

1200 G Street NW, Suite 400  
Washington, DC 20005-3814  
Tel: 202 783 8700  
Fax: 202 783 8750  
www.AdvaMed.org

0240 6 JAN -6 P2:46



January 3, 2006

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

**Re: Docket No. 2005D-0330: Draft Guidance for Industry and FDA Staff: Collection of Platelets by Automated Methods**

Dear Sir or Madam:

AdvaMed provides this submission in response to the Food and Drug Administration's (FDA's) request for comments on its draft guidance titled "Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods (Draft Guidance)." AdvaMed is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. AdvaMed's more than 1,300 members and subsidiaries manufacture nearly 90 percent of the \$75 billion of health care technology products purchased annually in the United States, and more than 50 percent of the \$175 billion purchased annually around the world. AdvaMed members range from the largest to the smallest medical technology innovators and companies. More than 70 percent of our members have less than \$30 million in domestic sales annually. Among our member companies are companies that manufacture automated platelet collection devices. Our companies, thus, have a keen interest in guidance that impacts the collection of platelets by automated methods.

#### GENERAL COMMENTS

We support FDA's efforts to update and consolidate all relevant information for the manufacture of platelets by automated methods. Providing this information in a single document should greatly assist blood establishments in their efforts to collect by automated methods. However, restrictions imposed by the guidance document may have the unintended consequence of reducing the platelet availability. The Draft Guidance outlines requirements for platelet content, process validation, and quality assurance monitoring for automated platelet collection. We believe that a greater burden is being placed on facilities that collect platelets by automated methods than on those that collect platelets from whole blood.

2005D-0330

C 43

We note that FDA guidance documents are not intended to create legally binding requirements. This Draft Guidance does. In the introduction, the Draft Guidance states "*Insofar as this guidance adjusts reporting categories for manufacturing changes pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 601.12, it does have binding effect.*" This implies that a guidance document can make binding changes to the regulations. A change of this nature is considered a rule change. Pursuant to the Administrative Procedures Act, rule changes are subject to formal notice and comment and cannot be hidden away in a guidance document.

The requirements outlined in the section on Process Validation -- Product Performance Qualification are confusing, sometimes overly burdensome, and in some cases inconsistent with current blood banking standards. The collection performance qualification criteria are central to the activities of blood establishments, determining to a great extent the total validation burden for a process, the timeliness of data collection, and ultimately the availability of products to the clinical setting. The Agency is confusing in its attempt to distinguish when criteria apply to an automated collection procedure and when they apply to a therapeutic dose. The Agency also uses terminology of "per container" which we believe means per therapeutic dose. However, the Agency should be cognizant of the fact that in many systems a single therapeutic dose can, and at times, must be held in more than one container to preserve the proper storage conditions.

We support the Agency's desire to protect the safety of donors and to standardize care throughout the blood collection industry. FDA should not forget that the blood collection industry has considerable medical knowledge and practical experience in this arena. Before FDA finalizes the Draft Guidance, we recommend that it convene an open public meeting to address the medical concerns, practical considerations and scientific rationale for requirements outlined in the document.

## SPECIFIC COMMENTS

### DONOR SELECTION AND MANAGEMENT

#### A. Donor Selection

Page 5, paragraph 1, bullet 2 states "*Prior to the first donation, test Platelets, Pheresis donors for levels of the following laboratory values that are acceptable under the manufacturer's direction for use: WBC count, Platelet count.*" Bullet 3 states "*If you cannot test the donor before the first donation (for example, because the donor presents at a mobile collection site), you should evaluate the donor's WBC and platelet counts after the first collection.*" There is currently no industry standard range for a donor's pre-donation WBC count. The value is not routinely used to assess donor eligibility and is not needed to program the automated cell collection device.

**RECOMMENDATION:** We recommend deleting the WBC requirement until a pre-donation range is established.

Paragraph 2 addresses deferral of donors who have ingested drugs that adversely affect platelet function. The Draft Guidance changes the current standard that has been in place over 20 years. It is not clear why FDA is suggesting such a change.

**RECOMMENDATION:** We ask that FDA explain the need for this change since there are no known issues with the current standard. The AABB Technical Manual, 15<sup>th</sup> Edition<sup>1</sup> and the Standards for Blood Banks and Transfusion Services (23<sup>rd</sup> edition, 2004)<sup>2</sup> both suggest that a period of 36 hours for aspirin deferral is adequate. We refer you to a 1972 article published in *The New England Journal of Medicine*<sup>3</sup> on which AABB bases its policy of a 3-day deferral.

