



BloodSourceTM
— SACRAMENTO

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December 23, 2005

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

RE: Docket No. 2005D-0330

Thank you for the opportunity to comment on the proposed guidance document, *Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods*, FR Doc. 05-19727.

Enclosed please find the comments we have on the guidance document, listed by section. To support our position on a number of the suggested limits and requirements proposed, we have included data from our facility that we collect routinely. The data is reviewed and utilized on an ongoing basis by a cross-section of staff - MDs, RNs, CLSs, QA, Executive Management, in the organization to assure both donor safety and the safety, purity and potency of the Platelet, Pheresis products issued for patient care.

As always, we view the FDA as our partner in our work to provide safe and therapeutic support to patients and to protect our donors. We welcome all dialogue with the FDA; please feel free to contact me regarding this data or for any questions or discussion on these comments.

Thank you for your careful consideration of this feedback and data.

Sincerely,

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Comments on *Draft Guidance for Industry and FDA Review Staff on
Collection of Platelets by Automated Methods* (FR Oct. 3, 2005)

General Comments

Overall, this document appears to have been written by different groups without overall coordination of its information. There are many repetitive sections and other sections that are discrepant with each other. Much of the proposed changes indicate a lack of understanding of the functioning of a blood center apheresis program and the apheresis devices' features in use today. Please reissue this guidance once revised, for comments.

Section II. Discussion

B. Definitions

- Add definitions for: Process Performance Qualification
Product Performance Qualification
Collection Performance Qualification
Process validation*
*(Devices are not a process; devices are *qualified*, and the process in which they are used are *process validated*)
- Terms used throughout this document are inconsistent.
- Distinguish between Operational Qualification (OQ) and Produce Performance Qualification (PPQ) – not clear as used.

Section III. Donor Selection and Management

A. Donor Selection

1. Pre-donation tests

- Drop the pre-donation tests in second bullet, for WBC and Platelet count for first time donors. In 2 years and approximately 75,000 Platelet Pheresis components, we have seen only 1 very high WBC count.
- Satellite collection sites do not have the ability to perform this testing. Donors are monitored for platelet counts already; this detail is in SOP and processes submitted via BLA for approval.
- The 510(k) cleared devices alert the operator if the WBC count is potentially too high to produce a leukoreduced product, allowing follow up by facility to confirm or rule out prior to final labeling.
- Inconsistent use of should vs. recommended on donor pre-counts in this section.

2. Drugs that adversely affect platelet function –

- Drop use of Reference 9. It is just one example of a medications list – this one is listed without a source.

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- Why were named aspirin-containing drugs listed – FDA just approved the Uniform Donor History Questionnaire, and it only asks about aspirin ingestion. It will be too complex to have one set of donor suitability for apheresis donors and another for whole blood donors. Many of our donors go back and forth, depending on what is needed in the community the day of donation.
- New medications are introduced frequently to public. It would be best to allow local physician to control SOP and medication list for facility.
- There are discrepancies between Reference 9 deferral dates and the Reference 10 deferral date for aspirin. There are no scientific data to support the deferrals listed in Reference 9.
- NSAIDS – data limited for affects on platelet function (Ibuprofen – 24h; no data for naproxen); Use DOD list for medications; literature does not support proposed deferral
- A large number of male donors take aspirin and NSAIDS, but they stop taking their preventive dose for the 3 days prior to their donations. If the period were changed to 5 days, we believe many of these donors will stop donating, rather than stop taking their medication for 5 days.

B. Donor Management

- Repetitive with Section A. *Donor Selection*.

1. Platelet Count

- Second bullet: Delete restriction to only collect a single product from a first-time donor. What data is this change based upon? If the donor's total body mass is sufficient, the donor should be able to give a double product. Did FDA review the vendors' data and information that was supplied for 510(k) clearance? See **Data #10**.
- Is the 150,000 count a pre- or post- count?; We are providing data to support why we would not need a re-count. What is FDA's scientific data to support the requirement of a post-count? We recommend deferring donors with a pre-count of <150,000 for 4 weeks rather than obtaining a post-count. See **Data #2**.

