

Blood Innovations

an integrated blood organization

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December 27, 2005

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

Re: Docket No. 2005D-0330

Dear Sir or Madam,

Blood Innovations appreciates the opportunity to comment on the draft guidance document entitled: "Collection of Platelets by Automated Methods", dated September 15, 2005. The original draft guidance text is represented in ***bold italic*** type, while the comments from Blood Innovations are depicted in a plain font.

III. DONOR SELECTION AND MANAGEMENT

A. Donor Selection

You should not collect Platelets, Pheresis from donors who have ingested drugs that adversely affect platelet function. These include, but may not be limited to:

- *Aspirin (ASA)/ASA-containing drugs – 5 days from last dose (Ref. 10)*
- *Non-steroidal Anti-inflammatory Drugs (NSAIDS) – 3 days from last dose (Ref. 9)*
- *Plavix (Clopidogrel) – 5 days from last dose (Ref. 9)*
- *Ticlid (Ticlopidine) – 14 days from last dose (Ref. 9)*

The current FDA approved Uniform Donor History Questionnaire and donor education materials instruct that platelet donors must wait 48 hours from the last dose of ASA/ASA containing drugs. If the current approved instructions are to be changed, the change must be incorporated in to other significant FDA documents and education materials.

2005D-0330

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joint venture partners:
Stanford Medical School Blood Center
Northern California Community Blood Bank
Blood Bank of the Redwoods
BloodSource

B. Donor Management

2. Donation Frequency

To protect the safety of the donor:

"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. "

Current guidelines recommend no more than 24 procedures for Platelets, Pheresis. The limitation of 24 products of Platelets, Pheresis would have an impact on our collections capabilities for Platelets, Pheresis. We currently have many donors who routinely donate greater than 12 times per year. These donors generally donate double or triple platelet products. The proposed guidance claims to limit donations in order to protect the health of the donor. The single study would indicate that the current guidelines are sufficient to protect the health of the donor. In fact, the cited article maintains that it is unusual for donors to fall to levels that would classify them as thrombocytopenic. Donor safety data from the platelet collection device manufacturers' submission for 510k clearances obviously supported the approval of the current devices for use within the current guidelines. There are no studies cited by FDA that would indicate that these original data sets are no longer valid.

The interval between each collection of Platelets, Pheresis should be at least two (2) days with no more than two procedures in a 7-day period.

The interval between collection of a double Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 7 days.

The interval between collection of a triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 14 days.

It is unclear as to why the donation intervals for donors of double and triple collections of Platelets, Pheresis have been extended from the current guidelines. The single study cited, *Sustained decreases in platelet count associated with multiple, regular platelet pheresis donations. Transfusion. 2001 June; 41: 756-761.*, indicated that the current guidelines are sufficient to protect the health of the donor through the monitoring of the donor pre procedure platelet count. Very few donors in the study dropped below a threshold that would require deferral. The few who were deferred permanently were identified as having hematological disorders unrelated to the serial collection of platelets. Donor safety data from the platelet collection device manufacturers' submission for 510k clearance obviously supported the guidance that is currently in place. There are no studies cited by FDA that would indicate that these original data sets are no longer valid.

A post-donation platelet count should be performed after each collection.

Current technology performs a post procedure platelet count estimate that was cleared by FDA with the device. There is no evidence presented or cited that would invalidate the approved calculation method used by the manufacturer. Additionally, a post procedure platelet count would require an additional venipuncture. This additional step would add up to three venipunctures on a new donor when a historical platelet count is unknown. The advent of an additional venipuncture would make the procedure less attractive to donors, and greatly impact the ability to convert donors to the apheresis program. It is recommended that the current practice of performing pre-procedure counts or estimates based on previous counts be kept in place.

Total volume loss per collection procedure

The total volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis 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.

This proposed change in collection volumes would make the collection of triple platelet products nearly impossible. The current technology by Gambro BCT is licensed to collect no more than 15% of the donor's total blood volume (TBV). There is no evidence or data cited that would invalidate the current licensing or collection practices. This proposed guidance would severely impact the net collections by blood centers and would limit availability of Platelets, Pheresis in local areas.

