

American Red Cross Comment on  
“Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated  
Methods (Draft)”

Presented by Dr. Richard Benjamin, MD, PhD to the  
Blood Products Advisory Committee  
86<sup>th</sup> Meeting – March 9-10, 2006

The American Red Cross thanks the Committee for the opportunity to comment on the three recommendations in the Draft guidance that are the subject of discussion at today’s meeting.

The Red Cross has been engaged in the collection of Platelets by automated methods for over 15 years. More than 150 Red Cross facilities are currently licensed to collect Platelets by automated methods. In calendar year 2004, 97,411 Red Cross donors made 437,015 donation appointments, resulting in 638,971 Platelet components collected. Periodic shortages continue to suggest that patient needs are not being fully met by current production.

Based on internal data and the available published literature, we provide the following responses to the following three areas in the Draft guidance:

1. Process validation of microbial safety of blood collections
2. Deferral period for platelet collection in donors who have taken platelet function inhibitors
3. The number of platelet components that may be collected safely from an individual donor within one year

Item 1: Process validation for bacterial safety:

The draft guidance requires process validation for microbial safety to include culture-based testing of 500 consecutive collections for bacterial contamination, with no more than one positive test result. The rationale given in the draft guidance for this sample size is to assure with >95% confidence that the true bacterial contamination rate is less than 1%.

ARC (and most, if not all other, plateletpheresis establishments) tests 100% of units collected and all of the products that test positive, false positive or indeterminate are discarded. The following data demonstrates our process performance:

ARC bacterial Detection Testing rate (1/1/05 – 10/31/05, n = 350,840)

- Total Positive      65.8 / 100K    or      1:1,519
- True Positive        20.0 / 100K    or      1:5,012
- False Positive      38.8 / 100K    or      1:2,580
- Indeterminate      7.1 / 100K     or      1:14,034

More than two-thirds of positive results obtained with bacterial testing are unrelated to the actual apheresis collection procedure. False positive and indeterminate results reflect contamination at the time of inoculating the culture bottle and BacT/ALERT false signals. In most cases, the root cause of true positives (eg. donor bacteremia, or incomplete skin preparation) cannot be determined. The requirement for an adequate sample size to assure with confidence that the bacterial rate is less than 1% has no medical significance, because bacterial contamination rates this high would be clinically unacceptable.

The requirement for 500 consecutive negative cultures would delay licensure of platelet products (a single apheresis machine would take 10-12 months to validate for licensure) without adding additional safety or assurance of product purity or integrity. All products are cultured before release, and there have been no products released that have been associated with positive cultures. Therefore, Red Cross recommends that consideration be given to modifying this requirement to 60 consecutive products to prove process integrity.

Item 2: Deferral period for platelet collection in donors who have taken platelet function inhibitors

The requirement in the draft guidance for a 5 day deferral for aspirin (ASA) is inconsistent with the current AABB Standards which requires 36 hour deferral after the last dose of aspirin. The rationale to support the 36 hour deferral includes the published report of Stuart et al. (New Engl J Med 287:1105-1109; 1972) which demonstrated that the prolonged bleeding times were corrected to normal in recipients of platelets from donors who had taken aspirin 36 hours before donation. Additional in vitro studies of platelet function in volunteers who have taken aspirin support the 36 hour deferral (Zeiler et al. Transfusion 2004; 44:1300-5).

The requirement in the draft guidance for deferral for NSAIDs (3 days from last dose) is not necessary for the most commonly used NSAIDs (eg. ibuprofen). Currently AABB standards do not require deferral for medications that reversibly inhibit platelet function. Nonaspirin NSAIDs cause transient, dose-dependent and modest bleeding time abnormalities; however, these abnormalities usually do not exceed the upper limit of normal (Schafer, J Clin Pharmacol. 35:209-19; 1995). Platelet function normalizes within 24 hours of cessation of regular ibuprofen use in healthy individuals (Goldenberg et al. Ann Intern Med 2005; 142: 506-509). Although data is not available on platelet recovery after transfusion of platelets collected from donors on NSAIDs with long half-lives, these drugs are used less commonly than short acting NSAIDs and the effect of residual drug would be diluted after transfusion. An estimated 15 million to 20 million people use NSAIDs on a long-term basis in the United States (Fennerty MB. Postgrad Med

2001:110(3):87-94), so an imposed restriction would have a significant impact on the donor base.