## **B. Donor Management**

### 1. Platelet Count

Page 5, we recommend bullet 1 be reworded to clarify that the Draft Guidance is not intended to restrict collection of all components, just platelets.

**RECOMMENDATION:** We suggest the following wording: **“You should collect only a single Platelet, Pheresis component from first-time donors who do not have a pre-donation platelet count test result.”**

Bullet 2 provides the option of using the post-donation from a previous collection to set the target platelet yield. To our knowledge, this option has not been validated. If the donor’s platelet count is set to an artificially low value, unnecessary cycles may be drawn in an attempt to reach the target yield.

### 2. Donation Frequency

Bullet 2 states that *“You should collect no more than 24 total Platelets, Pheresis components in a 12-month period. Two components collected from a double collection of Platelets, Pheresis and three components collected from a triple collection of Platelets, Pheresis would be counted as two components and three components respectively.”* We believe that this requirement will have a negative impact on platelet availability. It is being imposed without any evidence that collection of multiple platelet components presents a risk to the donor. Reference 21 presents some data that multiple, regular platelet apheresis donations may result in a decrease in platelet count. There are no other studies to support those observations, and there were no adverse events reported from this facility. Furthermore, the potential for an adverse event is reduced by the requirement to determine the donor’s pre-procedure platelet count and to disqualify the donor if the count is less than 150K platelets/ $\mu$ L.

**RECOMMENDATION:** We recommend that the frequency of donation be maintained at 24 donations (sessions) per 12-month and apply to all donors regardless of the quantity of platelets donated. The inter-donation interval when RBCs are also collected should be consistent with the RBC Guidelines.

### 4. Total volume loss per collection procedure

The Draft Guidance recommends that the total volume of all blood components obtained per collection “should not exceed 500 mL (600 mL for donors weighing 175 lbs or greater) or the volume described in the labeling for the device, whichever is less.” Medical devices have been

---

<sup>1</sup> AABB Technical Manual, 15<sup>th</sup> Edition, p 141, Donor Selection and Monitoring

<sup>2</sup> Standards for Blood Banks and Transfusion Services (23<sup>rd</sup> edition, 2004) Reference Standard 5.4.1A-Requirements for Allogeneic Donor Qualification

<sup>3</sup> Stuart MJ, Murphy S et al. Platelet Function in Recipients of Platelets from Donors Ingesting Aspirin. NEJM 1972; 287:22, pp 1105-1109.

cleared by the Agency for collection of 500 mL (600 mL for donors weighing 175 lbs or greater) or the volume described in the labeling for the device. However, guidance adds a restriction that is inconsistent with current labeling – “whichever is less.” We believe that this subtle change will have a negative impact on product availability and is inconsistent with the AABB standard that recommends the total volume retained from a collection not exceed 10.5 mL per kg.

**RECOMMENDATION:** We recommend FDA delete “whichever is less” or change to maximum of 10.5 mL/kg blood component retained, to be consistent with the current AABB standard.

### **C. Dedicated Donations**

This section of the Draft Guidance states “The use of the procedure to obtain a Platelets, Pheresis component for a specific recipient may be at variance with the terms described in your license. . .” This comment is true for all registered blood establishments, not just licensed establishments. Expand the statement to include all registered blood establishments.

**RECOMMENDATION:** We recommend rewording as follows: “The use of the procedure to obtain a Platelets, Pheresis component for a specific recipient may be at variance with routine allogeneic donor acceptance criteria . . .”

### **D. Medical Coverage**

The Draft Guidance requires that a physician be on the premises within 15 minutes. Advances in apheresis technology have made automated collection a safe procedure. Studies of moderate and severe reactions during plateletpheresis demonstrate a safety profile better than that of whole blood collections.<sup>4</sup> The demand for platelets has forced blood centers to look at ways to increase their collections of Platelets, Pheresis, including mobile blood drives. The requirement of having a physician on premises within 15 minutes would severely hamper a blood center’s ability to collect platelets in a mobile environment and does not provide added safety for the donor. We note that the reference (reference 11) to substantiate the 15-minute on premise requirement is a proposed rule published in 1985. To our knowledge, this 20-year-old rule has never been finalized and is not specific to blood collection facilities, including references to superfund clean-up and transportation.

Apheresis devices are typically operated and monitored by health care professionals that are trained to detect and treat donor reactions. Understanding that reactions can occur regardless of the component being collected, i.e., even whole blood donors, sensitive, or first-time donors can experience mild to moderate reactions, there is no reason to single out platelet collections as requiring an on-site physician. If the goal is donor safety, then the requirement should be a reasonable time to an emergency facility.

