



America's Blood Centers[®]
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December 30, 2005

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2005D-0330, Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods

Dear Docket Officer:

On 3 October 2005 the Food and Drug Administration published in the Federal Register a Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods. America's Blood Centers (ABC) would like to take this opportunity to provide our comments.

ABC is an association of independent, FDA licensed, community based blood centers. ABC member centers supply about half of the United States of America's blood and blood components for transfusion.

This Draft Guidance is a comprehensive revision of previous guidance issued in 1988. Attached you will find detailed technical comments pertaining to this Draft. We have several concerns about the significant negative impact that implementation of parts of this Draft Guidance would have on availability of Platelets, Pheresis and consequently on patient care. We also believe that the proposed requirements are extremely burdensome and were not generated in response to a perceived threat to public health. There are no reports of adverse events that justify the imposition of many of the additional requirements.

The concerns are so serious that, in our opinion, they require public discussion, presentation of relevant data and expert input. ABC is willing to sponsor a public workshop that would include other blood banking organizations to accomplish this purpose, and would like to invite the FDA to participate. The following is a summary of our major concerns:

- Restriction of the number of products to no more than 24 products per year, instead of the current guidance limiting the number of collections, not products per year. A brief survey of some of our members indicates a potential loss of over 20% on average, with some centers estimating a reduction of over 50% of Platelets, Pheresis products, without clear quality or safety benefit. In addition, the restriction of the volume of plasma collected permitted by this

Draft Guidance is less than exceeds that prescribed in the AABB Standards and less than some licensed collection systems; yet the rationale for this change is not provided.

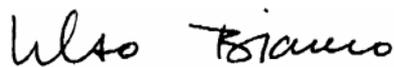
- The new expanded interpretation of physician availability within 15 minutes in case of emergencies. This too has the potential to further reduce Platelet, Pheresis inventories by eliminating 50-75% of off-site collections and all expanded hours collections. The procedure is recognizably safe, and the frequency of donor reactions is lower than that for whole blood donors. We strongly believe that it is safer and appropriate to have validated emergency response plans that rely on trained emergency personnel rather than on physicians physically present at blood collection facilities. whose training may not include emergency response (e.g. pathologists, hematologists, etc.)
- Extension of donor deferral for ingestion of drugs that affect platelet activity beyond currently applied criteria. We do not believe that this extension is supported by peer-reviewed scientific literature and again, it would further erode Platelets, Pheresis product availability.
- Reliance on a deferral list of drugs posted on the web by the Armed Services Blood Program Office (ASBPO) for their own use. While we respect the ASBPO decisions, we do not consider it appropriate for the FDA to mandate in guidance the use of a list that is created and maintained by an individual or committee that is not named, based on information that is not referenced, not subjected to scrutiny by identified experts and not discussed in public.
- The endorsement of scan statistics and the large numbers of products its use would require as part of validations and quality control. Scan statistics have been proposed as a potential statistical method to evaluate non-conformity in cellular blood products (Lachenbruch, PA, Foulkes, MA, Williams, AE and Epstein, JS. Potential use of the Scan Statistic for Quality Control in Blood Product Manufacturing. *J. Biopharmaceutical Statistics*, 15:353-366, 2005). While scan statistics have been successfully applied in gene mapping, hot spot detection in spatial geography, analysis of the geography of 911 calls, and even the detection of fraud in the Enron bankruptcy case, the approach has not been applied or validated in quality control of cellular products of blood. In essence, Scan Statistic is an untested model with no live experience in a blood collection facility. We are concerned about the large number of products required by application of this model would significantly affect the availability of Platelets, Pheresis, because of the number of products reserved for QC. Furthermore, platelet donors, as human beings, present a considerable degree of biological variability. Apheresis, when performed in donors, depends on a number of variables that cannot be totally controlled (hydration of the donors, hematocrit, platelet count above 150,000, etc.). Thus, we are also concerned that an inflexible quantitative approach may not be appropriate for process control. The applicability and compatibility with existing processes needs to be documented by data prior to a recommendation for implementation of this procedure. The approach needs to be validated by real time pilot studies performed in blood establishments prior to a recommendation for implementation. Finally, there is no evidence that these changes would improve the quality or safety of the product beyond the already required platelet count for every product before release for transfusion.
- The requirement to perform both pre and post donation platelet and WBC counts. There is no scientific data to support the need for WBC monitoring as part of plateletpheresis procedures. This draft guidance is very prescriptive regarding testing pre and post counts.

