidly inactivated $\geq$ 5.0 logs (HCV) to $\geq$7.5 logs (vesicular stomatitis virus). Potentially life threatening emerging viruses (e.g.,

West Nile, SARS, chikungunya and avian influenza) are all enveloped and would be inactivated. Non-enveloped viruses (e.g., herpes simplex, hepatitis A, coxackie-B-6 and polio) are neutralized by antibodies in the 380 liter (650-1150 units) manufacturing pool. Release specifications include negative HAV RNA NAT, anti-HAV ≥ 2 IU/ml, parvovirus B-19 DNA NAT ≤ 4 $\log_{10}$ IU/ml and anti-parvovirus B-19 IgG ≥ 20 IU/ml. Filtration steps remove all cells and cell debris. Studies with hamster scrapie suggest that about 2.5 logs were removed by the processing procedures. A new prion removal filtration system achieves ≥5 logs reduction (Western Blot analysis).

In general, the frequency of TRALI is increasing, in part because of better reporting. The most common implicated component is plasma. Nevertheless, in the 13 years that Octaplas has been used 100% in Norway, there have been no TRALI case reports from plasma, but some from red cells and platelets.

There have been no pathogen transmission and no reports of TRALI in 229 patients, 1,290 bags and 58 batches in clinical trials and in post-marketing experience (pharmacovigilance and hemovigilance) with 1.8 M patients treated, more than 5.3 M bags and 3,000 batches. There also has been a very low rate of other adverse events.

This The next speaker was Dr. Marie Scully, Consultant Haematologist (sub-specializing in hemostasis and thrombosis), University College London Hospitals/University College London, UK to speak on "Clinical Experience with Octaplas (S/D inactivated plasma for transfusion)." She reported no conflicts of interest, but disclosed participation in unrestricted educational grants from Baxter (UK) and Octapharma.

Two protocols were developed for making solvent-detergent treated plasma, Octaplas and Plas-SD. After the initial treatment with solvent and detergent, the remaining production steps are quite different. The pool size for Plas-SD was 2,500 single units; with Octaplas the maximum is 1,100-1,200 single units. For Plas-SD, coagulation factors were stabilized with calcium chloride and the solvent/detergent removed with soybean oil. For Octaplas, sodium phosphate at a pH of 6.0 – 7.4 was used and SD was removed with castor oil. Octaplas is prepared without the final concentration and ultrafiltration steps used for Plas-SD, a factor in the coagulation levels in the final product. With the lower final citrate concentration of Plas-SD, there may be activation of coagulation factors and fibrin formation. There is a significant reduction in protein S activity in Plas-SD. Plas-SD was used in the US until it was withdrawn, primarily because of problems with thrombosis. Octaplas is used in Europe, but not the US.

Octaplas used in UK has reduced Factor V, VIII and plasminogen inactivator, perhaps because the source plasma is frozen within 15 hours of collection. That in use in Norway is frozen within four hours and the final product has no reduction in Factors V, VIII and protein S.

Thrombotic thrombocytopenic purpura (TTP) is an acute life-threatening illness. Without plasma therapy, the mortality is 90% and even with plasma therapy, 20% will die. Occasional venous thromboembolic events occur, mostly IV line associated and often many days after the first plasma exchange. It is not clear if these events are related to the use of Octaplas. Newly produced platelets are very reactive and TTP is a very prothrombotic disorder so that the patients are potential candidates for venous thrombotic

episodes (VTEs). She now administers prophylactic low molecular weight heparin when the platelet count goes above 50,000, they.

Patients receive about 40 liters of plasma per TTP episode and allergic reactions have been frequent. Since they began using anticoagulation and later added the exclusive use of Octaplas (January 2006), there has been a marked reduction in both allergic and thrombotic episodes. Methylene Blue treated FFP was introduced in January 2006 for the treatment of all children. Small retrospective studies from Spain suggested that patients treated with Methylene Blue plasma required more plasma exchanges, longer hospital stays and suffered more relapses than patients treated with Octaplas. A multicenter prospective trial confirmed these findings.

She summarized testimonial experience from several sources on the use of Octaplas compared with standard FFP and found the Octaplas to be satisfactory. Disorders included liver transplantation, congenital hereditary clotting disorders. Side effects are limited; there was no formation of inhibitors or neoantigens.