2. Donation Frequency

- The device is 510(k) cleared based on vendor supplied data to show that donor safety is protected by the device regarding platelet count. We also have considerable data, over many years, to show this is a safe approach for the donors. See **Data #2, #3, #9 and #10**.

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- *To protect the safety of the donor* - Delete the restriction for a maximum of 24 components collected in 12 months. The experience with the devices we use clearly shows there is no donor safety issue collecting what the device controls internally as safe for the donor on that particular day of collection. The number of components collected with each donation and their type are irrelevant, if the donor values are monitored and the device and process are validated to assure protection of the donor. The devices will not allow the donor to donate more volume or types of products than is safe for the donor. **See Data #3, #6 #7, #9 & #10.**
- A donor chart/file review will capture any abnormal test values. The MD/RN chart review can be performed quarterly. In addition, you could require that a MD review all abnormal labs; it is irresponsible to have abnormal labs not reviewed by a MD. **See Data #7 & #9.**
- Trima has built in algorithms, controlling that no more than 15% of TBV may be collected. Refer to device manuals. **See Data #10.**
- In 2004, 275 apheresis donors gave more than 24 platelet components, totaling 3655 platelet products, which equates ~10% of total platelet availability for our blood center. We are a major exporter to other regions of the country. This would have a big impact on plateletpheresis availability for patients, and may force many facilities back to random platelet concentrates, a definite safety issue.
- We disagree with 7 and 14 day deferrals for doubles and triples respectively; platelet availability in the donor drives collection and is controlled by the Trima device.
- Delete last bullet under B.2. By the nature of pre-count and collection, the donor's platelet count will drop, however, the Trima machine's program will not allow collection if platelet count would drop below 100,000 (See section 7.B.1)
- The additional testing required in this guidance will double cost of donor test counts (pre and post) nationally, based on what evidence? We have data to show this is not required. **See Data #6 & #9.** Who will pay for this new requirement?

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3. RBC loss prior to a collection of Platelets, Pheresis

- First bullet - states 450mL; does not allow for 500mL WB collections for RBC loss; delete reference to 450mL, or address both, or leave as "WB" generic.
- The total volume requirement would eliminate the ability to draw triple plateletpheresis at all. FDA cleared devices are safe to collect triples, (all concurrent technology). All facilities already have to validate that these machine controls work as expected. **See Data #3, #9 & #10.**

4. Total volume loss per collection procedure

- Strikethrough from "500mL" to "or" that follows parentheses and strikethrough "whichever is less". This is all covered in the device operator's manual.
- Total volume loss per procedure. We currently have Trimas set at "no more than 15% TBV" which allows for more volume to be collected than the suggestion in the draft. We would have a significant loss of multiple products with the guidance numbers. **See Data #3.**

D. Medical Coverage

- Change from physician present on premises, to blood bank physician available to respond within 15 minutes. We believe that the blood bank physician needs to be available for consultation. **See enclosed NEJM articles (Data #1).**
- The low number of serious adverse reactions really does not support this need. MD's could not render any more care than an RN can with the equipment we keep for emergencies. Require an RN on site at every collection center, and training in basic life support (CPR) for collection staff at each site. This is what we do and what is required in California. The impact on apheresis product availability nationwide would be enormous if MDs were required to be at every site; there are not enough blood bank-trained, apheresis-knowledgeable MDs to be present at every collection site in the country. **See Data #4 & #8.**
- Emergency Medical Services (EMS) could be dispatched to address the rare, serious adverse event. The EMS responders have the necessary equipment to address donor needs and can transport to a medical facility, as necessary. Our data supports that EMS could be dispatched and respond in well under the 15 minute timeframe specified in the draft guidance document. **See Data #5.**

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Section V. Component Collection and Management

A. Collection

- “Single uninterrupted” – Please define or clarify. Does that phrase refer to ‘starting over’ or ‘continuing’.
- Strike “minimal manipulation” if not in CFR. See Trima manufacturer information for use of SCD to attach a second needle to ensure a closed system; approved by FDA under 510(k) clearance for device. Our QC data on bacterial detection supports that this is a safe and effective process.

