Food and Drug Administration
Center for Biologics Evaluation and Research
SUMMARY MINUTES
BLOOD PRODUCTS ADVISORY COMMITTEE
89th Meeting: April 26-27, 2007
Hilton Hotel, Gaithersburg, MD

Committee Members
Dr. Frederick Siegal, Chair
Dr. Adrian Di Bisceglie
Dr. Willarda Edwards
Dr. Maureen Finnegan
Dr. Matthew Kuehnert
Dr. Catherine Manno
Dr. George Schreiber
Dr. Irma Szymanski
Dr. Donna Whittaker
Ms. Judith Baker *
Dr. Louis Katz **

Committee Members Absent
Dr. Mark Ballow
Dr. Henry Cryer III
Dr. Roshni Kulkarni
Dr. Thomas Quinn
Dr. Keith Quirolo

Temporary Voting Members
Dr. Simone Glynn
Dr. Harvey Klein
Dr. Kenrad Nelson
Dr. William Tomford ***

FDA Participants
Dr. Robert Duncan
Dr. Melissa Greenwald
Dr. Dorothy Scott
Dr. Mark Weinstein
Ms. Sheryl Kochman
Dr. Alan Williams
Dr. Maria Rios
Dr. Jay Epstein
Dr. Karen Midthun

Guest Speakers
Dr. Richard Benjamin
Dr. Celso Bianco
Dr. Michael Busch
Dr. Brian Custer
Dr. Eileen Farnon
Dr. Jerry Holmberg
Dr. Steven Kleinman
Dr. Susan Montgomery
Dr. Ravindra Sarode
Dr. Susan Stramer
Dr. David Stroncek

Executive Secretary
Donald Jehn, M.S.

Committee Management Specialist
Pearline Muckelvene

These summary minutes for the April 26-27, 2007 Meeting of the Blood Products Advisory Committee were approved on May 31, 2007.

I certify that I participated in the April 26-27, 2007 Meeting of the Blood Products Advisory Committee and that these minutes accurately reflect what transpired.

/// original signed ///
Donald Jehn, M.S.
Executive Secretary

/// original signed ///
Frederick Siegal, M.D.
Chair

*Consumer Representative
** Non-Voting Industry Representative
*** April 26, 2007 only

Topic I: Issues Related to Implementation of Blood Donor Screening for Infection with *Trypanosoma cruzi* and the Potential Transmission of *Trypanosoma cruzi* by Human Cells, Tissue and Cellular and Tissue-Based Products

On April 26, 2007, Dr. Robert Duncan introduced the topic and issues related to implementation of blood donor screening for infection with *Tyrpanosoma cruzi (T. cruzi)*. CDR Melissa Greenwald, M.D. then provided an introduction to the issues related to the potential transmission of *T. cruzi* by human cells, tissues and cellular and tissue-based products (HCT/Ps). Following the FDA presentations, Dr. Susan Stramer presented American Red Cross' experience with Ortho Clinical Diagnostics' T. Cruzi ELISA test system. Next, Dr. Susan Montgomery from the Centers for Disease Control and Prevention discussed the public health impact of blood donor screening for T. cruzi infection. Finally, Dr. Michael Busch and Dr. Brian Custer from Blood Systems Research Institute presented potential strategies for targeted testing of T. cruzi infection in repeat blood donors.

During the Open Public Hearing, Dr. Ben Marchlewicz, Ph.D. from Abbott Diagnostics presented Abbott's strategy for blood donor screening for Chagas Disease. Also, Brian McDonough, Vice President, Donor Screening from Ortho-Clinical Diagnostics spoke regarding Ortho's approved test kit and Dr. Celso Bianco from ABC offered his comments regarding screening of blood donors for Chagas Disease. Additionally, Linda Fraiser of the Rochester Eye and Human Parts Bank and Scott Brubaker representing the American Association of Tissue Banks commented on the potential transmission of *T. cruzi* by HCT/Ps.

The Committee then discussed the following questions:

1. Please comment on any scientific issues that FDA should further consider in developing its recommendations on implementation of blood donor screening for antibodies to *T. cruzi*.

   Committee members commented on the following issues:

   - Additional data are needed on the incidence and risk of transmission of *T. cruzi* by transfusion.
   - More data is needed on the correlation of test results with parasitemia.
   - The financial expense of testing should be considered.
   - Chagas disease is not an insignificant disease and the licensed test performs very well.
   - A surveillance system for Chagas diseases in the United States is lacking. Therefore, we can not conclude that we haven't seen any cases of transmission. Available lookback data are too limited. More data and follow up are needed to gain a better understanding of the transmission.
   - A better understanding of the window period and follow up testing is needed.

- More data is needed to support the hypothesis that freezing kills the parasite.
- Lack of confirmatory testing is a major issue. FDA should encourage development of a licensed confirmatory test. However, screening should not wait for licensed confirmatory testing, since the false positive rate is low. The performance of the RIPA test should be compared against other tests in other countries (such as Brazil).
- FDA should begin thinking about a reentry algorithm for donors deferred due to falsely positive reactive tests.
- Donor questions for selective donor screening need validation.