---

<sup>4</sup> Rossi’s Principles of Transfusion Medicine. Eds. T Simon, W Dzik, E Synder, C Stowell, R Strauss. 3rd Edition. Lippincott Eilliams & Wilkins. Philadelphia. 2002. pp 648-658.

## COMPONENT COLLECTION AND MANAGEMENT

### B. Target Platelet Yield

The Draft Guidance suggests targets to be used to achieve certain platelet counts. Platelet yield varies based on laboratory methods, hematology analyzers, apheresis practices, and the specific apheresis device. Manufacturers are practiced and expert in guiding the facilities to an understanding of how to determine appropriate yield targets for their device. We believe that it is inappropriate for the Agency to set these targets since there is such a wide range of experience. The numbers proposed in the guidance are currently incorrect for many locations and will not stand the test of time as technology improves.

**RECOMMENDATION:** We believe that it is sufficient for the Agency to set the minimum limits (i.e.,  $3.0 \times 10^{11}$  per therapeutic dose) and to encourage facilities to work with the respective manufacturer to determine the appropriate targets.

### C. Hemolysis During Collection

The guidance states that if there is a red tinge to the plasma in the return line and it is noted during the procedure, the center should determine whether it is the result of red blood cell contamination or from hemolysis. While a red tinge of the separated plasma anywhere in the collection system should be cause for evaluation, the return line may not be the best place to make this observation since there is no way to distinguish contamination from hemolysis during the procedure.

**RECOMMENDATION:** Users should be directed to follow the manufacturer's directions for use and other labeling regarding monitoring for hemolysis.

## PROCESS VALIDATION

Page 9, paragraph 3 requires process validation be performed on the delineated items. However the devices listed are not used in the collection process, with the possible exception of tubing welders. Rather, these are devices that may be used in the preparation, shipping and measurement of platelets, pheresis.

**RECOMMENDATION:** We recommend the following revision to indicate the appropriate use of the delineated devices: "In addition, you should perform Process Validation on the following processes used in the preparation, shipping and measurement of platelets, pheresis:

- Blood cell counting: platelets, WBC and residual WBC
- pH measurement:  
We recommend that a pH meter or blood gas analyzer be routinely used rather than pH (nitrazine) paper.
- Component weighing
- Sterile connection methods
- Preparation of blood components for shipping: Shipping containers should be appropriate for this purpose."

## **B. Validation Protocol**

The guidance recommends that the validation protocol include the minimum/maximum acceptable values for the target platelet yield. The target platelet yield is a fixed value. Specifying a minimum/maximum value for it does not make sense in this context. Target yield should be established by objective evidence that a process consistently produces components that meet predetermined specifications. 21CFR 606.60(a) does not require setting minimum/maximum acceptable values

## **D. Product Performance Qualification (Component Collection)**

We are recommending significant changes to this section and will provide our comments on the section followed by our recommended changes. Page 11, paragraph 1 states that product *“Qualification should include testing for the actual platelet yield, pH, volume, residual WBC count and percent component recovery (for leukocyte reduced components), RBC/hematocrit (if applicable) and bacterial contamination testing.”* Some of the requirements should not apply to Platelets, Pheresis. Percent component recovery only applies to leukocyte reduction by filtration and not by process. RBC/hematocrit is not associated with any specification.

Paragraph 2 outlines collection performance criteria. Bullet 1 of the guidance recommends 2 sample sizes for performance qualifications: 60 units or 93 units. The acceptance criteria are 0 failures in 60 samples, or 1 failure in 93 samples with respect to yield, pH, volume, visible RBCs and residual WBC count and component recovery. We interpret this to mean that if, for example, a center encounters a failure at test number 40, it should continue with 93 samples and encounter no further failures in order to meet the acceptance criteria. However, the guidance recommends the opposite, stating that if a center tests 60 samples and encounters a failure, it should not continue with 33 more samples. This is inconsistent and confusing. In addition, there are no specifications for “visible RBCs” in platelets. We recommend this be dropped from the list of performance criteria. AABB Standard 5.14.5 requires a cross match be performed using donor cells if platelets, pheresis are not ABO-compatible or not produced from a method known to result in <2mL of red cells. Contamination with 2mL of RBC in platelets, pheresis is grossly obvious, due to unusual special causes, and can be incorporated into routine SOPs and need not be required in the process validation phase. With regard to bacterial contamination, testing on 500 collections is particularly burdensome; particularly for small collection facilities. It could take a year or more for these facilities to obtain the number units required.