B. Target Platelet Yield

- Do NOT set target values in guidance, instead refer to manufacturer’s recommendations. Those values will vary from one facility to another, and also vary depending on the apheresis device(s) in use.
- The bottom line is each product needs to have $\geq 3.0 \times 10^{11}$, or it will be recombined before final labeling. Each apheresis device’s *target platelet yield* is calibrated to the specific hematology counter in use by that facility’s lab, based on data and QA oversight, including validation and re-validation periodically.

VI. Process Validation

- Section VI: Section unclear for sites/process/device/machine throughout; no detail about initial or re-qualification requirements for process validation; scale require qualification not “process validation”; shipping container is not a “device”
- Be careful and consistent with terms. Devices are not a *process*; they are *qualified* and part of a *process that is validated*. We agree a validated process includes all the devices, instruments, etc. that are part of the process, and must be qualified for their intended use.

B. Validation Protocol

- What is meant by “maximum values”? Are you referring to the maximum concentrations per mL for plateletpheresis products per each manufacturer’s manuals?
- Total volumes as a percentage of target yields are specified by the manufacturer of the device. We recommend deleting “target platelet yield”.
- “Count per container” should be required for validation, but not after the process is validated. We have validated that counting parent bags only, and not individual progeny, is safe, reliable and much more efficient and cost-effective. **See Data #11.**
- Strike “percent recovery” from residual WBC count for collection; this only applies if you are not using an in-line leuko-reduction device or separate filtration.

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- Drop all mention of bacterial testing. This is not an FDA requirement and should not be put into an FDA guidance document.
- Platelet concentration ‘failures’ (Too high a concentration) are already monitored by the lab to assure manufacturer’s specifications are met. This is seen so infrequently, it is not appropriate to be in a validation packet. It must be monitored, though, and acted upon while product is *in process*.
- Drop need to add “description of supplies used” to validation packet. Critical supplies are managed through other processes, not validation.
- Define “failure investigation process”, or allow each facility to define per its specific process/equipment in use.
- Last bullet – delete - Why is “documentation of the validation protocol criteria (all of the above)” here? It is redundant to information already listed

C. Process Performance Qualification (Operator)

- Recommend changing title to “Operator Training and Competency”, and using this phrase throughout.

D. Product Performance Qualification (Component Collection)

- Recommend changing title to “Operational Qualification (OQ)”, and using this phrase throughout.
- Do not dictate the number of each product to be included in the OQ portion of validation; this may vary by site due to volume differences in collection. Instead, allow each facility to establish reasonable numbers per product type, per site for validation. For instance, at a small collection site with 1-2 Trima machines, it may take 4-6 months to get even a modest number of triple products, dependent solely on the donors who donate at that site and who qualify for triples.
- Do not specify parameters that must be included – the specific device(s) in use may not even allow for that parameter to be measured, e.g., on the Trima platform “percent recovery of leukoreduced component” is not possible.
- Remove all reference to and requirements for bacterial testing; not required by CFR. FDA should not add this into a guidance document. If it is felt to be necessary, it should be a formal requirement.
- Testing on all progeny products is not necessary except for a site’s validation.

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- Testing during first 3rd, second 3rd, and last 3rd of product dating - if counts are good at beginning and at end, what is the purpose of checking throughout storage? If initially validated for length of storage; do you need to hold 1/3 until the end of storage? Why? This will adversely affect patient care and product availability; residual WBC count at day five will have degraded to a point where the count will be erroneous due to cellular breakdown. Delete this section.
- Bacterial detection testing using CBER cleared or approved – remove. Not currently required to perform bacterial detection testing per FDA

Table #1

- Gambro manual allows 90% to be $\geq 3.0 \times 10^{11}$; this table requires 95%; inconsistent with 510(k) cleared device manual. Our own data shows the actual data is much better. Recommend referring to vendor manual as the requirement.
- Volume numbers do not match vendor device information for Trima. Require use of vendor's specifications, and keep this document generic for changes in devices/software and variation among the vendors' devices.
- Residual WBC count should be clarified to apply to post collection filtration only.
- Bacterial contamination testing – Delete, not required by FDA.
- Does this guidance document (Table #1) require that all platelets be leukoreduced? This is not a requirement.