D. Medical Coverage

Under 21 CFR 640.22(c), the procedure for collection of Platelets, Pheresis, including the availability of medical care during the donation, must conform to the standards described in the biologics license application or supplement. We believe that a physician should be present on the premises during the collection of Platelets, Pheresis to ensure that necessary medical treatment be available to the donor in a timely fashion. We interpret "present on the premises" to include a qualified physician able to arrive at the premises within 15 minutes (Ref. 11). In case of an emergency, calling 911 may be used to obtain emergency medical care and transportation to another facility for further care, but we do not believe this is a sufficient substitute for an available physician as previously described.

The interpretation of "present on the premises" to include a qualified physician able to arrive at the premises within 15 minutes may present problems for centers who employ a Medical Director that is at any one time on different part of a large medical center campus, who is on call and off site, or who is part-time. Establishments use Registered Nurses as qualified medical personnel in the event of an emergency. A Registered Nurse is a first responder in any medical emergency in a collections setting. The physical availability of a MD within 15 minutes would be moot in the instance of a medical emergency.

V. COMPONENT COLLECTION AND MANAGEMENT

Improvements in collection of Platelets, Pheresis have enabled blood establishments to obtain from a single collection procedure one, two, or three Platelets, Pheresis component(s) (and concurrent Plasma and/or Red Blood Cells).

A. Collection

Under 21 CFR 640.22(c), the collection procedure must conform to the standards described in the biologics license application or supplement. In addition, the phlebotomy must be performed by single uninterrupted venipuncture with minimal damage to, and minimal manipulation of, the donor's tissue (21 CFR 640.22(d)). The automated apheresis device must perform in the manner for which it was designed (21 CFR 606.60(a)). Accordingly, your collection procedures must be consistent with the Operator's Manual, directions for use, or manufacturer's specifications. Specifications identified by the manufacturer may include, but not be limited to, the donor's platelet count, weight, height or hematocrit; the minimum/maximum volume of the storage container; platelet concentration per uL in the storage container, or target platelet yield. In addition, supplies and reagents must be used in a manner consistent with instructions provided by the manufacturer (21 CFR 606.65(e)).

The current guidance does not limit a procedure to a single uninterrupted venipuncture. Centers are currently allowed to sterile dock a new needle onto an access line if the venous access is lost during a procedure. There is no evidence or data cited that would invalidate the current licensing or collection practices.

B. Target Platelet Yield

To assure that each component obtained from a multiple collection of Platelets, Pheresis results in an actual platelet yield of at least 3.0×10^{11} platelets, you should use the following targets. When collecting:

***Double components, the device's target platelet yield setting be at least 6.5×10^{11} .
Triple components, the device's target platelet yield setting be at least 10.0×10^{11} .***

Current licensed technology from Gambro BCT utilizes collection data and hematological data to adjust yield scaling factors to maximize the product yield. A fixed device target yield will limit flexibility in adjusting yield-scaling factors and adversely affect the ability of a collection facility to maximize yields. The yield-scaling factor is tied directly to target yields. The formula is:

$$Y_t = Y_{\min} / (1 - Z_{cl} * CV) * Y_{sf} / Y_{rt}$$

where :

Y_t = Target yield

Y_{min} = the minimum lab yield

Z_{cl} = statistical factor based of confidence level

CV = the coefficient of variation of the process (from data supplied from the collection center)

YSF = Yield scaling factor

Y_{rt} = a term that adjusts the Y_t for differences in collection efficiencies at different targets

A fixed platelet target would soon become outdated with recalibration of hematology analyzers. The ability to scale yield targets is critical to maintaining efficient collection procedures and eliminates collection of unnecessary cycles from donors due to a fixed target yield that is not tied to the hematology instrumentation in the laboratory. It is recommended that FDA allow utilization of flexible target yields, as is the current practice.

