Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods

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Thank you for the opportunity to speak to these important provisions of the draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods. AABB formed a work group comprised of scientists as well as members who have primary responsibilities for quality assurance and BLA submissions to study and critique the recommendations listed in the draft guidance. The work group submitted comments to the docket, and now wishes to provide additional information concerning the three areas listed in the Issue Summary.

Number of Platelet Components Collected Per Year

As a prelude to this issue, it may be useful to review the history of the upper limits of allowable plateletpheresis collections over the last 25 years. The 1981 FDA platelet guidance limited collections to 12 per year based on concerns that the apheresis equipment in use at that time required the apheresis operator to dip into the buffy coat. This created the possibility that a large number of leukocytes could be collected in error, with the potential to deplete donors of “memory lymphocytes” which were poorly understood at that time. With no evidence for immune memory problems appearing, the 1985 guidance criteria were revised to allow for 24 collections per year. As far as we can determine, neither of these recommendations were based upon solid scientific evidence. Similarly, the current thinking represented in the draft guidance (i.e. restricting collections to 24 components per year rather than 24 apheresis procedures) is not supported by scientific data. Rather it appears to be based upon keeping the total annual number of platelets removed from the donor at a level similar to that allowed in the mid 1980s. Furthermore, increasing the interval between collection sessions when a double or triple product is collected appears to also be an arbitrary recommendation without a strong scientific rationale.

Dr. Sherrill Slichter published a study in Transfusion in 1980 which analyzed the influence of daily or every other day plateletpheresis procedures over a 5 to 30 day...
interval on donor’s platelet counts.\textsuperscript{1} The platelet yield per procedure was comparable to that of a contemporary collection of a single unit apheresis product, but the high frequency with which procedures were performed simulates the current extent of platelet removal for donors who may donate two double products in a seven day interval. Most donors showed a platelet count that reached a nadir of about 70\% of their baseline value after 6 to 8 donations. The platelet count then returned to the normal range and remained there in spite of continued platelet apheresis procedures at the same donation frequency. Only one of 61 serially evaluated donors had a platelet count below 100,000/µL at any time during their donation course. In this study, no donors were put at risk either for short term complications (i.e. acute bleeding due to low counts) or for long term persistent thrombocytopenia.

Data compiled by Hemacare and presented in the AABB’s submission to the docket, show that in 105 contemporary donors undergoing standard plateletpheresis procedures with collections of single, double, or triple products, the donors’ post-donation platelet counts never dropped below 100,000/µL, indicating that no donors were placed at acute risk for bleeding. Furthermore, in all cases in which the post donation count fell below 150,000/µL, the pre-donation count prior to the next plateletpheresis (at two to four weeks following the index donation) had risen to well above 150,000/µL.

Monitoring donor platelet counts based on the FDA lower limit of 150,000 platelets/uL provides the appropriate safeguard to protect the safety of the donor. It is not necessary for either scientific or medical reasons to restrict the number of annual components to 24, nor is it necessary to increase the interval between donations when the collection session results in a double or triple platelet product.

The requirement to limit donors to no more than 24 components per year rather than 24 collections per year will have an immediate negative impact on the ability to provide adequate inventories of platelets. Today’s extremely sophisticated platelet collection devices have allowed for many platelet donors to donate 24 times each year with the ability to provide a double product at each donation. Four facilities represented in the AABB work group reviewed their data bases and reported that available platelet products would have decreased by 3.5 – 13.7\% if their donors had been restricted to 24 components per year.

**Duration of Medication Deferral for Platelet Inhibitors**

AABB *Standards for Blood Banks and Transfusion Services* (Reference Standard 5.4.1A) uses a 36 hour deferral for ASA ingestion that is compatible with current FDA guidelines. There are at least two studies that specifically address the issue of aspirin ingestion by platelet donors and the length of time that platelet function is affected. The 36 hour AABB Standard is supported by data presented by Stuart MJ et al. in a study that compared bleeding time corrections in patients transfused with platelets from donors who had taken aspirin 36 hours prior to donation to results when patients were transfused with platelets from donors who had taken no aspirin. Correction was the same for the control recipients (no aspirin ingested by the donors) as for the patients who received platelets
from donors who had ingested aspirin 36 hours prior to donating. An additional study by Slichter and Harker showed that in donors ingesting aspirin, the aspirin-induced platelet dysfunction was reversible in vivo in the transfusion recipients (leading to an appropriate correction of the recipient’s bleeding time) within 6 to 18 hours.

The draft guidance references a review (Reference 10), published in the journal Chest, which looks at cardiac patients rather than a healthy “blood donor” population, and concludes that 5 days is needed following aspirin ingestion for 50% of platelets to be unaffected. However, a review of primary studies referenced in the Chest publication shows that only 10–30% of platelets need to be unaffected for total platelet function to be normal. Once aspirin is discontinued, new platelets produced by the marrow – about 10% of the population per day – are unaffected. Furthermore, this review article and other manuscripts which show that platelet function returns to normal in 2-5 days after aspirin ingestion are intended to assess risk in patients about to undergo surgical procedures, which is a different issue than aspirin ingestion in a platelet donor. This type of assessment is clearly less informative than the studies that directly assessed the efficacy of transfused platelets from donors ingesting aspirin.

Non-steroidal anti-inflammatory drugs (NSAIDs) affect platelet function through a mechanism that is reversible. Consequently platelets from a donor on an NSAID would be expected to function normally upon transfusion to a recipient not on a similar medication. This indicates that there is no need for deferring donors who take such medication. If such a deferral were to be required, the 3 day donor deferral recommended in the guidance is not warranted since the in vivo half-lives for most NSAIDs are less than 24 hours. If there is one NSAID that has a prolonged half life, then a longer deferral could be implemented for that particular drug rather than arbitrarily establishing a 3 day deferral for all NSAIDs.

There is anecdotal evidence that implementing these proposed deferral periods for ASA and NSAIDs use will adversely affect the available supply of platelets. Data could be gathered to better understand the ramifications of such a change. Furthermore, given the wide range of over-the-counter products that incorporate ASA and NSAIDs, it is also not clear how knowledgeable a donor will be with regard to intake of either of these substances.

**Process Validation for Bacterial Safety**

Bacterial contamination testing is currently regulated by FDA as a quality control test, not as a product qualification requirement. Neither the FDA nor collection device manufacturers routinely require bacterial contamination testing; bacterial testing of 100% of platelet products is a self imposed industry standard (as required by AABB) or has been specified by the device manufacturer and approved by FDA in special instances (e.g., 7-day platelet storage). Since this testing is not a uniform FDA requirement, we do not think that such testing should be required in process validation.
Current bacterial testing methods employed in the United States vary. For example, baseline bacterial contamination rates have been determined using aerobic cultures only whereas some facilities perform both aerobic and anaerobic cultures. Since the baseline positive rates for these different testing schemes have not yet been determined, it is inappropriate for FDA to specify a specific rate at which action needs to be taken.

Therefore, we recommend that bacterial contamination testing should be conducted at the frequency and by the method established by the blood center after consideration of industry standards and any specific requirements by device manufacturers. Facilities should set alert and action levels for positive rates based on their detection methods, and establish a plan for investigation of rates exceeding expected levels. This should be treated as part of a quality control plan and removed from the process validation section of the proposed guidance.

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include 1800 hospital and community blood centers, transfusion and transplantation services and 8000 individuals involved in activities related to transfusion and transplantation medicine. For over 50 years, AABB has established voluntary standards and inspected and accredited institutions. Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. AABB’s highest priority is to maintain and enhance the safety and availability of the nation's blood supply.