Blood Systems, Inc.

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January 3, 2006

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

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

Dear Docket Officer:

Since automated apheresis techniques were introduced more than 3 decades ago, there have been technical modifications and improvements to make these instruments very safe for donors and ideal to produce highly effective leukoreduced platelets.

Over these years, there has been a continuous update of regulations and standards. To our knowledge, there have not been any reports of significant concern about the safety of apheresis donation that could not be detected and managed by existing monitoring procedures. Our data indicate that the frequency of adverse events with apheresis is lower than the frequency with manual whole blood donations. There have been studies indicating no alarming trends in platelet counts with multiple platelet donations. There have been no data to suggest that medical coverage for platelet apheresis has been inadequate.

Based on the universally positive safety record of platelet donation accumulated from the time of the 1988 guidance to present, one could conclude that the platelet apheresis guidelines do adequately protect donors. The fact that the new platelet guidance document suggests dramatic restrictions and changes to the guidelines in the face of this accumulated evidence of safety is a major concern.

The intent of the proposed draft guidance is stated as "to ensure donor safety and the safety, purity, and potency of platelets by apheresis." While blood collection establishments have anticipated an update to the 1988 guidance, the scope and depth of the changes proposed in this draft were not expected.

Changes with potential significant impact on operations and components availability were made without indication to the shortcomings of current practices on donor safety or component quality to justify these changes. The draft touches every aspect and adds or changes current practices developed by blood establishments which diligently maintained donor safety and product quality by following current regulations, voluntary standards and scientific /medical advances.

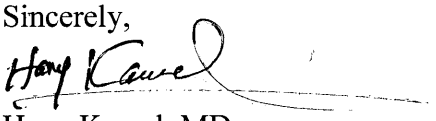
As we will address in the comment to follow, the draft extensively re-states existing regulations, modifies regulatory requirements without stating that the regulatory changes are intended or forthcoming; and provides detailed operational instructions beyond the objectives of guidance documents.

Of special note is the issue of testing for bacterial contamination: The AABB took the initiative and instituted Standard 5.1.5.1, and blood collection agencies implemented this standard using a CBER cleared or approved bacterial detection systems specifically labeled for testing of plateletpheresis components. FDA should refrain from including any guidance on bacterial detection in this document. Once the agency licenses a bacterial detection test system for the purpose of screening and labeling of the components, then the agency should issue a comprehensive guidance document on "screening platelets, apheresis components for bacterial contamination."

In our opinion, the agency should have started by observing the remarkable record of safety of platelet apheresis accumulated over the past 17 years under the previous FDA guidance and by sponsoring a public workshop where experts may present pertinent data that the agency may use in drafting this document. .

Thank you for the opportunity to comment. If you have any questions, please contact me at (480) 675-5659 or at hkamel@bloodsystems.org.

Sincerely,



Hany Kamel, MD
Corporate Medical Director

Guidance for Industry and FDA Review Staff,
Collection of Platelets by Automated Methods, Draft Guidance

Section III. DONOR SELECTION AND MANAGEMENT

Donor Selection (Section III A)

- During the past few years, instruments and procedures have been adjusted to minimize the leukocyte content. As a result , most plateletpheresis procedures today remove about 1x10 (6) to 5x10 (7) leukocytes, a number that is very unlikely to lead to leukocyte depletion (McCullough J. Transfusion Medicine. 2nd edition, 2005)
    - **Specific recommendation: Delete the requirement for WBC count.**
- The guidance document should keep operational instruction to minimum to avoid the need for frequent updates every time a new anti-platelet medication is introduced.
    - **Specific recommendation**: "You should not collect Platelets, Pheresis from donors who have ingested drugs that irreversibly adversely affect platelet function. Deferral period should be based on the medication's prescribing information.
        - Note: Donors on NSAIDs should be able to continue to donate. NSAIDs inhibition of platelets aggregation is reversible, quantitatively less, and of shorter duration than aspirin.

Donor Management (Section III.B)

Platelet Count (Section III B1):

- First two Bullets: It suffices to emphasize that donor management should be consistent with the device manufacturer's direction for use.
- Third Bullet: The guidance should keep operational instruction to minimum. Blood establishments do not accept donor's whose platelets count is <150,000/uL and have developed policies for re-qualification that may include deferral for a defined period of time or by obtaining a platelet count prior to donation before the deferral period elapses.
    - **Specific recommendation**: Deferral policies and Management of donors whose platelet counts are less than 150,000/uL should be described in the establishment Standard Operating Procedures.

Donation Frequency (Section III, B2):

We believe that AABB Standards 5.5.3 Automated Cytapheresis Donations and 5.5.4 Multiple Concurrent Apheresis Collection adequately protect the safety of the donor.

- The proposed restrictions on frequency and annual cap on number of components collected from a donor will have significant negative impact on component availability. The way in which the regulation is written may not achieve the perceived goal. It is possible to collect as a triple but divide and distribute as a double component. This would allow the donor to return in a shorter time period.