VI. PROCESS VALIDATION

D. Product Performance Qualification (Component Collection)

You should use the following collection performance qualification criteria: Test a minimum of 60 consecutive single (30 for double and 20 for triple) collections for each type of automated blood cell separator for (1) actual platelet yield, pH, volume, visible RBCs; and (2) for residual WBC count and percent recovery (Ref. 2), with 0 failures in each category. Another option is to test 93 consecutive single (47 for double and 31 for triple), which allows for 1 failure. Perform bacterial contamination testing on 500 collections with 0 failures. Refer to Table 1. Determine the sample size selection before starting the qualification process. For example, if you test 60 and encounter a failure, you should not continue with the testing of an additional 33 components.

A bar of 0 failures in each category would result in a collection system never being successfully qualified. By manufacturers own literature there is only a percent probability that a target yield will result in a product with a corresponding actual yield. According to one manufacturer (Gambro BCT), the probability that a product actual yield will be attained from a predicted yield are as follows:

Target Yield	Probability of corresponding actual product yield
Single Product ($\geq 3.0 \times 10^{11}$)	0.95
Double Product ($\geq 6.2 \times 10^{11}$)	0.85
Triple Product ($\geq 9.3 \times 10^{11}$)	0.75

It would be unreasonable to expect blood centers to validate processes using the proposed performance levels. Current licensed collection technologies cannot meet the zero failures criteria in the area of predicted yield. There are several extenuating variables that could affect the collection process that are not due to the process itself, but related to the donor, such as platelet clumping or pasting. Yield Targets are just that: targets, based on estimates.

- a. Product performance qualification should be completed for each automated blood cell separator used in your establishment.*
- Testing be conducted on both containers from double collection and on all three containers for triple collection;*
 - Qualification include Platelets, Pheresis collection by all trained personnel;*
 - Residual WBC count be performed within 24 hours of collection, or per the manufacturer's directions for the cell counting methodology (Ref. 2);*
 - An RBC count/hematocrit be performed on Platelets, Pheresis or concurrent Plasma (when collected) containing visibly apparent RBCs to determine total packed RBC volume. You should hold Platelets, Pheresis containing more than 2 mL of RBCs until the residual WBC count has been determined and found to be less than 5.0×10^6 for platelet or plasma components labeled as leukocyte reduced;*
 - 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. For example, for Platelets, Pheresis with a 5-day dating period, test one third at 1-2 days, one third at 3-4 days and the final third on day 5 after collection. Components that expire may be used for qualification if tested within 12 hours after expiration. You should not release such outdated components for transfusion, however.*

It is unclear as to why FDA would require testing on validation products *during the second third of the dating period*, when testing is being performed at the end of the product life. The work would appear to be superfluous, as the beginning and end points of the product life would supply sufficient data sufficient to give assurance of potency of the products in question. The life span of Platelets Pheresis is only 5 days. There is little value in collecting data at 1, 3 and 5 days. It is recommended that FDA utilize data for licensure from the initial collection of the product and from data collected at the distribution of the product or at expiration of the product.

VII. QUALITY ASSURANCE (QA) AND MONITORING

B. Donor Monitoring

1. Platelet counts

You should notify your Medical Director when a donor has a post collection platelet count less than 100,000/uL, and you should defer the donor until his/her platelet count has returned to at least 150,000/uL. Transient decreases in platelet counts have been reported in donors undergoing multiple collections of Platelets, Pheresis (Ref. 21). Although the effect of long-term regular collection of Platelets, Pheresis on donor platelet counts is unknown, clinically significant thrombocytopenia in these donors is unusual. You should review a donor's records before each donation to monitor the donor's ability to recover his/her baseline platelet count.

Current technology performs an estimate of the post procedure platelet count and flags post count estimates of less than 80,000/uL. FDA cleared this estimate algorithm with the device. There is no evidence presented or cited that would invalidate the approved calculation method used by the manufacturer. Additionally, a post procedure platelet count would require an additional venipuncture. This additional step would require up to three venipunctures on a new donor when a historical platelet count is unknown. The advent of an additional venipuncture would make the procedure less attractive to donors, and greatly impact the ability to convert donors to the apheresis program.

