



December 28, 2005

FDA Dockets Manager

RE Docket No. 2005D-0330, 03 October 2005, "Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods"

Dear Sirs:

Florida Blood Services staff has reviewed the recommendations listed in the draft *Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods* identified under the Docket Number listed above and has identified several areas that would be improved through use of alternative language, use of different approaches, or should be removed from the document.

Each of the areas we wish to bring to your attention ~~is~~ listed in the order they appear in the Draft document, and is identified at the beginning of each comment for ease of reference.

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Review and comments on:

Section III. DONOR SELECTION AND MANAGEMENT

A. Donor Selection (p. 5)

Text on Draft Guidance: "Prior to the first donation, test Platelets, Pheresis donors for levels of the following laboratory values that are acceptable under the manufacturer's directions for use:

- WBC Count
- Platelet Count

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."

Operational Impact: Additional record keeping and review. Implementation would be difficult due to the lack of data on the cutoff value that must be used. This could result in regulatory risk due to the application of different criteria used by FDA field staff.

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Recommendation – Delete the requirement to obtain a WBC count (pre or post collection).

Comment on Recommendation - There are no manufacturer’s directions for use of the WBC count nor is there any other rationale stated for which the WBC should be evaluated. Requiring the use of WBC count without guidance as to how to determine suitability for blood donation leaves that to the arbitrary, capricious, and/or “intuition-based” interpretation of field inspection personnel, who will apply individual acceptance criteria at their own volition. If a cutoff for WBC count values is being considered, it should be based on data that support the use of such cutoff as to how it affects the safety, purity or potency of the blood components.

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Text on Draft Guidance: “You should not collect Platelets, Pheresis from donors who have ingested drugs that adversely affect platelet function.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 the last dose (Ref. 10)
- Non-steroidal Anti-inflammatory Drugs (NSAIDs) – 3 days from last dose (Ref. 9)”

Operational Impact: unnecessary loss of collections (estimated at approximately 10 to 15% per annum at our facility).

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Recommendations:

- The requirement for lapsed time from last dose of Aspirin (ASA) should be 36 hours.
- The requirement for lapsed time from last dose of a non-steroidal anti-inflammatory drug should be 1 day / 24 hours.

Comment on Recommendations - We understand that the concern is that platelets need to be functional, but the guidance does not provide data to substantiate five days as the appropriate deferral period. The authors of the article published in the journal Chest (your Reference number 10), looked at cardiac patients rather than healthy blood donors. In their study they conclude that days are needed for 50% of platelets to be unaffected. However, an accompanying review of articles in the Chest publication shows that only 10-30% of the platelets need to be unaffected for total platelet function to be normal. Once aspirin is discontinued, the platelets produced by the marrow – at a rate of about 10% of the total platelet population per day - are unaffected. (also see O’Brien JR: Effects of salicylates on human platelets, Lancet 1968; 1:779.)

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Current FDA guidelines and AABB Standards utilize a 36 hour deferral following ingestion of aspirin. Furthermore, this criterion is empirically supported by Stuart MJ et al: Platelet Function in Recipients of Platelets from Donors Ingesting Aspirin. NEJM 1972; 287:1105. This study compared bleeding time corrections in patients transfused

with platelets from donors who had taken aspirin 36 hours prior to donation to results when patients were transfused with platelets from donors who had taken no aspirin. Correction was the same with the controls (no aspirin ingested by the donors) as with the platelets from donors who had ingested aspirin 36 hours prior to donating.

As to the use of NSAIDS prior to platelet donation, these drugs are noted to have reversible platelet action that is already evident at 24 hrs from the last dose as noted in the reference you cite in the Draft Guidance.

Section III. B. Donor Management

1. Platelet Count (p. 5-6)

Text on Draft Guidance: “You should perform a pre-donation platelet count (Ref. 10), which will allow the device operator to more accurately set the target platelet yield parameters for each collection of Platelets, Pheresis. This is consistent with the device manufacturer’s directions for use.”

Operational Impact: Additional record keeping and review. Inability to obtain platelet counts on a timely basis at collections sites that do not have capability for performing platelet counts (due to regulatory requirements imposed by the State of Florida). Potential loss of sites for 90% of our plateletpheresis.

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Recommendation – The following alternative language is suggested as more appropriate for guidance compliance: “You should follow the device manufacturer’s directions to set the target platelet yield parameters for each collection of Platelets, Pheresis.”

Comment on Recommendation – A pre-donation platelet count is only one of the ways recommended by the manufacturer (and approved by FDA) to set the target yield parameters. (We note that Reference 10 may be a misprint since it is an inappropriate reference for this recommendation.)

Section III. B. Donor Management

2. Donation Frequency (p. 6)

Text on Draft Guidance: “To protect the safety of the donor:

- A donor should undergo no more than 24 Platelet, Pheresis collections in a 12 month period
- 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.”

Operational Impact: Loss of approximately 11% of our total Platelet, Pheresis units collected

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Recommendation – Delete the second bullet, concerning no more than 24 total components in a 12-month period.