- The proposed changes to the interval between procedures based on components collected does not add to donor's safety so long as a predonation platelet count of ≥ 150,000/uL is a requirement.
- **Specific Recommendation**: Update the 1988 guidelines to be consistent with the AABB standards listed above.

United Blood Services Data:
In 12 months period:

- Total SDP pheresis donors: 15,327
- Total # SDP components: 96228
- Average: 6.3 platelets apheresis component per donor
- Donors with more than 24 platelets component in 12 months, N(%): 718 (4.7)
- Platelets Loss (Platelets collected in excess of 24 from donors above), N(%): 8,748 (9.1)

Blood Centers of the Pacific Data:
In 12 months period:

- Total SDP pheresis donors: 2,917
- Total # SDP components: 23,051
- Average: 7.9 platelets apheresis component per donor
- Donors with more than 24 platelets component in 12 months, N(%): 197 (6.8)
- Platelets Loss (Platelets collected in excess of 24 from donors above), N(%): 2759 (12.0)

Medical Coverage (Section III, D)
We strongly disagree with the agency's belief that calling 911 to obtain emergency medical care is not a sufficient substitute for an available physician on premises.

- The requirement under 21 CFR 640.22(c) is sufficient.
- Reference 11 refers to a proposed rule published in the Federal Register in 1985.
- Blood establishments developed policy and procedures for management of donors' adverse reactions, including notification of and consultation with the medical director as necessary.
- The mere physical presence of a physician without tools for assessment and resources for therapeutic intervention is inadequate medical practice. Blood centers routinely don't have diagnostic instruments (requires validation, calibration, preventative maintenance, etc.) and do not stock pharmaceutical agents (risk of outdating).
- Conversely, fully trained and equipped EMT personnel can promptly arrive on the scene to provide the necessary medical care.
- The proposal is impractical and will have major operational impact on blood centers:
- Only 10 out of 45 Blood Systems Inc apheresis collection sites (22%) would have physicians available with 15 minutes.

United Blood Services Data:

- Number of fixed plateletpheresis collection sites: 38
- Number with MD available within 15 minutes: 8 (21%)

Blood Centers of the Pacific Data:

- Number of fixed plateletpheresis collection sites: 7
- Number with MD available within 15 minutes: 2 (29%)

- A number of United Blood Services sites are performing plateletpheresis on mobile visits to maintain an adequate supply. The proposal as written will gravely restrict the expansion of apheresis collections at mobile sites and therefore jeopardize our ability to maintain supply.
- Lastly, the proposal is unnecessary. Platelets, Pheresis collections have 30 years track history of safety supported by donor's adverse reaction rate much lower than those observed in whole blood donors. See Table A.

Table A. Blood Systems Inc

All Reported Reactions	Number of Donations	Mean Rates of Moderate and Severe Reactions/ 10,000 Procedures	Relative Risk for a Reaction
Whole Blood	4,203,649	22.84	1.00
Plateletpheresis	248,985	10.24	0.45

Section IV. INFORMATION PROVIDED TO THE DONOR

Specific recommendation: Delete the last bullet in this section "A description of the number of Whole Blood, apheresis Red Blood Cells or plateletpheresis collection procedures and/or components that may be collected per year and the donation interval for each".

- This is not necessary for the donor's informed consent process.
- Overwhelming the donor with extraneous information may be a distraction of donor's attention to pertinent information.

Section V. COMPONENT COLLECTION AND MANAGEMENT

Collection (Section V, A): General comment: This section contains/provides no new information. It cites 4 CFR requirements that are in practice today.

Target Platelet Yield (Section V, B): The guidance should keep operational instruction to minimum. Blood establishments developed procedures (collection, preparation and quality control) to ensure 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. Defining the target yield is unnecessary.

- **Specific recommendation**: Blood establishment should ensure 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.

Section VI. PROCESS VALIDATION

Equipment used for the routine collection and manufacturing of Platelets, Pheresis is validated prior to use. Clarify the following questions:

- Does this validation satisfy the proposed requirement to perform Process Validation on all affected devices (i.e., blood counting devices, scales)?
- Is it the intent that equipment validation and qualifications are to be included with the blood license application?
- Do equipment identification numbers need to be recorded for all equipment used?
- Isn't it enough that all equipment has been calibrated?

Validation Protocol (Section VI, B): Clarify if bacterial contamination testing refers to sterility testing or quality control testing.

Process Performance Qualification (Operator) (Section VI, C):

- **General comment**: This section is redundant, restating existing regulation and guidance.
- Please define what personnel training should include "successful, consecutive performance" and meet relevant "component specifications" mean? Should component specifications be defined by the operator's manual or quality control requirements?

Product Performance Qualification (Component Collection) (Section VI, D):

The collection process of Platelets, Pheresis was studied and validated by the FDA. Product performance qualification is basically requalifying the equipment and instrumentation.