We believe it is best to set minimum standards, such as the minimum of 150,000 that already exists for plateletpheresis, and allow the centers to develop and validate the processes that best achieve them rather than mandating arbitrary and unnecessary testing. Furthermore, pre donation counts are not always available in smaller fixed sites and mobile sites. This would further restrict the availability of products without a clear quality or safety benefit.

A number of other issues are discussed in detail in the following pages. Ultimately, we are concerned that the requirements proposed in the draft guidance are so burdensome that the Guidance may reverse the movement of collecting facilities toward apheresis platelets, bringing back reliance upon whole blood derived platelets. We obviously do not know if this is the intention of the Agency.

Thank you for the opportunity to comment on this docket.

Yours truly,

A handwritten signature in black ink that reads "Celso Bianco". The signature is written in a cursive, slightly slanted style.

Celso Bianco, MD
Executive Vice President

A. Section II: Discussion

- 1. Recommendation: The guidance should standardize the pH at ≥ 6.2 and the CFR should be changed appropriately.**

In three locations (Page 2, Section II A, Page 15, VII A 1, Page 20, VII C 2) two different specifications for pH are given: the current requirement in 21 CFR 640.25(b)(2) of pH ≥ 6.0 and a statement “should be ≥ 6.2 .”

- 2. Recommendation: The proposed extension of deferrals for ingestion of aspirin or other drugs that affect platelet function should be deleted from the Guidance. Such deferrals should continue to be determined by expert committees in standard-setting organizations like the AABB.**

The Draft Guidance seeks to significantly increase the Platelet, Pheresis donor deferral period for ingested drugs that affect platelet function (page 5, Section III A). These increases will affect platelet product availability. Donors and their physicians are less likely to interrupt aspirin therapy for greater than 3 days. References for these new requirements are based on the Armed Services Blood Program Office Donor Deferral Criteria: Drugs and Medication Impact on Blood Donors Eligibility. This reference is not a peer-reviewed publication, there has been no opportunity for the industry to have input into it, and it is not updated on a regular basis. Additionally, this document has a specific disclaimer “NOTICE: The Department of Defense (DoD) assumes no risk for the use of this information by non-DoD personnel, blood programs, or individual medical institutions.” This document was developed specifically for use by DoD and its special needs and circumstances.

The Draft Guidance bases the extended deferral for aspirin on a review published in Chest by Patrono et al. (reference 10 in the Draft Guidance). This review quotes two papers, one published in 1968 and one in 1980 to indicate that about 10% of platelets are replaced every day (page 40S) and assumes that “5 to 6 days following aspirin ingestion, approximately 50% of the platelets function normally.” Unfortunately, the review does not provide specific data to support this assumption. Other publications in the literature indicate that a shorter deferral period for the intake of aspirin would not be detrimental to platelet recipients. For instance, Minno, GD, Silver, MJ and Murphy, S. Blood. 1983;61:1081-1085, 1983) studied the entry of new platelets into the circulation after ingestion of aspirin. They showed that as early as 4 hours after ingestion, there are sufficient new platelets to allow aggregation and thromboxane formation, and that “these observations help explain why the hemostatic defect following ingestion of aspirin is relatively mild.” In another study (Zeiler, T, Gritza, D., Karger, R. and Kretschmer, V. Transfusion, 44:1300-1305, 2004) attempted to use aspirin to “protect” platelets from damage during apheresis and storage. They found no significant differences in expression of CD62p and fibrinogen binding on day one of storage, between platelets from donors who took aspirin before donation, and donors who did not take aspirin. These authors concluded that aspirin ingestion “may not be detrimental to the clinical effectiveness of the stored product.” They do however, recommend further in vivo studies. Another study looked at the effect of preoperative aspirin-free interval on red cell transfusion requirements in cardiac surgical patients and concluded “patients who stop taking aspirin 3-7 days preoperatively have little or no increased requirement for allogeneic red blood cell

