

Thank you, for the opportunity to comment on the Collection of Platelets by Automated Methods; Draft Guidance
Docket No 2005D-0330

This draft guidance has the potential to update and consolidate relevant information for collection of platelets by automated methods, including guidance on licensing applications. Bringing all of this information into one document should assist the community in executing the appropriate activities for collection of platelets by automated methods. Gambro BCT is dedicated to providing the public with the safest blood supply possible, and will utilize our resources to insure and improve blood supply safety, quality, and availability.

Even though these provisions are in the form of a guidance and thus do not create legally binding requirements, the Agency should be aware that by common practice any such statements in guidance are taken by the blood establishments as a rule. This is especially true for any establishments that may find themselves in the unfortunate circumstance of being under consent decree. Gambro BCT would like to comment on specific items in this document that may reduce platelet availability and increase the costs to the health care system, while not contributing incremental advancement to the safety of the blood supply.

We support the Agency's desire to protect the safety of the donor and to standardize care throughout the blood collection industry. The blood collection industry has a wealth of medical knowledge and practical experience. It is our belief that the best approach would be a public forum or workshop, where open discussions could take place regarding the medical concerns, practical considerations and scientific rationale prior to issuing another draft of the guidance.

We have arranged our comments in the order of greatest potential impact on the supply of donor platelets, impact to donor safety, product safety and purity. We offer the following comments and recommendations for the Agency's consideration. We have followed with comments we consider of lesser impact.

CRITICAL ISSUE COMMENTS:

(Page 6) The change to limit donors to 24 total Platelets, Pheresis components 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.”

Comments: This action is likely to have a significant negative impact on availability of blood products. It will result in platelet shortages and hardships to both blood centers and patients. There is no evidence that there is a risk to volunteers who donate, multiple platelet components 24 times in a 12-month period. Reference 21 presents some data that multiple, regular platelet apheresis donation 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 the facility. Furthermore, this potentiality is protected by the requirement to determine the donor pre-procedure platelet count and disqualification of the donor if the pre-count is less than 150K platelets/ μ L.

We examined electronic donation records from one large blood center for the period December 5, 2004, through December 5, 2005. All personal identifiers had been removed from the database. In this 12 month period, 1535 donors sat for 6371 donation sessions resulting in 10,621 therapeutic doses of apheresis platelets; therapeutic dose being defined as Trima predicted final yield $3.0-5.9 \times 10^{11}$ platelets. The number of donation sessions resulting in various quantities of therapeutic doses were: triple platelet products 992 (15.6%), double platelet products 2743 (43.1%), single platelet product 2199 (33.9%) and less than 3×10^{11} platelets in 477 sessions (7.5%). Maximum donation sessions per year were 24 for any given donor.

There was no significant change in the donor platelet count, with more donors experiencing an increase in count over the period than experiencing a decrease. The change in platelet count over time is independent of both donation frequency and the number of therapeutic doses donated per session. The changes are small and are easily monitored using the pre-donation platelet count. See Appendix A for the complete analysis.

Regarding the impact on platelet availability in this data set 102 donors (6.6%) provided more than 24 therapeutic platelet doses over the period, for a total of 3902 products. If the donations would have been restricted to 24 therapeutic doses of apheresis platelets per year, there would have been **a loss of 1454 platelet products (13.7% of total production)**. Recruiting additional apheresis donors to fill this void requires a substantial increase in the donor base. For example, recruiting new donors that could only donate one therapeutic dose would necessitate an increase of 95% in the donor base. Making further assumptions that the new donors would follow the donation frequency pattern of the current donor base (44% one session per year, 11% two sessions, etc. up to 10 donation sessions per year) and half of these visits would result in double therapeutic doses, an additional 863 donors (56% of current donor base) would be required.

Recommendation: The donation frequency continues to be maintained at 24 donations (sessions) per 12-month interval irrespective of the number of therapeutic doses or products collected. We would also suggest a review of the data regarding platelet counts and Adverse Events. (5,6,7,8,9)

(Page 7) The requirement that a physician be on the premises within 15 minutes.