Sub-bullet 1 provides recommendations for “facilities using automated cell separators from a single manufacturer.” It is unclear what facilities means in this context. In addition, automated collection processes are defined by the device make and model (e.g., Baxter Amicus, Gambro Trima Accel, Haemonetics MCS+). We recommend FDA clarify the meaning of facilities to indicate whether it refers to a collection center at one geographic location or to the corporate establishment. In addition, the initial performance qualification should be performed by device type, and need not be performed at each fixed site provided that all sites operate under the same standard operating procedures, training program, etc.

Bullet 5 requires that an RBC count/hematocrit be performed on Platelets, Pheresis or concurrent Plasma (when collected) containing visibly apparent RBCs. However, there are no specifications associated with residual RBC in platelet products. This should be dropped from the qualification

criteria. The specific action stated for platelets (we assume the Agency means by therapeutic dose) should be included in an operational SOP, but not the qualification plan.

Bullet 6 suggests testing components during the first, middle and end of the dating period. We believe the testing requirements are excessive and will not contribute meaningful information to the qualification scheme. The only criteria that are expected to change over the course of storage are pH and the titer of contaminating bacteria. We presume the Agency intends this to be directed at pH.

Page 12, bullet 2 provides an example of a non-process failure. The example, a positive bacterial test from a donor with asymptomatic bacteremia, may be difficult to prove. Other examples of "non-process failures" would be helpful in interpreting and applying this concept in concrete terms.

#### **Table 1. Collection Performance Qualification Criteria**

**Yield**—currently available automated instruments intended for counting platelets in whole blood samples of patients provide widely divergent platelet counts when applied to platelet-rich plasma from platelet components and platelets, pheresis. The current state-of-the-art and inter-laboratory accuracy does not support an overly restrictive requirement for platelet yield. The current FDA thinking (Ref. 1) states 75% of products should be  $>3.0 \times 10^{11}$ . AABB Standards state that at least 90% should be  $\geq 3.0 \times 10^{11}$ . We believe there is no medical argument for a stricter interpretation for a therapeutic dose.

**pH**—storage characteristics with pH outcomes have been well studied and are described by manufacturers during FDA clearance/approval processes. As reported in Reference #6, 1 pH failure of 24 might be expected at out date. Therefore, the target criteria for process validation should not impose too strict of a burden on the blood establishment. We recommend 90% pH(22°C)  $\geq 6.2$  with 90% confidence. Monitoring for qualification purposes may be conducted concurrently with implementation of the preparation method.

pH should be evaluated at a higher surveillance level than routine QC with a minimum of 22 therapeutic doses tested at issue over the first 2 months of use. At expiration is defined as on day 5 or 6 for 5-day products, on day 7 or 8 for 7-day products. The 22 therapeutic doses would be stratified over single, double and triple collection. Acceptance is no failures in 22.

**Volume**—it is not clear what the Agency intends with the volume criteria nor is a rationale given for the tolerances. Perhaps the Agency means that the net volume of each therapeutic dose should be 50% of the original collection volume for a double collection and 33% of the original collection volume for a triple collection. If these numbers came from an original volume tolerance  $\pm 10\%$  of device indicated volume then apportioned to 2 or 3 subparts, this is an incorrect calculation of this allocation. We propose there should be no volume specification for divided products beyond the manufacturer's criteria for storage containers and minimum therapeutic dose for platelets of  $3 \times 10^{11}$  platelets. We further recommend the target criteria be 90% compliance with 90% confidence, reflecting the industry approach to platelet yield in AABB standards.

**Red blood cell content** – Red blood cell count is not associated with any specification. This should be dropped from the qualification testing criteria.

**Bacterial Contamination** – industry standards (AABB) provide clear direction on prevention and detection strategies. We believe bacterial testing for qualification purposes may be conducted concurrently with implementation of the preparation method. The testing should be conducted 100% according to industry standard using a method cleared for QC by FDA for the first 2 months of use. The expected outcomes of bacterial testing with anaerobic culturing methods on a broad scale are not known at this time. Therefore, we suggest more general wording for the target criteria and indications for follow-up.

**RECOMMENDATION FOR REVISION:** We recommend the section be reworded as follows:

Qualification should include testing for the actual platelet yield, pH, volume, residual WBC content, percent component recovery (if applicable) and bacterial contamination testing. Some of these outcomes should be evaluated by collection and others by therapeutic dose as indicated in the Table.