transfusion”. Essentially, their need for blood cell replacement was similar to that of patients who did not receive aspirin (Weightman, WM, Gibbs, NM, Weidman, CR et al. J. Cardiothorac Vasc Anesth, 2002; 16:54-58).

We asked Dr. C. R. Valery and his staff whether there is a need for change in deferral criteria for aspirin. They explained that “when a normal volunteer (or baboon) ingests aspirin, the platelets in the circulation become aspirinated and the aspirin remains in the blood for about 8 or 9 hours. After the aspirin is removed from the circulation, the platelets remain aspirinated until sufficient numbers of non-aspirinated platelets are produced. According to O’Brien (Lancet 1:779-783, 1968), these aspirinated platelets can be “turned on” and their functionality restored by the addition of new functional platelets. His studies demonstrated that only about 10-15% functional platelets were required to turn on the dysfunctional aspirinated platelets. With the platelet lifespan of 6-7 days and normal platelet production, this number of platelets could be produced in 1-2 days. Add this to the ~1 day to remove the aspirin from the circulation and you have the recommended 3-day period. They added that a published paper studying baboons supports the O’Brien data (Valery, CR, MacGregor, H, Giorgio, A, and Ragno, G. Transfusion, 42-1206-1216, 2002). Baboons who were given aspirin and not transfused with platelets, had extended bleeding times and platelets which did not produce thromboxane for 2-3 days following the aspirin ingestion. Fresh, 2-day liquid stored and previously frozen platelets, transfused in quantities sufficient to produce 10-15% non-aspirinated platelets in the circulation of the baboon, corrected the bleeding time over the 1-9 hour post-transfusion period.

These publications support the current criteria applied to donors who take aspirin or other non-steroidal anti-inflammatory agents as developed by organizations such as AABB. The current criteria have been used for many years, and there are no reports indicating that platelets collected under these criteria have produced undesired effects.

- 3. Recommendation: The FDA should eliminate contradictory requirements in statutory documents and should not utilize guidance documents to accomplish this. Additionally, the FDA should provide specific, validated statistical criteria that should be used, and not endorse any one system/model.**
4. The Draft Guidance describes the requirements of 21 CFR 640.25(b) (1)-(3) to test four units prepared from different donors for platelet count, pH, and volume (Page 3, Section II A). It then refers to 21CFR 211.160(b)’s requirement that laboratory controls include the establishment of scientifically sound and appropriate specifications ... and identifies “scan statistics” as one of the methods to comply with the regulation. This appears to be contradictory. If the FDA believes that four units per month are inadequate then it should seek to change the CFR appropriately and eliminate conflicting regulatory guidance. Additionally, the scan statistics methodology recommended has not been validated in actual blood manufacturing settings to demonstrate that the numbers generated are realistic and effective.

As stated in the cover of this document, scan statistics have been proposed as a potential statistical method to evaluate non-conformity in cellular blood products (Lachenbruch, PA, Foulkes, MA, Williams, AE and Epstein, JS. Potential use of the Scan Statistic for Quality