“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.”

Comments: There is no data presented that current practice has resulted in a health risk to donors because of inadequate medical care in the event of a complication during or immediately following donation. This change will have a significant impact on blood availability since staffing coverage is not reasonable for many donation settings. Especially impacted will be satellite or mobile collection sites. A non-specialized physician does not add to patient safety. References such as #1 (FDA draft guidance) should be more specific so they can be located. The citation is to all CFR proposed rules including superfund clean up and transportation. Additionally, the justification for using a 20 year old proposed rule citation, which apparently was never finalized, is perplexing.

Recommendation. We suggest dropping this requirement, or if patient safety truly benefited by emergency treatment, then the goal for collection should be access to an ER facility within a reasonable time. (10, 11, 12)

(Page 5) Donor Selection Aspirin Deferral Period

“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)”

Comments: We could not access Ref. 9 with numerous attempts nor could it be located from the home page using other search strategies. Current *Standards for Blood Banks and Transfusion Services* (23rd edition, 2004) reference Standard 5.4.1A-Requirements for *Allogeneic Donor Qualification: Medications that irreversibly inhibit platelet function preclude use of the donor as sole source of platelets*, and the *AABB Technical Manual*, 15th edition, p141, Donor Selection and Monitoring: both specify that donors who have taken aspirin-containing medications within 36 hours of donation are usually deferred because the platelets obtained by apheresis are often the single source of platelets given to a patient.

Recommendation: We suggest not changing the current standards. There have been no known issues under current standards for over 20 years.

(Page 11) Bacterial Testing on 500 collections

“Perform bacterial contamination testing on 500 collections with 0 failures.”

Comments: This requirement does not demonstrate that the device performs according to the manufacturer’s claims in the local facility’s hands. Furthermore, apheresis platelet products are 100% tested for bacteria, bacterial contamination risk has been described, and industry standards (AABB) have provided clear direction on prevention and detection strategies. Therefore, we believe 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 by FDA and reported 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.

Recommendation: We propose the first 2 months of testing results be submitted in lieu of this requirement and we suggest more general wording for the target criteria and indications for follow-up. See Table 1 in Appendix B.

(Page 12) Component Submission for CBER QC testing

“Licensed collection facilities with no prior experience in the collection of Platelets, Pheresis must schedule Platelets, Pheresis component submission for CBER QC testing. Licensed facilities that submit a CBE-30 for an additional facility under an approved Comparability Protocol do not need to send components for CBER QC testing. We may also request at any time that a facility submit components for CBER QC testing. In particular, we may require you to provide samples if, during our review of a submission, we determine that the submitted data is inadequate or if you are submitting an application under 21 CFR 640.120 to use procedures at variance with those required in regulation.”

Comment: We believe that the requirement to send platelet products to CBER for testing is a practice that does not make a meaningful contribution to the safety and efficacy of the product or manufacturing process. Since this practice was initiated, the technology for collection and laboratory methods have made tremendous strides and progressed through several generations of development. At this point, we believe this activity is wasteful to both CBER and blood centers in that it unnecessarily consumes resources, i.e., people and valuable blood products that could go to patients. This requirement is not applied to red blood cell products or plasma products.

Recommendation: We believe the requirement should be removed for platelets. We suggest that FDA 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 better obtained by a site visit. We believe this approach will result in more timely turn around of license applications and a saving of resources both in the blood center and at FDA.

(Page 11) Product Performance Qualification, last bullet

“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.”

Comment: The only criteria that are expected to change over the course of storage are pH and titer of contaminating bacteria. Although not stated in this bullet, we presume the Agency intends this to be directed at pH only.

Recommendation: We disagree that testing platelets over the storage period will contribute any meaningful information to the qualification scheme.

We propose, that test results by therapeutic dose be reported for two consecutive months. The manufacturers have already presented data as a basis of approval that shows storage characteristics if the device is used according to the manufacturer’s directions for use. This exercise does not demonstrate that the device performs according to the manufacturer’s claims in the local facility’s hands. We also believe the statement “You should not release such outdated components for transfusion” is obvious and does not need to be included in the document.