Product performance qualification should be completed for each automated blood cell separator (defined as type and model) used in your establishment. All devices should be included in the initial product performance qualification; and devices of the same type and model added following the initial qualification, be included in monthly QC testing only.

For example: A blood center plans to collect Platelet Pheresis at 3 fixed sites and select mobile locations. Two different collection devices will be utilized.

- Two process validations should be performed; one for each type/model of device.
- For each validation, product performance qualification should include all devices in use at the time of initial qualification, regardless of their physical location.

If the blood center subsequently decides to add devices of the same type/model as those qualified, product performance qualification would not be required. Instead, they would be immediately included in the monthly QC process.

Conduct an investigation of component qualification failure, and when appropriate, initiate corrective action and follow-up measures. We understand that some failures may occur due to conditions **not** resulting from a failure of the process. Examples of non-process failures include positive bacterial contamination testing resulting from the collection from a donor with asymptomatic bacteremia.

Outcome	Unit of Evaluation	Performance Criteria	Target	Acceptance Criteria <sup>1,2</sup> (# Collections / # failure)	
Platelet yield	Per therapeutic dose	> 3x 10 <sup>11</sup> platelets meet manufacturer's requirements	90/90	22/0	38/1
Volume	Per therapeutic dose	meet manufacturer's requirements	90/90	22/0	38/1
Residual WBC content <sup>3</sup>	Per collection	≤ 5 x 10 <sup>6</sup>	95/95	60/0	93/1
% recovery following leukocyte-reduction <sup>4</sup>	Per collection	≥ 85% component retention	95/95	60/0	93/1
pH @ 22°C	Per therapeutic dose	≥6.0 ≥6.2	90/90	2 month QC <sup>5</sup> 22/0	2 month QC <sup>5</sup> 38/1
Bacterial contamination	Per collection	No growth	See note	2 month QC <sup>6</sup>	

1. Samples should be stratified over single, double, and triple collection procedures as applicable. For example: 20 single collections, 20 double collections, and 20 triple collections. A facility or a method that would not include the collection of triples might perform 30 single and 30 double collections for initial qualification. Total sample size and acceptance criteria should be selected prior to initiation of validation (e.g., 60 collection with zero failure or 93 collections with one allowable failure). This approach is based on dichotomous outcomes (pass or fail). Other approaches using continuous outcomes and statistical approaches resulting in fewer required collections may be applied.

2. Process failures only; non-process failures should be excluded. False positive bacterial tests should be excluded (e.g., initial culture reads positive with negative gram stain and/or no growth on subculture). Exclude positive bacterial contamination testing which may have resulted from the collection from a donor with asymptomatic bacteremia, even though the bacteremia cannot be confirmed.

3. Samples for WBC counting should be handled, prepared and processed without delay according to the requirements of the counting method to ensure that a true and representative count is obtained.

4. Applicable only to WBC reduction processes using secondary methods such as filtration. This does not apply when leukocyte-reduction is performed automatically as part of the automated process.

5. Storage characteristics with pH outcomes have been well studied and described by manufacturers during FDA clearance/approval processes. Therefore, pH monitoring for qualification purposes may be conducted concurrently with implementation of the preparation method. pH should be evaluated at a higher surveillance level than routine QC with a minimum of 22 therapeutic doses tested at issue over the first 2 months of use. At expiration is defined as on day 5 or 6 for 5-day products, on day 7 or 8 for 7-day products. The 2 therapeutic doses would be stratified over single, double and triple collection. Acceptance is no failures in 22.

6. Bacterial contamination risk has been described, and industry standards (AABB) have provided clear direction on prevention and detection strategies. Therefore, bacterial testing for qualification purposes may be conducted concurrently with implementation of the preparation method. Bacterial testing should be conducted 100% according to industry standard using a method cleared for QC by FDA for the first 2 months of use. Action limits to indicate an investigation of component qualification failure should be based on current industry reported positive rates for the testing method used.

#### **E. Re-Qualification/Re-Validation**

Bullet 1 states that exceeding the allowable process failures during the *collection process qualification* may indicate that the process is not in control and requires that the failures be investigated, corrected and the collection process qualification completed. In all cases, the cause of the failures cannot be identified. In such cases, it may only be possible to document the steps taken to identify the cause of the failures.