2. What suggestions does the committee have on the design of research studies to validate a strategy for selective screening of repeat donors?

- The Committee stressed that validation of the donor questions for selective screening is critical, especially in non-English speakers. Additionally, the Committee expressed concern that questions regarding country of birth and travel history are politically sensitive and may not be answered truthfully since donors may fear they are being asked about immigration status.
- If all donors are screened at least once, then more data on incident cases will be gathered. Two years of incidence data would be beneficial.
- It may prove difficult to pinpoint Chagas endemic areas for the donor questions on residence and travel, similar to donor screening questions for malaria risk.
- Blood centers do not currently have a process to manage selective screening of repeat donors. Development of software for managing selective screening should be encouraged.

3. Please comment on the need for and design of studies to determine whether repeatedly reactive test results for antibodies to *T. cruzi* should be further investigated for cross-reactivity to *Leishmania, Plasmodium, Paracoccidioides braziliensis* or other agents when the donor lacks risk factors for *T. cruzi* infection or a test sample is found negative by other, more specific tests.

Concern was expressed that the lack of evidence from *T. cruzi* blood screening and follow up *Leishmania* testing of over 300 repeatedly reactive donors indicates no pressing need for more research. Concern was also expressed that more research needs to be done to understand how to counsel repeatedly reactive donors that are non-reactive on a more specific test or other medical follow up.

The Committee agreed that further investigation of cross-reactivity to other agents is a medical diagnostic issue and does not need to be conducted in the context of a blood establishment. One Committee member cautioned that while further investigation is a clinical issue, the incidence of Leishmania may not be rare in veterans from Iraq and Afghanistan.

4. Please comment on the implications of the current scientific data as it relates to the potential for transmission of Chagas Disease by HCT/Ps.

Committee members commented that there are significant differences between processing HCT/Ps and blood products since many tissues undergo various processing procedures, e.g., bone. However, members expressed concern for the potential transmission of Chagas disease by HCT/Ps considering the wide range of products considered HCT/Ps and the wide spectrum of processing of the products. The Committee also discussed that not all HCT/P products are highly processed, such as fresh soft tissue allografts, corneas, hematopoietic stem/progenitor cells and sperm, and that those products may be of more concern than some other products. Therefore, it was suggested by some Committee members that some distinction might be made based on the type of processing to which HCT/Ps are subjected. Some Committee members also commented that HCT/P products should be held to the same donor screening and testing standards as blood and blood products. One Committee member commented that any HCT/P processors who had validated processing methods to inactivate *T. cruzi* could submit a request an exemption from any *T. cruzi* testing. Although human organs are not considered HCT/Ps or regulated by the FDA, one Committee member stressed that organs for transplant should be screened for *T. cruzi*.

Committee Updates

On April 27, 2007 Dr. Jerry Holmberg presented to the Committee a summary of the August 30-31, 2006 meeting of the DHHS Advisory Committee on Blood Safety and Availability. The next update presented to the committee was by Dr. Dorothy Scott on the December 15, 2006 meeting of the Transmissible Spongiform Encephalopathies Advisory Committee. She summarized the Advisory Committee's discussion on the experimental clearance of TSE infectivity in plasma-derived Factor VIII products. Dr. Mark Weinstein then presented an update on FDA's risk communication on plasma-derived Factor VIII and Factor XI. Finally, Ms. Sheryl Kochman presented a summary of the September 25-26, 2006 FDA workshop on Molecular Methods in Immunohematology.

Topic II: Transfusion Related Acute Lung Injury (TRALI)

Dr. Alan Williams introduced the topic of TRALI to the Committee. Next, Dr. David Stroncek from the National Institutes of Health reviewed the clinical and laboratory aspects of TRALI. Dr. Ravi Sarode from University of Texas Southwestern Medical Center then discussed the current use of transfusable plasma. Dr. Steven Kleinman from the University of British Columbia reviewed the REDS-II LAPS study on HLA and granulocyte antibody prevalence in blood donors. Finally, Dr. Richard Benjamin representing the American Red Cross and Dr. Celso Bianco representing America's Blood Centers presented to the Committee their respective organizations' experience with TRALI.

No public comments were presented during the open public hearing.

The following issues were discussed before the Committee formally addressed the questions posed by FDA. The Committee was informed that in addition to recommending the preparation of plasma from donors known to be leukocyte-alloimmunized or at risk of leukocyte alloimmunization, the AABB's bulletin on TRALI published in November 2006 recommended transfusion facilities should works towards implementing appropriate evidence-based hemotherapy practices in order to minimize unnecessary transfusions and blood collection and transfusion facilities should monitor the incidence of reported TRALI and TRALI-related mortality.