C. Component Testing

1. Daily component specification check

- ***Bacterial contamination testing: as specified by the collection device manufacturer.***

The product insert for the Bio Merieux BacT/Alert 3D states:
"The BacT/Alert system, including the culture bottles, should not be used in determining suitability for release of platelets for transfusion"

The daily component specification check would indicate that this was a release test. There is no indication in this proposed guidance document that would provide instruction for any post sampling hold time required prior to product release.

2. QC monitoring

Each month four units prepared from different donors must be tested at the end of the storage period for the platelet count, pH of not less than 6.0 measured at the storage temperature of the unit, and volume (21 CFR 640.25(b)(1)-(3)). We interpret four to be a minimum number to be tested, and testing “at the end of the storage period” to include testing at the time of issue.

Under 21 CFR 211.160(b), laboratory controls must include the establishment of scientifically sound and appropriate specifications, standards, sampling plans and test procedures. One example of a scientifically sound statistical sampling plan is the use of scan statistics (see Appendix A). However, other statistical plans may also be appropriate. Statistical plans should:

- *Use an alpha of 0.05 and a power of > 80%.*
- *Detect a > 5% non-conformance rate.*

Sampling schemes for actual platelet yield/pH and residual WBC may be mutually exclusive.

Table 4. Quality control sample size, “window” and “trigger”

<i>N</i>	<i>m</i>	<i>Trigger</i>	<i>FP (%)</i>	<i>Power</i>
<i>400</i>	<i>60</i>	<i>2</i>	<i>2</i>	<i>82%</i>
<i>600</i>			<i>3</i>	
<i>1200</i>	<i>120</i>	<i>3</i>	<i>0.7</i>	<i>95%</i>
<i>2400</i>			<i>1.4</i>	
<i>3600</i>			<i>2</i>	
<i>4800</i>			<i>3</i>	

Facilities requiring sample sizes not listed in Table 4 should contact the Division of Blood Applications.

The above-mentioned QC requirements would represent an enormous quality control burden, especially for centers that must utilize Nagoette chambers to accomplish the enumeration of white blood cells in products. This process is extremely time consuming and would add a significant workload without a reasonable information gain. Unless there is evidence of the current 1% sampling plan being inadequate to monitor the quality of a validated process, it is recommended that the QC sampling plan remain unchanged from the current requirement.

- ***Test for percent component retention.***

It is unclear as to what is meant by percent component retention. Presumably, the reference is to the platelet count at product qualification versus at the end of the storage period.

- ***Residual WBC count should be $< 5.0 \times 10^6$ per collection; percent component recovery should be $> 85\%$ or per the manufacturer's specifications.***

It is unclear as to what is meant by percent component retention. Presumably, the reference is to the platelet count at product qualification versus at the end of the storage period.

- ***The volume in each container for double collections should be 50% + 5%; for triple collections 33 + 3%, or per the manufacturer's specifications.***

The volume is immaterial as long as each container for a double collection or triple collection meets the standard for minimum platelet count, provided the volume remains within the container specifications for the manufacturer.

F. Quality System Audits

- ***Component bacterial contamination testing: Rates of bacterial contamination of plateletpheresis should be monitored, and rates that exceed 1:3000 (Ref. 7) should be considered potentially non-conforming, and an investigation be initiated.***

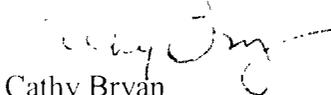
It is unclear as to whether the agency considers contamination events that are traced to inoculation issues would be included in the 1:3000 criteria. The guidance should indicate what the criteria are for inclusion into the 1:3000 rate to assure conformity in application of the guidance.

- ***The actual platelet yield of each component should be made available to the transfusion service.***

This would be a new labeling requirement. Does FDA intend to have blood centers re-submit product labeling? There are no accommodations for the inclusion of the actual platelet yield in the current approved labeling. Will the guidance be explicit about the placement of this information or will this be an auxiliary label?

Thank you for the opportunity to comment on this draft guidance.

Sincerely yours,


Cathy Bryan
President, Blood Innovations


Scott Montrose
Technical Operations Chair, Blood Innovations