E. Re-Qualification/Re-Validation

- What does “collection process qualification in its entirety” mean? Should be relative to the investigation findings (provide examples; arm scrub recall, repair/replacement part, dam filler problem with Spectra). Provide some examples of when NOT to do in entirety.
- Deviations from... bullet is unclear. Why would you need to re-qualify your whole process? Any deviation should be evaluated through deviation/error management process to determine proper CAPA.

VII. Quality Assurance (QA) and Monitoring

- SOP requirements section: should not utilize the word “must” in a guidance document. If all this is already in CFR, then just refer to those requirements.

A. 1. Requirements for SOPs

- Minimum and maximum values for a test or procedure - recommend changing to refer to existing suitability criteria of manufacturer.

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A. 2. Additional Provisions Applicable to SOPs

- Remove reference to phone numbers; “rescue squad”, EMS, etc. These numbers may change. SOP should refer to what to do, and where this emergency number(s) is posted – by phones, hopefully.
- Sample handling - recommend striking “of product (component)”.
- Delete Bacterial contamination testing section - not currently required by FDA.
- Actual platelet yield – Do not require this to be provided to the transfusion facility. It is already available if requested, so this is not necessary to place into guidance. We are a large blood center and get only 3-4 requests per year for the actual platelet count, for intrauterine fetal transfusion cases. Our three blood bank physicians, who also treat patients, see no use for this clinically. It only adds more work and manual steps that are not needed to support most patients.
- Total volume loss – Affects all collections, not just plasma; regulations apply to plasma loss only; Add “total plasma” after word “Annual...” This is already specified by the manufacturer of device, too, as 510(k) cleared.
- Leukocyte reduction filters – If used – this is not an FDA requirement, so it must be clear that this applies if you use filters for 100%. There is no reason a product that does not meet WBC specifications for leukoreduced cannot be labeled as a non-leukoreduced product. Is FDA trying to infer the requirement for 100% LR into a guidance document?
- Donors participating in a frequent plasma program may have greater plasma volume loss, as described per reference (Source Plasma Regulations). This change would eliminate the ability to have frequent plasma donors cross-over to apheresis platelet donations, even when device and MD reviews control donor safety.
- Performance specifications - Add wording to address specifications beyond the manufacturer’s limitations, as “You should have a procedure addressing the handling of components that exceed the manufacturer’s limitations, or your own specifications, whichever is narrower.”
- Labeling - Is the intent to know what is in final volume of the product? Can we not rely on our site-specific process validation to show that the final volume is within the manufacturer’s requirement of +/- 10% of what is on the label?
- Component Storage and Shipping - Containers for platelets should be *approved* by the manufacturer, but all are not necessarily from the same manufacturer.

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- Last bullet on shipping – delete. This guidance is titled “collection of” – shipping container details are not appropriate here.

VII. B. Donor Monitoring

1. Platelet counts

- We do not currently do post-counts. Recommend that process should require that the donor’s pre-count is >150K, or require a system or process to assure that donors will have an acceptable platelet count prior to donation. (Don’t state ‘how’ to do something, state the requirement to be met.) **See Data #2, #6 & #9.**
- As Medical Director, I have approved an SOP where the donor collection is stopped if the pre-count comes back <150K, and if the pre-count is <180K, the donor is temporarily deferred for two weeks. This works well to protect the platelet counts of donors.
- Review of donor’s records - Change back to 1988 document’s wording – have a process to monitor donor values to detect thrombocytopenia.

