

**Blood Products Advisory Committee
December 13-14, 2001
Gaithersburg, MD**

Summary for Topic II, Discussion on Leukocyte Reduction Guidance

Issue: FDA seeks the advice of the Committee on options for quality control of leukocyte reduction to be recommended in reissued draft guidance

Background:

In September 1998, the FDA's Blood Product Advisory Committee advised FDA that the benefit-to-risk ratio associated with leukocyte reduction is sufficient to justify universal leukocyte reduction of blood components for transfusion. In April 2001, the Public Health Service Advisory Committee on Blood Safety and Availability recommended that FDA move forward with rulemaking to require leukocyte reduction for non-leukocyte blood components. Leukocyte reduction by pre-storage filtration has been steadily increasing in the industry. Currently, approximately 90% of components provided by the American Red Cross and 60% of components provided by independent blood establishments are leukocyte reduced. Pending any rulemaking, and in recognition of the increasing use of leukocyte reduced products, FDA seeks to update the product standards applicable to such products.

In January 2001, FDA published draft guidance entitled "Pre-storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion." This document proposed updated standards for leukocyte reduction and included a statistically based quality control strategy. FDA is bringing the issue of quality control of leukocyte reduction to BPAC for discussion. The QC alternatives offered to the Committee for consideration include counting each donation for residual leukocytes (i.e. 100% validation), and a modification of the QC strategy outlined in the current leukoreduction draft guidance document.

The FDA has received numerous comments on the draft leukoreduction guidance. These comments included the following:

- the medical relevance of the proposed 1×10^6 residual white cells for a leukocyte reduced unit
- the recommendation to screen all donors for sickle trait
- the recommendation to count residual white cells in all units not tested for CMV antibodies that are released for CMV high risk patients
- the recommended validation and statistical quality control testing procedure

In June 2001 the FDA brought the issue of filtration failures, including problems related to sickle trait, to the BPAC for discussion. Based on the BPAC recommendation and comments received, it is FDA's intention to eliminate from the final guidance the proposed recommendation to screen all donors for sickle trait. In consideration of the loss of 1% or more collected units due to filter clogging, FDA also intends to recommend

that blood collectors should use validated shaker platforms or other validated systems to minimize clot formation during whole blood collection.

The FDA received numerous comments on the proposed standard for leukocyte reduced units of 1×10^6 residual white cells. Data presented to the BPAC in June indicate that there is a wide variation in filtration failures at this standard. In a survey conducted by Americas Blood Centers, 7 centers had failure rates of 1-3%, 8 of 18 centers reported failures of greater than 5%, and 3 had failure rates of less than 1% at 1×10^6 . Only one center of eighteen reported a failure rate greater than 1% when the 5×10^6 standard was used. Yomtovian et al. (Transfusion: 2001; 41:1030-1036) recently reported that 8.3% of units failed to meet the 1×10^6 proposed standard, but only 0.8% failed to meet the 5×10^6 standard. Based on comments received and published reports, the FDA is prepared to revise its proposed standard for leukocyte reduced units to 5×10^6 residual leukocytes.

Unexpectedly high levels of residual leukocytes may compromise the medical benefit of leukocyte reduced components. Such components are increasingly being substituted for CMV antibody negative products for use in low birth weight neonates and other immunocompromised patients. Because of these concerns, the FDA is also reconsidering its proposed quality control measures. In the draft guidance, the FDA proposed a validation/quality control strategy that 95% of the units labeled as leukocyte reduced meet product specifications with 95% confidence. To accomplish this, FDA proposed that a facility should test 60 consecutive products for each major process variation (e.g. filtration of Whole Blood; filtration of Red Blood Cells; filtration of Platelets; filtration of Platelets: apheresis) for each variation in filter and SOP to validate the process. As QC, the blood center would then test a minimum of 20 random products per month for each type of product or process. This would then establish a three month cycle within which the 95%/95% standard (i.e. 60 counts with no failures) would be evaluated. Because of the higher than expected filtration failure rate and reports of individuals who fail filtration for reasons not associated with the procedure, the FDA is considering alternatives.

Discussion:

Proposed modifications to the current draft guidance will be presented (see attachments). In consideration of the questions that will be proposed, the Committee will hear a discussion of the relationship between WBC reduction levels and the medically desirable outcomes of reduced febrile non-hemolytic (FNH) reactions, HLA alloimmunization, and CMV transmission. Also included will be a presentation about currently available methods to evaluate residual WBCs in leukoreduced products, and an update of current knowledge about leukoreduction failures. Finally, the proposed changes in the recommended validation/quality control strategy will be presented and explained.

FDA will then propose the following options for consideration by the committee:

Option 1: FDA should recommend that all products labeled as "leukocytes reduced" meet the defined standard as demonstrated by counting all such products being evaluated for residual WBC.