**RECOMMENDATION:** We recommend the following wording revision: “**Exceeding the allowable process failures of the Product Performance Qualification may indicate that the process is not in control. Document the investigation, the actions taken to identify the cause of the failure, and your findings. If the cause is identified, document the actions taken to correct the problem. Repeat the Product Performance Qualification.**” We also note that the terms used to describe the various sections of process validation, (i.e., *collection process qualification*) are inconsistent with those used in the previous wording - *Product Performance Qualification (Component Collection)*).

### **QUALITY ASSURANCE (QA) AND MONITORING**

The introductory paragraph of this section states that whether a process is operating in a state of control is determined by analyzing the day-to-day process and data for conformance with the manufacturer’s specification. Conformance to manufacturer’s specifications is only part of the expectations for a process. Conformance to federal and local regulations, and facility defined limits and ranges should also be taken into account.

**RECOMMENDATION:** We recommend re-wording as follows: “**Whether a process is operating in a state of control is determined by analyzing the day-to-day process and the data for conformance with federal and local regulations, facility defined limits and ranges, as well as manufacturer’s specifications and for unexpected variability.**”

#### **A. Standard Operating Procedures (SOPs) and Record Keeping**

Item 2 provides the additional provisions applicable to SOPs. Comments below refer to specific requirements referenced in this section.

**Hematocrit:** Hematocrit determination of visibly contaminated product is an abnormal occurrence and is not appropriate as a process monitoring parameter.

**RECOMMENDATION:** We recommend FDA delete this requirement.

**Actual platelet yield:** The guidance document requires that transfusion facility be provide the platelet yield for each product. We believe this is an unnecessary burden to the blood collection facility. There is a minimum therapeutic dose requirement for each issued platelet product. The precise value is not used by the clinical service in prescribing treatment for the patient, and providing it for all products will not improve patient care. The platelet content is available upon request of the clinical facility.

**RECOMMENDATION:** We recommend FDA delete this requirement.

**Residual WBC counts:** The guidance requires the SOP state the maximum acceptable WBC limits for each automated blood cell separator device in use. Care should be taken that the requirement is not misconstrued as 100% conformance without significance loss of available platelets. The maximum acceptable residual WBC limit for apheresis platelets as established by AABB standards and is  $5 \times 10^6$  per unit or transfusable dose.

**RECOMMENDATION:** Revise wording to "Your SOP should state the maximum desired WBC limits are  $5 \times 10^6$  per unit or transfusable dose".

**pH measurement:** There is no reference to the temperature at which the pH should be measured.

**RECOMMENDATION:** The Agency should specify that the pH be measured at 22°C or converted to this temperature by calculation.

**Leukocyte reduction filters:** The guidance document attempts to direct processing facilities to the correct filter to reduce leukocytes in Platelets, Pheresis. However, the SOP section seems the inappropriate place to include the statement.

**Total volume loss:** The guidance indicates that the annual volume loss should not exceed 12 liters (12,000 mL) per year for donors weighing 110-175 lbs; 14.4 liters (14,400 mL) per year for donors weighing more than 175 lbs. We assume that this section is referring to plasma loss.

**RECOMMENDATION:** Suggest the following wording: Total *plasma* volume loss: Annual *plasma* volume loss should not exceed 12 liters (12,000 mL) per year for donors weighing 110-175 lbs; 14.4 liters (14,400 mL) per year for donors weighing more than 175 lbs. Plasma in both the apheresis platelet components as well as the concurrent plasma component should be included in the total volume loss.

**Performance specifications:** The guidance requires SOP's that state the acceptable tolerance specifications for *each component collected* (single, double, triple) as described by the manufacturer and that address handling of components that exceed the manufacturer's limitations. It is not clear if this is addressing the collection/storage bag tolerance specifications or the acceptable tolerance specifications for the component. The manufacturer has tolerance specifications for the component collection/storage container. Specifications for the actual component are regulated by state and local agencies.

**RECOMMENDATION:** Modify the section title to clarify the intent Container Specifications/Component Specifications. Reword as follows: State the acceptable tolerance specifications for the volumes, platelet concentration, *and* actual platelet yield for *each component storage container* as described by the container manufacturer.

**Labeling:** The guidance document requires that Platelets, Pheresis components containing less than  $3.0 \times 10^{11}$  platelets per storage container be labeled with the actual platelet content. This fails to consider that single therapeutic doses of platelets may be stored in 2 containers based on the specifics of the storage container and manufacturer's recommendations.

**RECOMMENDATION:** Proposed wording: "Platelets issued as a single transfusable dose that contain less than  $3 \times 10^{11}$  platelets should be labeled with the actual platelet content."