In the discussion, it was questioned if the differences in side effects, especially thrombotic episodes, between Plas-SD and Octaplas were real. She was not aware of any head-to-head controlled studies, but does believe that Octaplas has an important lower level of side effects. When the UK ceased to use locally procured plasma and imported what was needed. They decided was to use Octplas and Octapharma chose US plasma to fulfill the additional demand because the population seemed free of vCJD. That plasma was converted into Octaplas by the usual procedures. Experience in the US does not substantiate a baseline risk for VTE in patients with TTP. Are there such baseline data in

UK? What is the basis for assuming that the VTEs at University College London are disease-associated rather than treatment-(Octaplas)associated? Baseline data are scanty and she was reporting conclusions from a publication rather than her own observations. It was questioned that the platelets in TTP are truly hyperreactive. There were also questions about the differences, if any, between Methylene Blue plasma, Octaplas and SD-plasma to account for apparent differences in their therapeutic use and side effects. Measured factors before and after production are similar. However, SD-plasma may be frozen within 15 hours of collection while Octaplas source plasma is frozen within 4-6 hours. There may be differences in the aggregate sizes of some proteins, one from another. No studies are available.

After lunch, the next speaker was Jaroslav Vostal, MD, PhD, Chief of the Laboratory of Cellular Hematology, Division of Hematology, OBRR, CBER, FDA to discuss "Regulatory Issues of Pathogen Reduction Technologies: Current Thinking."

To reduce the transmission of infectious agents, the FDA encourages the development of improvements in donor screening, skin disinfection, use of a pouch to divert the first few ml of blood collected from a donor for use in testing, asceptic collection with closed systems, testing for infectious disease markers (e.g., HIV 1 & 2, HCV, HBV, HTLV I & II, CMV, WNV, T. Cruzi and syphilis) and the detection of bacteria in platelet transfusion products. The exploration of novel technologies not yet approved, such as alternate storage conditions (e.g., cold stored platelets), pathogen reduction with chemical additives and the development of substitute or manufactured products is also encouraged.

In the development of new technologies and products, the benefits expected must be balanced against the risks of the new technology. Specifically, the benefits from pathogen reduction include the reduction of known viruses, bacteria, parasites and possibly emerging and unknown pathogens. We must ascertain that there is no undue damage to the transfusion product, increase in adverse events to the recipient and toxicity to processing personnel and the environment.

Previous speakers have outlined the residual risks from infectious agent contamination of blood products. They are small from donor selection and testing, but not zero. HBV transmission is the greatest virus risk at about 1:150,000. Septic transfusions occur in 1:75,000 platelet transfusions, with a fatality rate of 1:500,000. The risk-benefit ratio from donor selection and testing is very favorable.

For chemical or photochemical pathogen reduction technologies, the benefits are further reduction in current residual risk (virus 1:150,000; bacterial 1:75,000). These must be balanced against adverse events from the pathogen reduction process. This figure must be less than 1:75,000 to have a favorable risk-benefit ratio. To establish an adverse event rate of 1:75,000, one would need a study with 225,000 participants, not easy without a careful post-market study.

There are other more theoretical concerns about pathogen reduction technologies. A novel mixture of chemicals and biological products is infused intravenously to a broad range of patients of different ages and states of health. These chemicals interact with nucleic acids and are frequently mutagenic and/or carcionogenic. Direct damage to cells may be subtle enough as to defy detection with current testing strategies. He outlined the

usual pathway to licensure for products of this nature, from in vitro and in vivo animal toxicity studies to various stages of clinical trials to establish effects on transfusion kinetics, gross benefits and toxicity in specific patient populations and finally general efficacy for larger numbers of patients.

Cerus S-59 treated apheresis platelets are furthest along in this development pathway. The SPRINT trial, discussed earlier in this meeting, was a randomized, controlled, double-blind, non-inferiority study to compare safety and hemostatic efficacy of photochemically treated platelets to conventional platelets. The primary endpoint was grade 2 (WHO scale) bleeding; both arms were equivalent. However, mucosal bleeding (generally related to platelet numbers and function) and bleeding into the respiratory tract seemed to show a trend suggesting that the treated platelets were less effective (not statistically significant). There also were trends toward increased number of platelet transfusions, lower doses of platelets, lower post-transfusion platelet increment and an increased use of red cell transfusions in the treatment arm vs control. Adverse events (especially acute respiratory distress syndrome: ARDS) were more frequent in the treatment arm (about 1:60), so that the risks by present reading seemed to much outweigh the benefits to be gained by moving to this form of pathogen reduction.

He concluded that the Cerus approach to pathogen reduction may have a favorable risk:benefit ratio if a pathogen is widespread or has a high mortality. There may also be populations that are more susceptible to new or current pathogens and the risks could be offset in this group. However, use in the general population in anticipation of an unknown pathogen some years in the future is not justified by the current risk:benefit profile.

Questions raised by the SPRINT trial include: why didn't the adverse events turn up in the preliminary clinical testing? Is there a plausible mechanism for the frequency of ARDS in the highly complex hematological patients (most were stem cell transplant recipients)? Are there animal models to evaluate if treated platelets can participate in inflammatory lung disease? Plausible answers to each question were discussed.