Control in Blood Product Manufacturing. *J. Biopharmaceutical Statistics*, 15:353-366, 2005). While scan statistics have been successfully applied in gene mapping, hot spot detection in spatial geography, analysis of the geography of 911 calls, and even the detection of fraud in the Enron bankruptcy case, the approach has not been applied or validated in quality control of cellular products of blood. In essence, scan statistic is an untested model with no live experience in a blood collection facility. We are concerned about the large number of products required by application of this model would significantly affect the availability of Platelets, Pheresis, because of the number of products reserved for QC. Furthermore, platelet donors, as human beings, present a considerable degree of biological variability. Apheresis, when performed in donors, depends on a number of variables that cannot be totally controlled (hydration of the donors, hematocrit, platelet count above 150,000, etc.). Thus, we are also concerned that an inflexible quantitative approach may not be appropriate for process control. The applicability and compatibility with existing processes needs to be documented by data prior to a recommendation for implementation of this procedure. The approach needs to be validated by real time pilot studies performed in blood establishments prior to a recommendation for implementation. Finally, there is no evidence that these changes would improve the quality or safety of the product beyond the already required platelet count for every product before release for transfusion.

- 5. Recommendation: The FDA should establish the bacterial contamination testing requirement in statutory guidance and license products to meet this need. The proposed approach in this Draft Guidance is inconsistent with FDA's own Good Guidance Practices (GGPs).**

The FDA has publicly endorsed bacterial contamination testing and does again on Page 3, Section II A. We agree that bacterial contamination is an integral part of process validation and quality assurance monitoring. However, we disagree with the FDA's implication of 100% quality control bacterial testing when there are no assays licensed for release. A 100% check is no longer a quality control monitor but in fact release testing. The FDA should seek to license products to meet this requirement and eliminate contradictory terminology as a method of achieving their desired goal.

B. Section III: Donor Selection and Management

- 1. Recommendation: Delete the requirement for WBC counts.**

This Draft Guidance makes several recommendations for determination of White Blood Cell (WBC) Counts prior to and/or after the first donation (Page 5, Section III A). There is no current requirement for WBC count prior to, or after collections, including the manufacturer's recommendations, and no parameters for donor acceptance have been established. There is no indication that determination of WBC will increase the safety of donors or quality and safety transfused products.

2. Recommendation: Delete the requirement for single platelet collections from first time donors where platelet count is not known.

This Draft Guidance states that only a single Platelet, Pheresis product should be collected from first time donors who do not have a pre-donation platelet count (Page 5, Section III B 1). Operationally, this would be impossible to control as platelet collection is also dependent upon weight and hematocrit of the donor. We know of no data that shows collection of a double or triple product from a first time donor is harmful to the donor.

3. Recommendation: Retain the current guidelines for the frequency of platelet apheresis procedures for a donor, including frequency, platelet count requirements and physician review procedures.

The current established industry standard for platelet apheresis is no more than 24 platelet pheresis collections in a 12 month period. This draft guidance establishes an additional requirement to collect no more than 24 total Platelets, Pheresis components in a 12 month period (Page 6, Section III B, 2). This change would have a significant impact on the Platelet, Pheresis inventory. A small (n=11), informal survey of our members estimates a mean loss of 23.3% of platelet apheresis products (median 20, range 10-51%). The Draft cites a reference by Lazarus et al. (ref. 21) as the basis for this recommendation. Interestingly, the conclusion of the abstract of this paper states that “Regular plateletpheresis donors develop sustained decreases in platelet count. However, clinically significant thrombocytopenia is unusual when rigorous ongoing review and prudent deferral policies are established and followed.” The paper provides no evidence of harm to donors. On the contrary, it shows that decreases in platelet counts are transitory and are quickly reversed. We strongly believe that current platelet count limits for donor qualification fulfill these recommendations. Under current guidance, there are requirements for platelet counts and chart reviews of every donor and donation. We plan to conduct a larger, formal survey of all of our members in the near future to better assess the impact of this proposed change.

Moreover, it would be very difficult to track donations in a way that would comply with the suggested changes. All current computer systems are designed to track donation eligibility based on donation interval, not the number of products donated. Implementation of such a requirement would necessitate a manual tracking system in lieu of the computerized systems used by the majority of blood centers in the US today. Development and clearance of new software for this purpose would probably take years. In our opinion, there is no evidence that the proposed changes will increase donor safety. All evidence suggests that platelet apheresis is a safe procedure.

4. Recommendation: Delete specific testing requirements; retain the minimum qualifying platelet count of 150,000. Let collecting facilities establish validated methods to assure compliance.