The FDA asked about the feasibility of a compatibility test to reduce the incidence of TRALI. Dr. Klein remarked that early studies on leukocyte agglutination indicated that such tests may reveal of a lot of incompatibility, but that would not necessary correlate to problems with transfusion.

Additionally, a Committee member asked if there was any interest in the U.S. in S/D (solvent detergent) plasma to help reduce the incidence of TRALI.

The Committee then addressed the following questions.

1. Do current scientific data support the concept that the following interventions will reduce the incidence of TRALI?

    a. Use of predominantly male plasma for transfusion.
    b. Non-use of plasma for transfusion from donors with a history of prior transfusion.
    c. Selective donor screening for anti-neutrophil or anti-HLA antibodies.

In response to question 1a, the Committee unanimously agreed (13 yes votes) that the current scientific data support the concept that the use of predominantly male plasma will reduce the incidence of TRALI. Four of the thirteen voting Committee members commented that while the use of predominantly male plasma would reduce the incidence of TRALI, many female donors should not be eliminated from donation, especially those with no history of transfusion or pregnancy

In response to question 1b, the Committee unanimously disagreed (13 no votes) that current data support the concept that non-use of plasma from donors with a history of prior transfusion will reduce the incidence of TRALI. Committee members commented that additional data is needed to answer this question.

The Committee did not take a formal vote on question 1c, however, the consensus of the Committee was that more scientific data is needed to understand whether selective donor screening for anti-neutrophil or anti-HLA antibodies will reduce the incidence of TRALI.

2. Based upon available data, please comment on the effect on the US plasma supply of the following interventions:

a. Use of predominantly male plasma for transfusion.
b. Non-use of plasma for transfusion from donors with a history of prior transfusion.
c. Selective donor screening for anti-neutrophil or anti-HLA antibodies.

In response to question 2a, several Committee members representing blood establishments agreed that the use of predominantly male plasma is feasible and predicted this would become practice in blood establishments before FDA recommendations are issued. Further, it was noted that transfusion facilities have accepted the use of plasma frozen within 24 hours (FP 24). In response to the discussion on FP 24, FDA indicated it would be beneficial if data on FP 24 was submitted for review. While some Committee members expressed concern that use of predominantly male plasma would have a negative effect on supply, especially in times of a disaster, other members commented that female plasma could be used during a critical shortage.

Finally, one Committee member commented that recommendations should be given to physicians for the appropriate use of plasma. In response to this comment, a representative from AABB indicated that AABB's clinical transfusion medicine committee (CTMC) has initiated the development of guidelines on the appropriate clinical use of plasma.

The Committee did not comment on question 2b.

In response to question 2c, the Committee indicated that the data are too premature to comment on the impact of selective donor screening on plasma supply. Members commented that while screening for anti-neutrophil antibodies could be beneficial in reducing TRALI, the technology is not currently available. Conversely, the technology for anti-HLA antibodies screening is available, but it appears anti-HLA is less likely to be implicated in TRALI.

Topic III: Issues Related to Implementation of West Nile Virus Testing

Dr. Eileen Farnon from the Centers for Disease Control and Prevention provided the Committee with an update on the 2006 West Nile Virus (WNV) epidemic. This was followed by Dr. Maria Rios' presentation of an overview of the issues related to implementation of WNV testing, including approaches to confirmatory testing, blood donor and unit management, and individual donation nucleic acid testing (ID-NAT). Finally, Dr. Susan Stramer from the American Red Cross, representing the AABB West Nile Virus Task Force (AABB WNV-TF), presented data in support of the current criteria to trigger ID-NAT implementation.

The Committee was not asked a specific question on the issue, as it was presented as an informational topic. However, as requested in Dr Rios' presentation, the Committee discussed the issues related to WNV testing, and criteria used as a trigger to convert from MP-NAT to ID-NAT during the WNV activity season. The Committee inquired whether

ID-NAT should be used year-round, rather than triggered by a defined incidence in a geographic area. Dr. Stramer, representing the AABB W NV-TF, responded that year-round use of ID-NAT would lead to an increase in false positive results, donor deferral, incremental cost, and exhaustive laboratory resources. Rather, she advocated for converting the process to a uniform standard criterion to trigger ID-NAT implementation, and for focusing on improving communication of events that would result in triggering ID-NAT implementation in 2007. She reported that in 2006, 430 cases of WNV NAT reactive donors were reported to AABB as late as 10 days after donation. As a result, Committee members and individuals representing industry stressed the importance of early communication and triggering ID-NAT quickly to ensure detection of donors positive for WNV. There were public discussions regarding rates of transmission, donor follow up and the need for data to evaluate criteria to implement ID-NAT. The Committee cautioned that early conversion from MP-NAT to ID-NAT is especially important since the time period in which infectious donors appear is not clearly defined. The Committee also pointed out that compliance with a trigger for ID-NAT implementation would be challenging without FDA guidance.