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STATEMENT

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Transfusion Related Acute Lung Injury (TRALI)

Statement before the Food and Drug Administration's Blood Products Advisory Committee

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July 22, 2004 – America's Blood Centers, or ABC, is an association of 76 not-for-profit, community-based blood centers that collect nearly half of the US blood supply from volunteer donors. ABC thanks FDA's Center for Biologics Evaluation and Research for the opportunity to make public comments before the Blood Products Advisory Committee.

ABC members share FDA's concerns about Transfusion Related Acute Lung Injury (TRALI). While rare, this is a serious and sometimes fatal transfusion-associated event. We know that TRALI is a complex phenomenon, and there is no agreement in the published literature about the major mechanisms of disease. This was clearly documented at an outstanding Canadian Consensus Conference that took place this past April. At least two mechanisms appear to play a role, one involving antibodies to leukocytes, the other involving biologically active mediators. Interestingly, in the paper published by Silliman *et al* (Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood* 2003; 101:454-62) most of the TRALI events appear to be related to biologically active mediators and only one of the 90 reactions studied involved a plasma unit. Most reactions (74) involved whole blood derived and apheresis platelets.

Kopko (presentation at the Canadian Consensus Conference on TRALI, April 1-2, 2004) has indicated that many units implicated in TRALI reactions carry antibodies to white blood cells. However, she concluded from her studies that HLA antibodies in a donor corresponding to HLA antigens in a recipient are not sufficient to cause TRALI in all recipients. She also noted that, based on lookback studies, donors implicated in TRALI reactions can cause TRALI in other recipients, regardless of antigen-antibody correlations. While presentations also indicated that a higher rate of female plasma donors who have

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been pregnant carry anti-HLA antibodies, data is lacking that would establish a definitive link between gender and/or anti-HLA antibodies and TRALI.

Dr. Leslie Holness from FDA presented the FDA fatality data at that conference and a summary of the data today to BPAC. He showed an apparent increase in TRALI associated fatalities in recent years. He also indicated that the majority of the 49 fatalities that occurred between 2001 and 2003 were associated with plasma transfusions (number or % not indicated.) The donor data presented did not include donor gender or prevalence of antibodies to leukocytes, so we cannot estimate the impact of the three preventive strategies enumerated by FDA:

1. Only transfuse plasma containing components from male donors
2. Perform preventive antibody testing
3. Defer donors implicated in TRALI cases

We agree that FDA should review and consider interventions to address the issue of TRALI. The impacts of such strategies must be considered first by asking the following questions:

1. How many TRALI associated fatalities will be prevented by each of the strategies?
2. What blood components should be included in the strategy? (TRALI has been associated with all blood components, including red blood cells; an apheresis platelet unit contains as much or more plasma than a unit of fresh frozen plasma.)
3. What impact will this have on the availability of components?
4. Are there other strategies that could be considered?

The data presented by FDA, the current literature, the recommendations made by BPAC in 2001 and the conclusions of the Canadian Consensus Conference do NOT provide a clear basis for any of the regulatory strategies listed. Whole blood, whole blood derived platelets, apheresis platelets and plasma have been implicated in TRALI. Why restrict the approach to plasma? What about apheresis platelets?

We carried out a survey to assess the impact of using only male plasma and platelet apheresis products among ABC members. Forty-two centers collecting a total of almost 4 million whole blood and apheresis units a year responded. Based on the gender distribution of ABC donors, we estimate that a ban on female plasma and apheresis platelets would lead to the loss of 113,000 donors and 275,000 donations in a year. If we double this estimate to include collections by the American Red Cross, 550,000 donations would be lost in the US. They represent 44 percent of all apheresis donors. Our members indicated that they could not effect these changes without seriously impairing product availability.

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When our members were asked whether they could provide male plasma only to their hospitals, 55 percent responded yes. However, they indicated that it would take them between 18 and 24 months to implement the changes, including software modifications, in a cGMP environment. They also indicated that the change would create serious shortages of type specific plasma, particularly type AB.

ABC members disagree with FDA's point of view that Strategy 3, deferral of donors implicated in TRALI incidents, is inadequate because it allows for the first incident to occur before donor deferral is instituted and does not eliminate TRALI. Unfortunately, all proposed strategies suffer from this deficiency. Strategy 1 (deferral of female donors) addresses an undetermined fraction of TRALI cases and has more serious consequences for blood availability.

At the present time and with the present knowledge, regulatory action should be restricted to donors implicated in TRALI episodes, as stated in the third possible strategy. FDA also needs to support effective training of physicians and other hospital personnel for the early recognition of TRALI, based on the case definition being considered by a NHLBI task force under the leadership of Dr. Pearl Toy. This may be more efficient in the prevention of fatalities than any of the proposed strategies.

The implementation of a global strategy such as the deferral of male donors may have other adverse consequences. It may convey to the medical community and to the public the erroneous impression that the problem of TRALI has been addressed and resolved; leading physicians to consider other diagnoses and prescribe inappropriate therapy. Finally, we will have to deal with the frustration of female donors when they learn that their donations are not good for transfusion.

ABC members thank FDA and BPAC for the opportunity to comment.

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