**Component Storage and Shipping:** Sub-bullet 2 of the guidance document states that "If sterile docking of an additional container is necessary, use a container designed to achieve and protect a sterile conduit. *You should use containers from the same manufacturer.*" Concurrent plasma is frequently divided into 200 mL volumes prior to freezing; by transferring the fresh plasma to 300 mL transfer bags approved for blood storage, so that the finished Fresh Frozen Plasma product more closely resembles the FFP prepared from Whole Blood collections. This results in a more standardized component being provided to the consumer, and allows for a standardized process for packaging and storing the FFP. Several manufacturers of apheresis sets do not manufacture a 300 mL transfer bag. Requiring the use of containers from the same manufacturer would impact the current FFP production process of many blood centers. Dividing a large volume plasma into two or more transfusable doses allows the plasma from one collection to be transfused to more than one recipient. Requiring the use of a container from the same manufacturer would impact the blood centers ability to divide large volume plasma products, and could impact the availability of FFP to their customers.

Many transfusion services remove aliquots of packed red blood cells into smaller blood component bags, when small volumes are required for transfusion of infants and smaller children. This way the original red cell component can be used for more than one recipient rather than issuing the entire unit and only a portion of the component transfused. Requiring the aliquots be transferred to a container from the same manufacturer would preclude the use of RBCs from automated collections being used for infants and small children, but many of the apheresis set manufacturers do not manufacture the smaller volume bags.

The same is true for apheresis platelet. Many blood centers only distribute single donor platelet products. If containers from the same manufacturer were required, an entire apheresis component would have to be sacrificed for each transfusion of a child or infant, which is an unnecessary waste of an apheresis component.

**RECOMMENDATION:** Recommend re-wording: If sterile docking of an additional container is necessary, use a container designed to achieve and protect a sterile conduit. You should use containers designed for storage of the blood component. (Check any documentation re: approve manufactured standards.)

Sub-bullet 3 is unclear and states that "You should include the recommended shipping procedure including temperature and time for Platelets, Pheresis." Perhaps the Agency intends to recommend the shipping procedure to include the acceptable temperature range and allowable transit time (i.e., time off of the agitator) for Platelets, Pheresis.

**RECOMMENDATION:** We recommend the item be reworded as follows: "You should include the recommended shipping procedure which includes the acceptable temperature range and allowable transit time Platelets, Pheresis."

**Deviation:** This section appears to address deviations that require submission of an FDA Blood Product Deviation Report. It also references a draft guidance document that is not yet binding, and subject to change.

**RECOMMENDATION:** We suggest the following working revision: "Deviations associated with the manufacturing, testing, processing, packing, labeling or storage, holding or distribution should be documented. When they meet the criteria for Blood Product Deviation Reporting, described in 21 CFR 606.171(b)(1)(i) and(ii), they must also be reported to the FDA."

## **B. Donor Monitoring**

### **1. Platelet counts**

Page 17 of the Draft Guidance requires that platelet counts be performed post collection. We disagree. The Agency has not presented any data to support this extra step and how it would correct a demonstrated health risk to the donor.

**RECOMMENDATION:** We recommend the following wording, "Determination of donor post donation platelet counts is not required. However, if a post donation platelet count is known to be less than 100,000/uL, you should notify your Medical Director. You should defer the donor until his/her platelet count has returned to at least 150,000/uL."

### **3. Red Blood Cell**

Bullet 1 (Per Collection) states that "If the RBCs cannot be returned to the donor, you should determine the absolute RBC loss." The title (RBC loss - Per Collection) implies that the RBC loss must be calculated for both successful and incomplete procedures. The actual text of the section refers only to incomplete procedures.

**RECOMMENDATION:** We recommend the following wording: "If the RBCs cannot be returned to the donor, you should determine the absolute RBC loss for the discontinued procedure."

Page 18, bullet 2 (Total plasma volume loss per 12 months) provides the limits for plasma volume loss. It is unclear whether these limits are intended to include the plasma volume in the platelet product.

**RECOMMENDATION:** We recommend FDA clarify whether the limits include the plasma volume.

### **C. Component Testing**

#### **1. Daily component specification check**

The guidance suggests that platelet yields are to be determined at the “conclusion of each appropriate phase of manufacturing (21 CFR 211.103).” We believe this requirement is excessive, and, if applied to platelets, could create significant burden on the blood collection facility and needless loss of platelets for sampling. There are multiple phases of processing that platelets undergo from collection to issue, and we feel the definition of each appropriate phase of manufacturing is ambiguous. In addition, 21 CFR 211.103 requires that this yield determination (“calculation”) must be performed by one person and independently verified by another – a needless waste of resources. We do agree that the yield of the product should be determined prior to issue.