How can we move forward? A second SPRINT-type trial could be performed, adjusting the platelet dose so that both arms would be equivalent, more actively monitoring adverse events and ensuring sufficient numbers for power to confirm or rebut SPRINT conclusions. Post-market surveillance data could be analyzed for adverse events, but active surveillance would probably be needed rather than relying on passively collected data. Finally, approval could be sought only for situations where transfusion-transmitted disease risks increase, e.g., an emerging pathogen epidemic.

In the discussion, it was suggested that the Red Cross passively-collected data, as a baseline for platelet bacterial contamination issues, represented only 10% of the reactions that actually occurred. If this is correct, than 1:75,000 with current practice is much too low, and the risk:benefit relationship would be shifted closer to making pathogen reduction better. The relationship of passively-collected data to actual occurrence needs to be confirmed. The validity of hemovigilance data, even if collected actively, also need to be verified. Some of the differences between the two arms of the SPRINT study are close to the variability in day-to-day clinical transfusion practice and difficult to detect in individual patients.

Patients in the SPRINT trial were monitored for all adverse events for 35 days and charts were later reviewed, blinded as to arm, by experts to verify the event and classify its severity. This was more than routine hemogilance in which patients are monitored for 24 hours after transfusion. Both active and passive hemovigilance focus on events known to be related to blood transfusion. "Adverse event" reporting in trials like SPRINT allow detection not only of events recognized to be associated with blood transfusion but also those not clearly from transfusion. In France, a physician is required to complete a report form for every transfusion, whether or not there has been an adverse effect. It is more usual that reporting is more passive and not all adverse effects are included. The system set up by Cerus for their studies, including post-market studies, more resembles the French approach, except that the follow-up period is longer.

The final speaker was Brian Custer, PhD, MPH, Assistant Investigator of Epidemiology and Health, Blood Systems Research Institute, San Francisco, to address "Economic Issues of Pathogen Reduction." The Canadian Consensus Conference on Pathogen Reduction recommended that economic evaluation of pathogen reduction be done but that implementation be based on other consideration ias wel. There are two broad types of economic evaluation studies: 1) budget impact analysis including possible trade-offs and effect on other parts of the budget; and 2) cost-effectiveness or an estimate of the health value for the money spent. His model for making estimates was developed for pharmaceuticals; its use for blood has been and will continue to be debated, but it may be useful for our purposes.

If there are limited resources, necessary choices can be valued by opportunity costs, which includes the willingness to forego the benefits of alternatives, and/or the

differential monetary costs. Health economics attempts to place these on a common denominator, which is often "quality-adjusted life years (QALYs)." Cost-effective analysis results are relative comparisons between current practice and a new intervention (cost difference between interventions divided by the differences in efficacy of the two interventions = the incremental cost effectiveness ration, or ICER). WHO recommends the threshold for an acceptable value to be three times the Gross Domestic Product (about $120,000 for the US). Slide #7 graphs the incremental costs against QALYs for the various screening tests as they have been added, ending with an estimate for the addition of pathogen reduction technology.

Most previous cost-effectiveness analyses have addressed HIV, HCV, HBV, bacteria and sometimes HTLV and have assumed 100% efficacy of pathogen reduction and no adverse effects. More than one reference population is desirable. Pre-market estimates of cost-benefit are usually lower (better) than is found after the product has been available for a while (e.g., $300,000 per QALY compared with now nearly $10 million). The estimates of cost per QALY also depend on the inclusion or exclusion of NAT and an attempt to include a possible effect of preventing TRALI. Hence, the assumptions built into the analysis are very important to the result.

He then addressed cost-effective analysis using psoralen light treatment on apheresis and random-donor platelets and HIV, HCV, HBV, HTLV and bacteria. He used an estimated life expectancy for four groups of transfused patients (pediatric acute lymphocytic leukemia, adult hip arthroplasty, adult CABG and adult non-Hodgkins lymphoma). Cost per platelet unit in 2001 dollars was $100. Sensitivity analysis showed the most important adverse events to be sepsis and death due to bacterial sepsis, increased

transfusion of platelet units because of reduced recovery in processing, the introduction of an emerging HCV-like virus and quality adjusted life expectance (age). In the pediatric population, cost per QALY of pathogen reduction for apheresis platelets was $4.8 M (with pre-release bacterial culture and $1.3 M without bacterial culture). For whole blood derived platelets it was about $500,000 without culture and about $1 M with culture. For adult procedures, the cost were greater.

Similar data and analyses for methylene blue light treatment and riboflavin light treatment are not available.

There is no evidence, positive or negative, that addresses the issues of modifying donor selection criteria if pathogen reduction technology is introduced

The hemovigilance data for 2003 and 2004 (primarily Europe) suggest that the majority of transfusion adverse events are due to non-infectious problems. The effect of pathogen reduction technology in preventing these problems is not clear, although some effect on reducing TRALI has been suggested. There are no comparable hemovigilance data for the US nor are there well characterized cost data, making these model-driven analyses sensitive to the assumptions built into the models.