2. Adverse reactions in donors

- Add the word “adequate” after “... frequent multiple component collection of Platelets, Pheresis for...” in last line of paragraph.

3. Red blood cell loss, bullet Total plasma volume loss per 12 months

- This is a repeat from prior sections. Why not just refer to the Source Plasma document? Recommend a separate document that covers all frequent plasma donation loss; plasmapheresis, plateletpheresis, Source Plasma (in a volunteer donor setting)?

C. Component Testing

1. Daily component specification check

- This section repeats from D. p. 10 – consolidate or delete.
- Define ‘daily component specification check’- bullets not consistent to previous sections.
- Second bullet “Test for % Component retention” – Delete, or explain – not clear.
- Third bullet – Test for residual WBC – not consistent to prior section on testing intervals 1/3, 1/3, 1/3.
- Last bullet – we agree – keep as is. However, this is discrepant with prior sections.

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2. QC monitoring (Acceptance criteria)

- pH requirement – if CFR says 6.0, why not change CFR to match AABB? Appears like FDA is slipping requirements into guidance documents. pH is specified as both 6.0 and 6.2 in this document
- WBC – This bullet assumes all platelets by apheresis are leukoreduced; not true. Bullet two only applies if labeling as LR. Also, manufacturer specifies whether WBC is per component or collection – why not just “...follow manufacturer’s specifications”? If product qualifies as LR, then residual WBC count should be $< 5.0 \times 10^6$.
- Strike “percent component recovery” – not needed if process already validated to show this is in control. If final product meets all QC specifications, including concentration, this is not needed; it’s unnecessary work and documentation, and adds nothing to product safety.
- Volumes – this should be covered in process validation of component splitting, then not required as routine QC.
- If you have to count all progeny, one failure of a progeny component should not require that all companion products go through quarantine and re-test. If validated process to count only parent bags, parent bag testing is QC requirement. Our experience is that this is a very controlled process, and was process validated. **See Data #11.**
- Not realistic to select four units and to assure that they are from different donors (i.e., doubles and triples)
- Currently checking all platelets for count and bacterial detection; we monitor concentration and WBC; Why monitor pH?

F. Quality System Audits

- Bacterial detection rates $< 1:3000$. Delete as bacterial detection is not a required test.

IX. Labeling

- Second bullet - Platelet count on the bag for those $< 3.0 \times 10^{11}$ should be labeled with the actual platelet count (first bullet on page 15 contradictory)
- Platelet yield of each component *should be made available*... Why is this here? It is available and provided if requested. If the platelet yield is needed, the transfusion service or clinician may call now. (See p16 for “should be” for $< 3.0 \times 10^{11}$ and p15 VII.A.2. bullet 7, p22 IX. for contradictions); Can we delete “made”?

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Appendix A – Scan statistics

- Seems inappropriate to implement for entire country when no pilot or beta site testing has been done. Biologic systems, and thus products derived from them, are inherently variable. This approach has the potential to tie up product and decrease availability of platelets. Scan statistics is one method to monitor; we propose a percentage method as there is no published evidence that Scan statistics will be appropriate or effective in this application.
- QC failures are already required to be investigated and resolved to cause with corrective action, as needed.
- Page 1: Suggest that no particular reference to Scan statistics be utilized in the document (p.3, II.)

Data Enclosed:

1. Articles about ER care (Two NEJM articles)
2. Multiple TAY postings (>2)
3. Apheresis summary by donation and product type (>8000 components from triples)
4. Apheresis reaction rates vs. WB reaction rates (0.004% for severe reactions for both WB and apheresis)
5. EMS response times
6. Frequent plasma with platelet crossovers (lab values: WBC, TP average, SPE, HCT): no harm to donors
7. Percentage of lost product if component collection limits are changed to 24 components vs. 24 donations
8. MD on site in 15" projected loss (RN at each site already: meets State law)
9. Frequency of collection for triple donor
10. Gambro data for prediction accuracy of post platelet count algorithm
11. Parent bag vs. progeny testing data (Two documents)