(Page 7) Total Blood Volume lost per Collection

“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.”

Comment: Medical devices have been 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. Currently the agency has approved 15% TBV collection in the Gambro BCT 510K’s for Trima and Spectra. (e.g. BK 990025). The agency presents no data to support this more restrictive requirement of “whichever is less”. This change will have a negative impact on blood product availability.

Recommendation: We suggest rewording the statement to read, “The total plasma 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 collection device.”

(Page 12) Change of the Residual WBC content from per product to per collection

“Residual WBC count; $< 5.0 \times 10^6$ per collection and per component for double and triple collections”

Comments: The current automated technology produces platelets that are leukocyte reduced and experience shows no impact on donor ability to fight infection or effects on the immune system. (13) The average normal adult WBC count range is 4,000 to 11,000 WBC/ μ L of whole blood, leading to a WBC loss during a whole blood donation of 10^9 to 10^{10} WBCs. In contrast, a leukocyte reduced platelet donation will routinely contain less than 10^7 WBCs, even in a triple product collection. Thus platelet donation does not present a risk to the donor’s WBC count. From the recipient standpoint, the requirement

is meaningless, since there is no mechanism in place to ensure patients receive platelets from a single donor, and it is inconsistent with the AABB definition of a leukocyte reduced platelet product.

Recommendation: Reword to say “Residual WBC count; $<5.0 \times 10^6$ per transfusable dose.” Gambro BCT proposes using the Table 1 included in Appendix B (and values in lieu of the table on page 12 of the draft guidance) to address the two preceding points. Some of the suggested changes to the table are discussed in the additional comments section.

(Page 30) Use of Scan Statistics for QC monitoring

‘Scan statistics can be used to assess events that cluster, and compute the probability that a process is non-conforming to expectations based on the observer rate of failed test. To assess non-conformance, the samples tested for QC are evaluated on a rolling window of test results.’

Comment: We recognize and appreciate that CBER has devoted time and effort to this approach resulting in an intellectual contribution to the field (ref. Journal of Biopharmaceutical Statistics 2005:15; 353-366.) However, we feel strongly that it is premature to add this to the guidance document. We feel the agency should first partner with a variety of blood establishments (e.g., large, small, centralized, distributed, hospital-based) and conduct pilot studies to ascertain the true inspection burden this may place on facilities. It may be true that the scan statistics approach will fit very well in some situations, but on the other hand, it may be that the inspection burden would be overwhelming in other situations. By placing this so prominently in the guideline, FDA is, by default, requiring this to be implemented.

Recommendation: We believe the burden of proof resides with the Agency to demonstrate the utility of this approach in real life situations prior to including the requirement in the guidance, much as we would expect clinical evidence to be presented prior to implementing a change in clinical practice.

(Page 23) Prior Approval Supplement (PAS): third bullet

“FDA believes that such manufacturing changes include: increase in platelet yield; change in storage conditions; change in anticoagulant; leukocyte reduction; and collection of an additional or different product.”

Comment: Apheresis collection facilities experience different precision with respect to platelet yield predictions based on laboratory methods, hematology analyzers, and apheresis practices, but the final product specifications remain the same for a transfusable dose. Adjustments in the platelet target yield are routinely required to achieve the desired end product, when minor changes (ie, using the average pre-platelet count from prior collections vs. actual pre-platelet count to begin the collection process, changing cell counter analyzers) are made. The manufacturers of the apheresis devices are practiced and expert in guiding the facility in understanding this precision and how to determine appropriate target yields to assure the desired end product.

Recommendation: We suggest deleting “increase in platelet yield” from the list of PAS examples, since adjustments in target platelet yield are routinely required to assure the desired end product.

In addition to these Critical Issues, Gambro has other concerns with the guidance. We believe that although the following issues will have less impact, they still require consideration and modification to the guidance.