Possible consequences and forgone benefits of pathogen reduction include failure to address prion transmission or the emergence of other highly resistant pathogens. Will the introduction of pathogen reduction decrease interest in screening test development, which could also adversely affect infectious disease diagnostics. There are clear public health implications if infected donors are not identified and remain a threat to others.

In summary, pathogen reduction is not cost-effective according to traditional thresholds, although they have not been applied to blood safety. Cost-effectiveness would be improved if some current safety procedures could be discontinued.

He was asked to contrast models for which there are lots of data on secondary spread, cost of treatment, death and disability (e.g., HIV) with those for which there are very few data (e.g., WNV). A new emerging agent is likely to fall somewhere between those extremes. It is unlikely that a new agent will go unnoticed for long enough that many cases of blood transmission occur before action can be taken. What about the cost of lost donors and replacement recruitment? There are considerable costs involved in the development and introduction of new tests and changing information systems. Unfortunately, cost data for blood safety and transfusion medicine are too poor to address these issues adequately. Adding to the complexity, the costs of illnesses from blood is borne by the patients who were affected: cost of treatment, lost income, industry litigation costs, etc. Although pathogen reduction may not be cost effective compared with many medical interventions, it rates more favorably among the interventions directed at transfusion medicine.

The Committee then discussed recommendations based on the data presented. The current reactive approach is to identify a new or emerging agent and then scramble to take measures to avoid it. Pathogen reduction is more proactive, but it should be considered additive rather than a replacement. A proposal was drafted and extensively discussed. Key elements included implementation of pathogen reduction technology after regulatory approval (component by component, but nationwide rather than regional), the need for post market surveillance (a national hemovigilance system) and

maintenance of or improved product availability. The following recommendation to the Secretary was moved, seconded and approved unanimously:

"The Advisory Committee on Blood Safety and Availability (ACBSA) finds that accumulating evidence for the efficacy and safety of pathogen reduction warrants a commitment and concerted effort to add this technology as a broadly applicable safeguard which additionally would provide a reasonable protection against potential emerging infectious diseases. This would result in a proactive, pre-emptive strategy that would broadly render most known agents non-infectious and prevent emerging agents from becoming transfusion risks. To achieve this goal, government, industry, blood organizations and public stakeholders need to work in concert to commit the required financial and technical resources.

In particular, the Committee finds that:

a) Despite the overall safety of the blood supply based on credible scientific assessments, unmet needs exist to further reduce known infectious threats to blood transfusion recipients from infectious agents including bacteria, viruses, parasites and prions.
b) The well-established strategy of implementing donor screening and testing subsequent to the identification of infectious agents of concern to blood safety has inherent limitations including the possibility for widespread transmission of disease before a new agent is recognized or can be interdicted by specific methods.

c) The cost and complexity of agent-specific screening and testing is itself becoming a barrier to further blood safety innovations. At the same time, business models to not appear to favor continued aggressive investments in blood safety technologies.

d) The anticipated high costs of pathogen reduction technologies would likely be offset through the gradual elimination of some current blood safety interventions that would be rendered redundant.

e) Because the agents of variant Creutzfeldt Jakob Disease (vCJD) and other prion diseases cannot be inactivated in blood components, techniques to detect and remove these infectious agents need separate consideration.

Pathogen reduction offers the following potential benefits:

1. Reduction of current risks of known infectious agents,
2. Protection against the risk of emerging infectious agents including shielding the nation from introduction of biological threats to our blood supply.
3. Avoiding obligate blood recipient infectious risk before emerging infectious diseases are detected and new assays are developed.
4. Increase the availability of blood supply by avoiding unnecessary loss of blood donors as an undesired outcome attributable to false-positive infectious disease tests and non-specific donor screening strategies,
5. Avoidance of the need to develop new screening assays for emerging and/or localized infectious agents, and

6. Mitigation of non-viral threats associated with blood transfusion, such as transfusion related acute lung injury (TRALI), bacterial contamination, graft versus host disease (GVHD) and human leukocyte antigen (HLA) alloimmunization.

Based on these findings, the Committee recommends that the Secretary:

a) Adopt as a high priority the urgent development of safe and effective pathogen reduction technologies for all blood transfusion products and implementation as they become available;
b) Provide resources to overcome current barriers to development and validation of pathogen reduction technologies;
c) Ensure adequate safety monitoring of pathogen reduced blood products post-marketing using an active national hemovigilance system and
d) Ensure that other efforts to improve blood safety and availability are not compromised by these efforts."

The meeting adjourned at 5:24 PM.