Item 3: Number of Platelet Components collected per year

The proposed Guidance to limit plateletpheresis donations to a maximum of 24 Platelets, Apheresis components in a 12 month period and limit the interdonation interval based upon procedural yield is unnecessarily restrictive and not warranted based on the accumulated data on frequent plateletpheresis donors from several blood centers. Restricted to 24 component collections per donor per year, the American Red Cross would have been prevented from collecting 35,786 products (~6% of its distributable inventory) from high-frequency, high-yield donors in calendar year 2004 and compelled to increase its donation base by approximately 6% in an attempt to compensate. Additional product losses from donor dissatisfaction resulting from increasingly complex scheduling requirements at busy donor centers may further exacerbate platelet deficits throughout the system.

Extensive experience under the 1988 Guidance allowing 24 collections per year in concert with donor deferral for counts  $\leq 150,000/\mu\text{L}$  has established the safety of the current maximum component number and frequency of platelet collection.

The American Red Cross has evaluated changes in donor platelet counts for individuals undergoing plateletpheresis over 1 to 8 years and component frequencies ranging from ~4 to 45 per year. Two separate analyses were conducted. The second study, in particular, evaluated changes in the platelet counts of donors who donated at least 20 times in 2002 and continued donating through October 2005. An extensive data summary was included in the addendum of our submission. Significant conclusions from two separate analyses were:

1. There is no statistically significant relationship between the changes in donor platelet counts with repeated apheresis procedures and the number of platelet products donated each year.
2. A minority of donors experienced modest platelet count decrements in the course of repeated procedures. Another small group of donors sustained an equal but opposite increase in their platelet count. It is unclear whether these changes in platelet counts are related to apheresis, represent a true change in circulating platelet mass (mean platelet volume [MPV] values were unavailable), or have any long-term hematological significance.

Given the lack of published evidence demonstrating harm or refuting the safety of long-term repeated platelet donation, Red Cross recommends against the imposition of unnecessarily restrictive guidance that would negatively impact platelet availability and patient safety. Theoretical concerns should be studied and

would be an appropriate topic for prospective research and an FDA sponsored workshop.

The Red Cross is currently engaged in the design and development of processes to collect triple Platelet components by automated methods to meet unmet patient needs for apheresis platelets. Strategic planning for this project suggests that Red Cross could increase collections by as much as 36,000 additional Platelet components per year. The source of these additional components would primarily be from current double component donors. It is apparent that the proposed Draft guidance in its current form would adversely impact the yield of this program so that none of the anticipated increased availability would be realized and patient care would continue to be compromised.

Impact:

In estimating the impact on the supply and operations arising from the guidance, as written, the Red Cross evaluated the following four items:

- Donations limited to 24 platelet products/year/donor
- Physician required to be on site at each location where platelets are collected by apheresis
- NSAID deferrals instituted for 3 days from the last dose
- New limits on volume loss per collection procedure

The Red Cross estimates that these four requirements alone could potentially result in a loss of ~ 65,000 Platelet, Apheresis components per year (~10% of production) and \$40 million additional cost, at a time when there are indications that current patients needs are not being fully met.

Conclusion:

In conclusion, the American Red Cross respectfully submits the following recommendations to the Committee for the Draft guidance:

1. Modify the requirement for process validation for bacterial safety from 500 to 60 consecutive collections without a positive result, because most positive culture results that are encountered are not related to the collection or manufacturing process.
2. Maintain the 36 hour deferral for aspirin, and eliminate the requirement for the 3 day deferral for NSAIDs, based on the expected platelet function and recovery in the components after transfusion.
3. Eliminate the restrictions on donation frequency, interval between donations and number of components collected per year, because adequate measures are already in place to protect the donor and there is no evidence that the risk to donors who give more than 24 components per year are at greater risk than those who give fewer than 24 components per year.