Comment on Recommendation – Existing safety mechanisms already in place make this proposed guidance unnecessary. The Draft Guidance submitted for comment proposes restrictions on plateletpheresis frequency and annual number of contributions, based on extrapolation from data provided in a single study examining the long term effects of repeated platelet donation.

Lazarus et al (Lazarus EF, Browning J, Norman J, Oblitas J, Leitman SF. Sustained decreases in platelet count associated with multiple, regular plateletpheresis donations. Transfusion 2001 Jun;41(6):756-61) assess the difference in the initial and final platelet count in 939 donors who donated on 11,464 occasions over a four year period. Inter-donation, seasonal and temporal variability and trends over time during the 4-year period are neither shown nor analyzed. This is a poorly controlled, retrospective study that draws on selective subgroups to make conclusions that many reviewers might consider unwarranted. Their findings have not been confirmed by independent investigators. It is clear that the study provides no evidence that there is a relationship between the magnitude of platelet decrement and donation frequency above 7.5 donations/year, the interval between donations or the number of platelets harvested. This study provides no support for the FDA’s proposed guideline regarding donation frequency or the maximum annual number of components that may be collected. Indeed, the authors conclude that current safeguards are effective at preventing harm to donors.

Secondly, this requirement will have an immediate and significant negative impact on the ability to provide adequate inventories of platelets. Many platelet donors are being collected 24 times each year with the ability to provide a double product at each donation. At our institution, long term studies have not shown that the collection of platelets by apheresis in sufficient numbers to prepare two or three transfusion doses has a deleterious effect on the donors from whom the platelets are harvested. As a mode of example, the attached serial platelet counts on donors who participate in multiple dose platelet harvests depicted graphically to illustrate the lack of depletion trends in those donors. Data from the twenty donors who donated the greatest number platelets pheresis components in 2005 are included. Earliest available base line platelet counts are also included. (see Appendix A)

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Section III. B. Donor Management
2. Donation Frequency (p. 6)

Text on Draft Guidance:

- “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”

Operational Impact:

- Computer tracking of donation intervals is defined by the type of product collected, i.e. Platelets pheresis, whole blood, double red cell. Tracking intervals based on platelet pheresis split rates would be unmanageable and result in process control failures. Despite defining target rates for collection at each donation, variability among donors and equipment may result in a higher or lower yield than anticipated. This type of interval tracking is inconsistent with past FDA thinking.

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Recommendation – Delete bullets 2 and 3 concerning intervals between double and triple collections.

Comment on Recommendation – For the same reasons listed above a minimum platelet count of 150,000/uL and loss of no more than 500/600 mL plasma are adequate safeguards.

Section III. B. Donor Management
2. Donation Frequency (p. 6)

Text on Draft Guidance:

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

Operational Impact: Additional record keeping and review. Difficult implementation due to the lack of data on the cutoff value that must be used. Regulatory risk due to the application of different criteria used by FDA field staff.

Recommendation – Delete this statement.

Comment on Recommendation- Post-donation platelet counts are prone to transient low values and, as such, will add little useful knowledge about the donor. A pre-donation count is a more accurate reflection of the current state of the donor. For facilities that

choose to use it, the post count can serve to evaluate the donor's eligibility for a future collection.

Section III. B. Donor Management

4. Total volume loss per collection procedure (p. 7)

Text on Draft Guidance: 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.

Operational Impact: Additional record keeping and review. Difficult implementation due to the multiple kinds of devices deployed at our different collection sites.

Recommendation – Revise to read “The total volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis should meet the device manufacturer’s requirements as delineated in the device label.”

Comment on Recommendation – FDA has already approved some devices that collect more than the proposed limits in this guidance. Operators should be able to rely upon the cleared labeling of the devices to determine limits on collection volumes.

Section III. D. Medical Coverage (p. 7)

Text on Draft Guidance: “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.”

Operational Impact: It will be impossible to provide medical coverage as proposed given the multiple collection sites we operate, many of them 7 days a week. Cost and manpower availability would be insurmountable barriers, and plateletpheresis collections will have to be eliminated by 90%.

Recommendation – Revise to state that qualified medical care be available to the donor in the event of a medical emergency arising during collection procedures, and define qualified medical care to include nurses, emergency response professionals, physicians, and other personnel trained in the care of apheresis donors.

Comment on Recommendation – We acknowledge that the intent of this section is to ensure that adequate medical care is available, but this does not necessarily require a

physician. The draft guidance language would, in many instances, restrict a facility to one collection location per day. Current practice has not identified a need for more stringent medical intervention requirements. In the very rare case where immediate assistance provided by the apheresis collection staff is insufficient and further medical intervention is required, transport to an emergency medical facility would be necessary. The blood center physician on site would not have the appropriate medications or equipment to provide significant medical assistance.

Current apheresis instruments have an extremely high rate of reliability, utilize low extracorporeal volumes and minimize citrate usage. In fact, there is no evidence that fatalities in plateletpheresis centers are greater than that at whole blood collection facilities.

It would be more appropriate to require each establishment to have a well-constructed, viable plan to ensure timely access to medical care in the event of life threatening emergencies.

