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Quality assurance and monitoring of leuko-reduction

A California blood banker reports that after reviewing the FDA Guidance for Collection of Platelets by Automated Methods finalized in Dec 2007, she has a few questions:

- Q1:** How many units should be tested for quality assurance and monitoring of leuko-reduction? She realizes many variables need to be considered, however, she asks us to assume that during validation, 60 consecutive collections were tested for residual WBC and all were found to be considerably less than 5.0×10^6 WBC; and the Donor Center collects an average of 50 platelet products per month.
- Q2:** If 3 years worth of data show the process to be stable, would a "rolling number" of QC values be reasonable? (For example, test 5 collections per month [10%] and evaluate these results with the previous 25 results.) Part of the QC failure investigation procedure would be to re-validate the process if other causes for the failure are ruled out.
- Q3:** If only 5 collections per month are tested, would there be value to spreading the QC samples out over the month rather than to test the first 5 collections of every month?

Editors' note: The December 2007 guidance document, "[Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods](#)", provides revised recommendations for the collection of platelets by automated methods. The December 2007 guidance document supersedes FDA's "Revised Guideline for the Collection of Platelets, Pheresis" from October 1988 and finalizes the draft guidance "[Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods](#)," published in September 2005.

ADDENDA February 26, 2008

1. **Richard J. Benjamin MD PhD, Chief Medical Officer of the American Red Cross Biomedical Services at US National Headquarters** (attribution used with permission) reports that during the **validation** of leukocyte reduction for an automated platelet collection method, the American Red Cross determines the **residual leukocyte counts of 60 consecutive pheresis platelets units**. All of the products are required to contain less than 5.0×10^6 WBC. Once validation is complete, **1% of the collected products** have residual leukocyte counts determined; but **at least 4 products would be selected at minimum each month for each filter type or method**. He adds that the American Red Cross has not yet implemented a rolling number of QC values at this time and continues to follow 21CFR requirements for Product Quality Control testing. Finally, he comments that the American Red Cross believes that it is **best to spread the QC samples out over the month** in a **random sampling** fashion.

ADDENDA February 27, 2008

2. **A Compliance Specialist in Wisconsin** reports that it is her understanding that blood establishments **must still be compliant with the May 29, 1996 FDA Memorandum, "Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products."** That document requires that each month a **minimum of 1% of the monthly production (4 per month if less than 400 products are collected)** should be tested for residual WBC content. This needs to be done **for each type of automated device, each collection type and each collection location**. She adds that once the leukocyte-reduction process is validated at a given collection location, then if there is a monthly component qualification failure, it would be

necessary to perform a thorough investigation to determine the cause. If there is a process failure (not all failures are process failures, e.g. donor reactions), the concept of using a "rolling number" might be valid, but the numbers might be too small to show a 95% confidence that 95% of the products meet the standards. The **guidance document provides a table of numbers**. Finally, she believes that QC should be **spread out over the month**. If there is a process failure mid-month, it would be **detected sooner**.

ADDENDA May 7, 2008

3. **A transfusion medicine physician who oversees a community blood collection center in Southern California** comments that the **key** to understanding Quality Monitoring as outlined in the Guidance for Collection of Platelets by Automated Methods (GAM) is **being able to understand TABLE 1**. To do this use a Binomial Calculator along with the Table 1 to determine the "Recommendations" of a monitoring plan. One example of a **Binomial Calculator** is located [HERE](#).

In response to Question 1 (How many units should be tested for quality assurance and monitoring of leuko-reduction? She realizes many variables need to be considered, however, she asks us to assume that during validation, 60 consecutive collections were tested for residual WBC and all were found to be considerably less than 5.0×10^6 WBC; and the Donor Center collects an average of 50 platelet products per month) he writes: "The first thing that is difficult to understand is that the number of collections is not used in the Binomial Statistic approach. You are calculating the sample size based on three pieces of information

1. Confidence Level
2. Proportion Defective
3. Number Defective

The Confidence Level (CL) for all of the Recommended Results, listed in the GAM, is 95%. The CL simply means that you can be 95% confident that the components produced meet the recommended results.

The Proportion Defective (PD) is also listed in the GAM. These values are the percentages for allowable failures. There are two different PD levels:

1. 25% for the platelet yield of transfusable components: Product is no more than 25% defective.
2. 5% for the pH, component retention and residual WBC count: Product is no more than 5% defective.

The Number Defective (ND) is the number decisive factor in determining the sample size. The question is "How does one calculate the ND". One easy way to determine this is using historical data. From the historical data, calculate the ND per month or, referring back to Question 1, using validation data. With the validation data, since all were found to be considerably less than 5.0×10^6 WBC, the calculation will be made with zero defects.

What is the minimum sample size needed to be 95% confident that the product is no more than 5% defective? (rWBC allowable failures)

Calculator inputs are $p = .05$, $r = 0$, $CL = 95$, and calculate the sample size.

The minimum sample size will be 59.

The GAM Table 1 states 60 and I have not been able to determine why this discrepancy exists. All the other numbers on the Table 1 and the Binomial Calculator are concordant.

What is the minimum sample size needed to be 95% confident that the product is no more than 25% defective? (Platelet Yield allowable failures)

Calculator inputs are $p = .05$, $r = 0$, $CL = 95$, and calculate the sample size. The minimum sample size will be 11. "

In response to Question number 2 (If 3 years worth of data show the process to be stable, would a "rolling number" of QC values be reasonable? (For example, test 5 collections per month [10%] and evaluate these results with the previous 25 results.) Part of the QC failure investigation procedure would be to re-validate the process if other causes for the failure are ruled out.) he writes: "If the meaning of 'stable' means zero defects the sample size would be the same as in question number 1. In reviewing the stated example from above, it may not

meet the GAM recommendations found in C. Component Testing; 2. QC Monitoring ..." laboratory controls must include the establishment of scientifically sound approach..." Before implementing this type of program or any program differing from the recommended process, I would **suggest contacting your CSO and explaining the approach.**"

In response to Question 3 (If only 5 collections per month are tested, would there be value to spreading the QC samples out over the month rather than to test the first 5 collections of every month?) he writes: "The areas of concern listed in the GAM related to "collections to be tested" focus on device type, collection type and location. There is not a reference to time in this description of the protocol. Since there is no specific direction **use the process that works best in your environment that will provide the a quality product.**"

Please submit comments to the [e-Network Forum](#).

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