- Percent recovery – Specify that this is only applicable to leukocytes reduced components by filtration after collection since instruments currently process leukocyte reduced components
- If a facility plans to collect singles, doubles and triples, then does the facility need to collect 180 consecutive collections for product performance qualification?
  - Can collection for product performance qualification be from one specific site in an organization or an accumulation of data from many sites in an organization?
- If performing bacterial contamination testing on 500 Platelets, Pheresis collections becomes the requirement; the validation will take a considerable time to complete. Testing of this many components for validation will be an enormous burden for each center.

- Can a center use historical data, or is it 500 new collections? Can the 500 be accumulated from a system of blood centers, not just one collection site?
- Will the false positive result count, even if there is no bacterial growth in the product bag?

- We interpret performing bacterial contamination for process validation, as relating more to sterility testing.
- Validation of the process should test those components that stress the system the most. Our recommendation is to perform QC testing at time of distribution or day of expiration and not test a third during the first third of the dating period, a third during the second and a third the day of outdate.

Table 1. Collection Performance Qualification Criteria (Section VI, page 12)**:**

- Target column & Allowable Process Failures column do not equate. Change the Target column to Result or Confidence Level, or even eliminate this column or move to a reference section.
- Table does not discuss contamination of testing and how it would figure into the process. What is the FDA going to hold us to?

Section VII. QUALITY ASSURANCE AND MONITORING

All items listed in this section that cites specific CFR references are redundant. We recommend that information that can be found in the CFR be removed from this guidance document.

Standard Operating Procedures (SOPs) and Record Keeping (Section VII, A)

- Additional Provisions Applicable to SOPs
  - Bacterial contamination testing – Please clarify that components which fail bacterial contamination testing are those which are confirmed failures by culture testing, and not those which are initially positive by screening tests. In addition, this statement is not clear with regards to actions to take with other concurrent blood products, e.g. red cells, plasma, etc. when a platelet pheresis unit is found to be contaminated.
  - Actual platelet yield - Currently, the actual platelet yield is provided to the transfusion service, if requested. We recommend that this wording be changed to agree with Section IX – Labeling, which states "The actual platelet yield of each component should be made available to the transfusion service." This will make the statement consistent with other statements in the document.
  - Total volume loss - Does total volume loss describe only total plasma volume loss since volumes given are the same as in the Donor Monitoring section?
  - Component Storage and Shipping - The statement "You should use containers from the same manufacturer" is too limiting and may prohibit the use of future storage bags that have been approved for platelet storage.

Donor Monitoring (Section VII, B)

- Platelet counts (Section VII, B1): The second paragraph is redundant. This information is adequately covered in the first paragraph. Refer to comments on Section III B1 above.
- The statements found in Total volume loss (Section VII, A2) and Total plasma volume loss per 12 months (Section VII, B3) are not consistent. Does the volume defined in these sections apply only to plasma or to total volume loss, (total volume loss, not just plasma).

Daily Component Specification Check (Section VII, C1)

- Define what constitutes an "appropriate phase of manufacturing." Currently, our system obtains a platelet count from the original collection bag, and uses this count to calculate platelet yield in the subsequent split.
- The statement "Residual WBC count on all collections that do not utilize an automated leukocyte reduction methodology." implies that 100% WBC QC testing is required for manually filtered products. This is in conflict with the May 29, 1996 memorandum entitled *Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products*.
- To our knowledge, no collection device manufacturer currently specifies the use of bacterial contamination testing for apheresis products collected using their equipment. The requirement for this testing can be found in the current edition of AABB Standards. We are unclear as to what the FDA intends with this statement.

QC Monitoring (Section VII, C2)

- This section appears to be contradictory and confusing with regards to the quantity of units required for QC testing. In one instance, four is given to be the minimum number of units to test, and yet in the next paragraph, a statistically sound sampling plan is required. The example of the sampling plan given, Scan Statistics, requires QC testing on 10% of annual collections.
- For most blood centers, this would be a far larger number than the minimum of four. We question the value of such a significant increase in the amount of QC, given the impact it would have on operations. An in-depth knowledge of statistics is required to understand the intent of this section, and to develop a sampling plan that uses an alpha of 0.05 and a power of $\geq$ 80%, terms only a statistician would be adequately familiar with.
- In addition, there is no guidance on how to use scan statistics for a blood center with multiple collection sites. Would the sampling plan apply only to individual collection sites, or could it be applied across a large blood center system?
- One of the bullet points in this section states "Test for percent component retention." This should also state "if required", since this statement is only applicable to a manual filtration process. The 85% recovery mentioned in the Acceptance Criteria is also only applicable to a manual filtration process.
- In the Acceptance Criteria section, specific ranges for product volumes from double or triple collection are given. This is more restrictive than what is stated in the Labeling section of Requirements for SOPs, which only requires

that the volume range on the label be within reasonable limits. Is it the intent of the FDA to define these limits as stated in the Acceptance Criteria section?