Section IV. COMPONENT COLLECTION AND MANAGEMENT

B Target Platelet Yield (p. 8)

Text on Draft Guidance: “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} ”

Operational Impact: Additional record keeping and review. Difficult implementation.
Recommendation – Delete these requirements.

Comment on Recommendations - FDA should encourage facilities to utilize validation and monitoring data and work with the respective apheresis equipment manufacturer to determine the appropriate collection targets. Apheresis collection facilities experience different precision with respect to platelet yield predictions based on laboratory methods, hematology analyzers, apheresis practices, and apheresis device. The manufacturers of the apheresis devices are practiced and expert in guiding the facility in understanding this precision and how to determine appropriate yield targets. It is inappropriate for the agency to set these targets since there is such a wide range of experience. These numbers are currently incorrect for many locations and will not stand the test of time for new product developments as technology improves.

Section VI. PROCESS VALIDATION (p. 9)

Text on Draft Guidance: “In addition, you should perform Process Validation on the following devices used in the collection process:

- Blood cell counting devices, including devices used to determine the residual WBC count in leukocyte reduced components.
- pH measurement: We recommend that a pH meter be routinely used rather than pH (nitrazine) paper.
- The scale used to weigh the components.
- Sterile tubing welders used to attach leukoreduction filters or sampling containers (Ref. 13)
- Shipping containers”

Recommendation – Revise the language to focus on the entire process rather than the specific devices. An example of suggested wording:

“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.”

Comment on Recommendation - The listed devices are not used in the collection process. Rather, these are devices that may be used in various steps in the process such as preparation, shipping, and measurement of Platelets Pheresis.

Section VI. B. Validation Protocol (p.10, bullet 2)

Text on Draft Guidance: “Minimum/maximum acceptable values for the Platelets, Pheresis collection and or component as specified by the device manufacturer (see 21 CFR 606.60(a)).

-Target platelet yield “

Operational Impact: Additional record keeping and review. Difficult implementation

Recommendation – Delete Target platelet yield from this list.

Comment on Recommendation - A targeted platelet yield is a fixed value that is donor dependent. Although it serves as the collection projected outcome, it is not an actual measured value. For this reason, we do not understand how a minimum or maximum target platelet yield value would be defined and integrated into a validation protocol, nor do we understand why this would be necessary.

Section V. D. Product Performance Qualification (Component Collection) (p. 11)

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Text on Draft Guidance: “Qualification should include testing for the actual platelet yield, pH, volume, residual WBC count and percent component recovery (for leukoreduced components, RBC/hematocrit (if applicable) and bacterial contamination testing (Table 1)”

Recommendation - Revise to “Qualification should include testing for the actual platelet yield, pH, volume, residual WBC count and percent component recovery (for leukoreduced components, if applicable), and RBC/hematocrit (if applicable).

Comment on Recommendation - Percent component recovery only applies to leukocyte reduction by filtration that occurs after collection, and does not apply to leukocyte reduction by process.

Section V. D. Product Performance Qualification (Component Collection) (bullet 3)

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Text on Draft Guidance: “Qualification includes Platelets, Pheresis collection by all trained personnel; “

Recommendation – Delete this bullet.

Comment on Recommendation – It is not necessary to include data on products from every person that is trained in the process.

Section V. D. Product Performance Qualification (Component Collection) (bullet 4)

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Text on Draft Guidance: “Residual WBC count be performed within 24 hours of collection, or per manufacturer’s directions for the cell counting methodology (Ref 2);”

Recommendation – Revise language to read “Samples 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.”

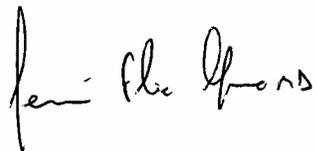
Comment – This language is identical to the language in Ref 2. (FDA Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Product, May 29, 2996). It is not clear why 24 hours is mentioned in this draft guidance. We have reviewed manufacturer’s directions and notes that many of them exceed 24 hours. For example, FacsCaliber calls for WBC to be completed within 48 hours of the product being leukoreduced and Nageotte indicates 24 hours. In addition, if the method has been internally validated, that timeframe determined by the validation procedure should be acceptable.

Given the breadth and complexity of the issues covered in the Draft Guidance, it would be advisable to organize a Consensus Conference or Workshop that would provide an

opportunity for timely input on the proposed Guidelines by experts in the field as well as by representatives of professional and trade associations, accrediting bodies, blood establishments, donors, hospitals, physicians and patients who will undoubtedly be affected by the implementation of the final Guidance document that will eventually emerge.

We are pleased to have had the opportunity to comment on the draft in the expectation that our recommendations will be considered in the formulation in a final document that will allow to maintain or improve the quality of the blood components provided to patients in need, while protecting donor safety and assuring the availability of a critical resource on which millions of patients depend as part of their medical or surgical therapies.

Sincerely,

A handwritten signature in black ink, appearing to read "Germán F. Leparc". The signature is written in a cursive style with a large initial 'G'.

Germán F. Leparc, M.D.
Chief Medical Officer
Florida Blood Services

Attachment: Appendix A (Appendix A - PLT Draft Guidance.xls)