Sections of the Draft Guidance (Page 5, Section IIIA and Page 6, Section III B, 2) establish the requirements for both a pre and post donation platelet count to be performed. No timing for a post count requirement is given, nor was the reasoning for performing both pre and post platelet counts provided. We believe the key requirement should be that donors not undergo

platelet pheresis if their platelet count is less than 150,000. This is the current requirement applied to all licensed facilities. There is no indication that performance of either a pre or post platelet count affects donor safety. It is important to note that many of the apheresis procedures are performed in secondary sites without available equipment or technicians to perform pre-counts. Such a requirement will eliminate many of these sites and affect availability of platelets collected by apheresis.

- 5. Recommendation: Add “or as specified in the labeling for the device manufacturer” to allow for approved medical devices to be used in accordance with their approved labeling.**

To protect the donor from significant RBC loss, the draft guidance recommends that donors who have donated a unit of red blood cells not undergo pheresis collections if the extracorporeal volume is greater than 100 mL (Page 6, Section III B 3): This would allow FDA to establish the requirements according to the characteristics of each of the cleared devices, without having to establish a generic limit.

- 6. Recommendation: Volume loss should be based on donor weight and not on product type.**

Page 7, Section III B 4 of the Draft Guidance establishes absolute values for total volume of blood components retained per collection. This is not consistent with the AABB recommendations of 15% of the donor’s total blood volume for total volume loss per collection procedure, and may not be consistent with current device labeling. Current technology takes donor size into account (using <15% of total blood volume loss as target) and there is no documented reason suggesting that a change is beneficial to donor or product.

- 7. Recommendation: Delete the proposed interpretation of available medical care and allow centers to develop SOPs with appropriate emergency response plans.**

Despite the common observation that the frequency of adverse reactions among apheresis donors is lower than that of whole blood donors, the Draft Guidance requires a physician on the donation premises or able to arrive within 15 minutes (Page 7, Section III D). The reference for this interpretation is a Proposed Rule from 1985 that was never formally issued. It is a widely accepted fact that the most qualified medical professionals to deal with an emergency are trained, practicing emergency physicians or emergency medical technicians using the proper equipment, who have the ability to transport an unstable patient to an appropriate health care setting. Furthermore, there are several publications in the peer reviewed literature showing that emergency medical personnel frequently respond to calls in 8 minutes or less (see Lerner et al, *The J. of Emergency Medicine*, 25:171-174, 2003; Pons et al. *ibid* 23:43-48, 2002). Requiring a physician to be available at donation sites within 15 minutes would significantly impact platelet product availability eliminating mobile platelet pheresis as well as collections during extended hours and at donor facilities at some distance from the collection facility’s central office.

- 8. Recommendation: Change bullet 3 on page 8 to “There are no known long-term effects of repeated plateletpheresis on platelet counts, but such decrease cannot be ruled out.” Change bullet 4 to “information about donor eligibility requirements including the number of procedures that may be performed per year.”**

The Draft Guidance indicates what information should be provided to the donor. Among the requirements is a statement that the long-term effects of repeated plateletpheresis... are not understood (Page 8, Section VII). Actually, the evidence, even as quoted in reference 21 of the Draft, is that there are no known adverse effects. Another recommendation is the description of number of collections and components. This information is complex and may require explanation of products and donation types that may not ever impact a particular donor. We wish our donors to have the information necessary to make a rational decision about donation, and to assist us in determining their eligibility and to be informed when they are approaching the maximum numbers of components or loss volumes. The information supplied should be applicable to the situation and the donor.

C. Section V: Component Collection and Management

- 1. Recommendation: Allow the sterile docking of a new needle unless there is evidence of contamination of the apheresis set.**

This Draft Guidance states that the phlebotomy must be performed by a single uninterrupted venipuncture (Page 8, Section V A). This does not appear to allow for the common practice of sterile docking a new needle set to save the procedure.