**RECOMMENDATION:** We suggest the following wording: “Actual yields (volume x platelet count) should be determined prior to issue.”

Sub bullet 1 in this section states that “A weight/volume conversion is necessary to determine the volume.” This statement may be too restrictive for new technologies

**RECOMMENDATION:** We recommend the following wording: “When volume is determined gravimetrically (i.e., by weight), an appropriate weight to volume conversion factor (i.e., density) should be applied.”

On Page 19, bullet 1 requires WBC counts on collections that do not utilize automated leukocyte reduction methodology. We believe this requirement should be deleted. Universal leukocyte-reduction is not required. Also, there are methods to produce platelets, pheresis and co-components that do not employ an automated leukocyte reduction methodology. Further, there are instances of platelets, pheresis and co-components collection that result in non-leukocyte reduced products that are secondarily leukocyte-reduced by technologies such as filtration. These latter technologies have been reviewed and cleared for this application by FDA and should be treated as a standard process that has been appropriately qualified and subject to routine in-process controls, not 100% testing.

**RECOMMENDATION:** Delete this requirement.

Bullet 3 on page 19 suggests bacterial contamination testing be done according to the collection device manufacturer’s instructions. However, device manufacturers generally do not provide instructions regarding bacterial contamination testing (e.g., method and frequency). It is not a requirement for device clearance or approval. Bacterial testing requirements are based on an industry standard (AABB).

**RECOMMENDATION:** Modify the statement as follows: “Bacterial contamination testing: bacterial 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.”

## 2. QC monitoring

The guidance recommends the use of scan statistics as a sampling method. While the guidance has indicated that use of scan statistics is one option, by placing it so prominently in the document, FDA is, by default, requiring this to be implemented. In addition, use of an alternative model leaves statistical issues open to interpretation by inspectors who may not have knowledge of statistical process control. Another concern is that scan statistics does not allow the site to monitor the process and make correction prior to failure. An alternative method should be provided that uses a continuous data model. (See additional comments on Appendix A.)

**RECOMMENDATION:** Either remove reference from guidance or provide an alternative method that uses a continuous data model.

## **REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA)**

### **B. Changes Being Effected in 30 Days (CBE-30) Supplement: Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (21 CFR 601.12(c)).**

The guidance document suggests that any upgrades provided by the manufacturer require a CBE-30 to be submitted. Some device updates have already been subjected to the premarket notification process. There is only a small risk that the change would impact the "Identity, strength, quality, purity, and potency of the product as they relate to the safety and or effectiveness of the product..." In some cases, including the change in the annual report may be sufficient.

### **D. Component Submission for CBER QC Testing**

On page 26, the guidance indicates that CBER may at any time request that a facility provide samples of components for CBER QC testing. We believe that the requirement to send platelet products to CBER for testing is an outdated practice that does not make a meaningful contribution to the safety and efficacy of the product or manufacturing process. It also reduces product availability. Moreover, this requirement is not applied to red blood cell products or plasma products.

We believe FDA can obtain all necessary information related to the manufacturing process of Platelets, Pheresis through examination of the qualification and QC records from the facility. In exceptional cases, additional meaningful information could be obtained during a site visit. We believe this approach will result in more timely turn-around of license applications and spare resources both in the blood center and at FDA.

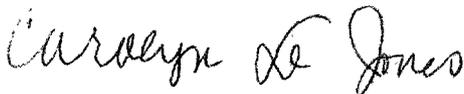
**RECOMMENDATION:** Delete requirement for platelets.

## APPENDIX A

### Scan statistics

We recognize and appreciate that CBER has devoted time and effort to this approach resulting in it being referenced in the *Journal of Biopharmaceutical Statistics* (2005:15;353-366.) However, we believe that it is premature to add this to Draft Guidance. Before recommending facilities implement this requirement, the Agency should first partner with a variety of blood establishments (e.g., large, small, centralized, distributed) to conduct a pilot study to ascertain the true burden of this approach. The scan statistics approach may work well in some situations, but in others, it may be that the inspection burden would be overwhelming. By placing this so prominently in the guideline, FDA is, by default, requiring this to be implemented. We believe the burden of proof resides with the Agency to demonstrate the utility of this approach in real-life situations prior to including in Guidance, much as we would expect clinical evidence to be presented prior to implementing a change in clinical practice.

Sincerely,



Carolyn D. Jones  
Associate Vice President  
Technology & Regulatory Affairs