

BLOOD PRODUCTS ADVISORY COMMITTEE MEETING
Friday, March 19, 2004
Gaithersburg, MD

Issue Summary for Topic III: FDA's Current Thinking on Product Standards, Quality Assurance, and Submission Requirements for Platelets, Pheresis

Issue: FDA intends to develop updated policies regarding product standards and quality assurance for apheresis platelets (Platelets, Pheresis). In order to define a regulatory policy that best addresses recent developments in the field, CBER seeks the advice of the Committee on FDA's current thinking regarding donor selection, component collection, process validation, quality assurance testing, and standards for licensure applicable to apheresis platelets.

Background

The practice of preparing platelets by apheresis using automated blood cell separators has expanded exponentially since publication of FDA's current guidance "Revised Guideline for the Collection of Platelets, Pheresis – October 10, 1988." However, since that time, many improvements have been made to the collection process, storage containers, and methods to determine platelet yields. In addition, apheresis collection procedures may now incorporate the collection of double and triple platelet components from a single procedure, the use of in-process leukocyte reduction, and the collection of concurrent plasma or Red Blood Cell components. CBER plans to update this guidance document to reflect new developments in the area of platelet component preparation. To address these issues, FDA will provide presentations on its current thinking, and an industry representative will discuss the complexities of plateletpheresis quality control in a large collection center, including related cost-benefit considerations.

Discussion

It is important that platelet components should adhere to defined standards to ensure that their therapeutic value is characterized and predictable, and to minimize the overall number of donor exposures necessary to reach a therapeutic end point. In addition, CBER seeks to define and recommend an effective program for quality assurance monitoring of plateletpheresis components. FDA's current thinking in these areas is as follows:

Product standards: Published research indicates that there is poor recovery of viable platelets stored at a pH of less than 6.2. Therefore, we currently believe that while pH 6.0 remains as a minimal acceptable pH (per 21 CFR 640.25 (b)(2)), 90% of plateletpheresis components tested should be = pH 6.2. Because of the continuing problem of bacterial contamination of blood components and associated transfusion risks we continue to recommend bacteriological testing as a part of process validation, but now also believe that bacteriological testing should be recommended as part of quality assurance monitoring. Finally, QC testing at CBER has indicated that 8.2% of components had a

greater than 10% difference in actual volume when compared with the component label as required in 21 CFR 606.121(c)(6) [5], and 12% had a discrepancy between the double collection volumes in each bag [5]. This separation volume discrepancy can result in platelet counts $< 3.0 \times 10^{11}$. We therefore are considering whether to propose a recommendation for an audit system that assesses the total volume and equal volume distribution in double and triple collections, by performing actual tared measurement, and weight volume conversion.

Quality Control: As defined in 21 CFR 640.25 (b)(1-3), four collections per month prepared from different donors shall be tested at the end of the storage period for platelet count, pH, and actual plasma volume. FDA has interpreted that this requirement be applied across all possible production strata (machine type, site, product type). When this QC requirement is applied, it results in a large QC workload, and may also require that a substantial number of components be held for testing making them temporarily unavailable for distribution. At the same time, a small number of samples in each stratum limits the power of testing to detect process deviations.

FDA seeks to establish a statistical framework for quality control strategies appropriate to address low volume production with a low rate of expected failures. FDA will discuss possible approaches involving product conformance within a defined confidence interval based upon binomial statistics, as well as a rate-ratio approach with pre-defined failure tolerance limits as they might apply to platelet apheresis quality control testing.

FDA's current thinking regarding necessary elements of quality control for apheresis platelet components includes the following:

- a) Assessment of four collections from different donors per machine type, per collection site, and per product type for platelet count, pH, and actual plasma volume. This assessment is to be conducted at the end of the storage period (or at time of issue).
- b) Establishment of an internal audit system to assess the total volume and equal volume distribution in double and triple collections, by performing actual tared measurement, and weight volume conversion.
- c) Establishment of internal procedures to include bacteriological testing as part of quality assurance monitoring.

Questions for the Committee

- 1. Does the Committee agree that the proposed recommendations for quality control testing are adequate to assure quality of Platelets, Pheresis?**
- 2. If not, please comment on alternate approaches to quality control for Platelets, Pheresis.**