Advantages: Products labeled as "leukocytes reduced" will be 100% validated for residual WBC content. When used in lieu of CMV-seronegative products for patients who are susceptible to severe CMV infection, 100% validation will help ensure that a product labeled as "leukocytes reduced" does not have a WBC level that exceeds the product standard. A recommendation for 100% WBC counting will also stimulate the appearance of new technologies that will facilitate cost-effective WBC enumeration.

Disadvantages: A recommendation for 100% validation has practical difficulties because of the current high cost and/or unavailability of reagents to automate the WBC counting process. The workload to manually count every product may be an overwhelming burden for blood centers. Blood centers may choose to provide fewer leukoreduced products.

Option 2: FDA should recommend that blood centers validate the leukoreduction process utilizing statistical quality control strategy (as proposed below) to ensure with a defined level of confidence that products labeled as "leukocytes reduced" meet a defined standard.

Elements of the proposed Validation/QC strategy include the following: (See attached table for more detail)

- 1. Incomplete filtration and a post-filtration residual white blood cell (WBC) count in excess of the defined standard are to be considered as two distinct types of process failure.**
- 2. Incomplete filtration rates should not exceed 0.5% of filtered products (excluding incomplete filtration due to identified donor-specific factors).**
- 3. The recommended standard for residual WBC in filtered RBC and platelet products is $\leq 5 \times 10^6$.**
- 4. For purposes of validation, 95% of products should contain $\leq 5 \times 10^6$ residual WBC with 95% confidence (zero failures per SOP @ n= 60 consecutive counts). This calculation is based upon an exact binomial distribution, therefore validation and QC may be accomplished either by enumeration of residual WBC, or by a validated method that will provide a simple pass/fail designation for evaluated products.**
- 5. Variations in time after collection, temperature of filtration, duration of filtration, type of filter, or other process variables may require separate SOPs with individual validation and QC procedures.**

6. As a QC minimum, a random 1% of all leukoreduced products should be evaluated for residual WBC content. SOPs used for filtration in a given week should be considered individually so that as part of the QC process a minimum of 5 random products/week (60 products/3 months) are counted per SOP. (Note: Revised draft guidance will provide examples to help clarify this recommendation)

7. If a post-filtration WBC count exceeds 5×10^6 , the cause should be investigated. Simultaneously, the next consecutive 60 products prepared under that SOP should be counted.

a. If the observed failure is due to a donor-specific factor, it does not constitute a process failure. The consecutive counting may be discontinued and donor management procedures as described below should be implemented.

b. If the observed failure is not due to a donor-specific factor, it should be assumed to be a process failure. Failure investigation should be initiated and corrective action taken.

c. If the 60 consecutive counts following the observed failure do not identify product failures and corrective action has been taken, normal QC should resume.

d. If the 60 consecutive counts following the observed failure identify one or more additional process failures, the process should be considered out of control. Failure investigation should be initiated and corrective action taken. The SOP should then be re-validated as described above. All leukoreduced products produced under that SOP since the last acceptable QC cycle (n=60 counted units) should be counted prior to release if less than 48 hrs has elapsed since filtration. If unavailable, the center SOP should define procedures for product withdrawal, consignee notification, and product recall.

8. When a failure is due to an identified donor-specific factor, the donor record should be flagged. Upon a second occurrence of incomplete filtration or inadequate WBC removal, the donor should become ineligible for donation of filtered products, unless a validated alternative procedure is used that prevents such failure.

9. Alternate approaches to the recommended validation/QC procedure will be considered. Appropriate SOPs should be submitted to FDA as prior approval supplements.

Advantages: The proposed strategy assures that ninety five percent of products labeled as "leukocytes reduced" will meet the product standard with 95% confidence. The quality control workload at blood collection centers will be considerably less than would be needed to count all products. (Note: Protection for CMV-susceptible patients will be considered by discussing (but not recommending) that transfusing physicians may also wish to provide such patients with products that are CMV seronegative.)

Disadvantages: While not recommended by FDA as "CMV-safe", leukoreduced products are currently commonly substituted for CMV-seronegative products. Occasional products that have levels of residual WBCs that exceed the product standard may unknowingly be transfused to CMV-susceptible patients. The QC strategy proposed is somewhat complex for blood centers, as well as QA and regulatory inspectors.

Questions for the Committee

1. Does the Committee recommend Option 1; i.e. that FDA should recommend to industry that all products labeled as "leukocytes reduced" meet the defined standard as demonstrated by evaluating all such products for residual WBC content.
2. If no to question 1, does the Committee concur with the modified statistical quality control strategy as outlined?
3. If no to questions 1 and 2, what elements of the modified statistical quality control strategy outlined in Table 1 are in need of further consideration?