- 2. Recommendation: Use manufacturer’s device labeling and site’s validation protocol to establish target yield.**

The target values for double and triple collections listed in the draft document (Page 8, III V B) are extremely prescriptive and do not allow for instrument variability that will produce consistently acceptable products with slightly lower target yields. As the actual platelet yield is verified on each product by the product quality control program, each facility should be allowed to set its own target yields for split products.

D. Section VI: Process Validation

- 1. Recommendation: Change “process operator performance” to “operational qualification” that includes but is not limited to operator qualification.**

The FDA’s interpretation of Process Validation includes “process operator performance qualification (Page 10, Section VI).” References for validation refer to *operational* qualification which includes operator qualification as well as process and procedures. Operational qualification along with those stated in this document; installation qualification and product performance qualification comprise a complete validation protocol. We concur

with the need to adequately train users and ensure competency through appropriate supervision. However, we believe operational qualification is more than just training and competency.

2. **Recommendations: Add “if applicable” to leukocyte reduced percent recovery for non-filter requirement. Clarify what testing is required for bacterial contamination and indicate whether a licensed product is available for such purpose.**

The Validation Protocol (Page 10, Section VI B) recommends residual WBC count for collection (if leukocyte reduced) and percent recovery as well as bacterial contamination testing. Percent recovery may not be applicable if a non-filter process for leukocyte reduction is used, as is the case on many current machines. Additionally, what is meant by bacterial contamination testing? Is the FDA referring to sterility checks, or to other testing?

3. **Recommendation: Reevaluate and clarify of the number of components to be tested as part of product performance qualification.** This large number will adversely impact product availability. Additionally:
 - a. **Clarify how the number of collections for testing was determined and what is considered a failure in the context of this sentence.**
 - b. **Change the requirement to: test each type of instrument rather than each instrument, so as not to adversely affect product availability.**
 - c. **Allow each center to establish the process for component selection during validation as part of the validation protocol.**

Product performance qualification criteria listed in the Draft Guidance (Page 11, Section VII D) calls for testing “a minimum of 60 consecutive single (30 for double and 20 for triple) collections.” It goes on to require performing “bacterial contamination testing on 500 collections with 0 failures.” The Draft Guidance states that “Product performance qualification should be completed for each automated blood cell separator in your establishment.” Finally, it specifies to “Test one third of the components collected for qualification during the first third of the dating period; one third during the second third of the dating period, and one third the day of outdate.” These requirements are confusing. Is it intended to be 60 singles plus 30 doubles *and* 20 triples (a total of 110 products) or a total of 60 products in a combination? Is the requirement to test 60 consecutive single collections from each instrument or each type of instrument? These are very large numbers of components and will compromise product availability.

4. **Recommendation: Change the target column to result or confidence level. Alternatively, this column could be eliminated or moved to a reference section.**

Table 1 on page 12, Section VI does not discuss the possible contamination of testing. The Target column and Allowable process failures do not agree.

5. **Recommendation: Clarify the intent of this requirement.**

The Re-Qualification/Re-Validation section (Page 13, VI E) states that when a process fails during validation, you investigate, correct the source of the failure and “complete the process qualification in its entirety.” We concur that all failures should be investigated. However, this statement implies that we need to start validation all over again, instead of completing the validation from that point in the protocol on.

E. Section VII: Quality Assurance and Monitoring

1. **Recommendation: Delete this requirement, as the Circular of Information provides adequate information for the transfusion facilities. If it is the desire of the FDA to add this as a labeling requirement, the appropriate labeling regulations should be modified concurrently.**

This Draft Guidance mandates that the platelet yield from each collection of Platelets, Pheresis should be provided to the transfusion facility (Page 15, Section VII A). There is no current requirement for the manufacturing facility to include platelet yield on the container label. Platelet yields must be determined and recorded in the facility records. The Circular of Information includes the minimum platelet count of 3.0×10^{11} for platelets apheresis. This is therefore a new labeling requirement above and beyond that currently in place. Besides creating a new opportunity for manual processes and consequent errors, it will provide no clear benefit to the transfusion facility. Every unit has more than 3.0×10^{11} platelets.

2. **Recommendation: Clarify the intent and specifics of this requirement.**

The FDA has established limits for residual WBC counts in leukoreduced products. Additional Provisions Applicable to SOPs, Residual WBC counts (Page 15, Section VII, A, 2) implies that limits should be established for all devices. This requirement should not apply when non-leukoreduced products are being produced. Leukoreduction is not a mandated procedure.

3. **Failure Investigations**, described on Page 15, Section VII A, 2, is very clearly written and provides specific guidance that is helpful to the industry.
4. **Recommendation: Delete the first paragraph defining limits at which medical directors should be notified.**

Donor Monitoring, described on Page 17, Section VII, B, requires medical director notification when post collection platelet counts are $<100,000/\mu\text{l}$. While we understand the intent to protect the donor, there is no established requirement to perform a post collection platelet count or what the timing of a post collection count should be. As previously stated, it is the medical director’s responsibility to ensure that no donor with a platelet count below 150,000 be allowed to donate Platelets, Pheresis. It should also be incumbent upon medical directors to establish limits at which they should be notified of donor conditions. The second paragraph of this section clearly defines the purpose and intent of monitoring donor platelet counts.

5. **Recommendation: Restrict the requirement for physician or designee review to severe donor reactions (as defined by the collection center’s SOPs) that required medical intervention and hospitalization.**

In this same Donor Monitoring Section, there is a requirement for a donor who has experienced an adverse reaction to be evaluated by a qualified physician or designee before a subsequent donation. Many sites categorize their reactions by severity, e.g. a minor hematoma is an adverse reaction, but should not require physician review and subsequent investigation.

6. **Recommendation: Delete of this requirement.**

Component Testing (Page 19, Section VII, C, 1) requires “residual WBC count on all collections that do not utilize an automated leukocyte reduction methodology.” This requirement should not apply if the product is not labeled as leukocyte reduced.

7. **QC monitoring** (Page 19-20, Section VII, C 2) lists the components of a QC protocol. We concur with these components **except as listed below:**

a. **Recommendation: Clarify that testing for % component retention is only applicable to leukoreduced products that are not produced by processes within the collection “for leukoreduced products.”**

b. **Recommendation: The final guidance should be worded in such a way to allow for simultaneous testing of residual WBC and bacterial detection.**

Test for residual WBC within 24 hours of collection, while bacterial detection testing is after 24 hours. This establishes the inappropriate requirement to sample the product twice, increasing the risks of accident and of contamination.

c. **Recommendation: Adopt $\pm 10\%$ acceptance criteria to allow for both technique and measuring deviations as well as to be consistent with the allowance given for plasma.**

The volume in each container for double collections should be $50\% \pm 5\%$; for triple collections $33 \pm 3\%$, or per the manufacturer’s specifications. The measuring technology is not as accurate as the proposed specifications.

8. **Recommendation: Delete prescriptive audit checks, replacing them with the requirement to perform appropriate audits.**

The audits listed under quality systems audits (Page 21, Section VII, F) are too specific and prescriptive, e.g. bullet two lists checking the performance of the scale, tare weight, etc. According to FDA’s Quality Guidelines, audits are intended to ensure such checks are done, not to actually do the checks.

F. Section X, Reporting Changes to an Approved License Application (BLA)

1. Recommendation: Use the language and procedures prescribed in the July 2001 Guidance cited above.

Changes Being Effected in 30 days (CBE-30) includes upgrades provided by the manufacturer to a cleared apheresis device (Page 24, Section X B). The July 2001 FDA Guidance - Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture lists “Changes or upgrades by the device manufacturer of automated apheresis equipment that does not affect the purity, potency or quality of the product(s), if the facility is already approved for the original procedure, e.g., upgrade in plasmapheresis equipment from Haemonetics PCS to Haemonetics PCS2 or upgrade to Haemonetics PCS2 Version G to display red blood cell loss” as “minor change to be reported in an annual report.”