ADDITIONAL COMMENTS:

Page 5, B. Donor Management, 1. Platelet Count

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

Comment: This imposes added cost, extends the donor time, and adds to the overall RBC loss by the donor. Samples for post-donation platelet counts require skill to collect and are prone to falsely low values. Thus, donors could be unnecessarily subjected to added time loss, added blood loss, additional needle sticks, and unnecessary concern over risk. This will also cause additional cost for medical follow-up. The potential of chronic platelet depletion is addressed with the pre-procedure platelet count requirement. The agency presents no data that the safety of donors has been compromised because of current practice.

Recommendation: Remove this requirement.

Page 5, Donor Selection:

“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. 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.”

Comment: 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 the value is not needed to program the automated cell collection device. The current automated technology produces platelets that are leukocyte reduced and experience shows no impact on donor ability to fight infection or effects on the immune system. (13) The average WBC count range is 4,000 to 11,000 WBC/ μ L of whole blood, leading to a WBC loss during a whole blood donation of 10^9 to 10^{10} WBCs. In contrast, a leukocyte reduced platelet donation will routinely contain less than 10^7 WBCs, even in a triple product collection. Thus platelet donation does not represent a risk to the donor’s WBC count.

RECOMMENDATION: Delete the WBC pre-count reference in the guidance.

Page 5, B. Donor Management, Platelet Count

You should collect only a single Platelet, Pheresis collection from first-time donors who do not have a pre-donation platelet count.

Recommendation: Re-word: “You should collect only a single therapeutic dose of Platelet, Pheresis from first-time donors who do not have a pre-donation platelet count available either prior to or immediately following the initiation of the procedure.” The guidance document needs to clearly state that this restriction is only for the collection of platelets and does not apply to concurrently collected RBC or plasma.

Page 7, C. Dedicated Donations

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, including

Comment: This comment is true for all registered blood establishments, not just licensed establishments. Expand the statement to include all registered blood establishments.

Recommendation: re-word - Dedicated Donations – The use of the procedure to obtain a Platelets, Pheresis product for a specific recipient may be at variance with routine allogeneic donor acceptance criteria, including

COMPONENT COLLECTION AND MANAGEMENT

Page 8, 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 is at least 6.5×10^{11} . Triple components, the device’s target platelet yield setting is at least 10.0×10^{11} . “

Comment: Apheresis collection facilities experience different precision with respect to platelet yield predictions based on laboratory methods, hematology analyzers, apheresis practices, and apheresis device. Variability in donor qualification methods within an establishment (ie, use of pre-platelet counts from a prior donation, averaging of prior pre-platelet counts, or day of donation pre-platelet counts) is also a contributing factor. 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 fixed targets since there is such a wide range in current practice. These numbers are currently incorrect for many locations and will not stand the test of time for new product developments as technology improves. It is enough for the agency to set the product definition and confidence intervals (e.g., 3.0×10^{11} per therapeutic dose 90% of the time with 90% confidence. See proposed Table 1 in Appendix B).

Recommendation: Encourage facilities to work with the respective manufacturer to determine the appropriate targets.

Page 8, C. Hemolysis During Collection

During the course of the apheresis collection procedure, you should visually inspect separated plasma for hemolysis. A red tinge to the plasma in the return line is cause for evaluation (prior to re-infusion to the donor) to determine whether this is a result of red blood cell contamination of plasma or from hemolysis.

Comment: A red tinge of the separated plasma anywhere in the collection system should be cause for evaluation. In some instances the return line is not the best place to make this observation. Technology could be developed to detect hemolysis, which is more sensitive to the event than a visual inspection.

Recommendation: Re-word: “Users should closely follow the manufacturer’s directions for use and other labeling regarding monitoring for hemolysis.”

**Page 11, D. Product Performance Qualification (Component Collection),
Paragraph 2 PROCESS VALIDATION, B. Validation Protocol**

“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.”

Comment: Percent product recovery only applies to leukocyte reduction by filtration and not by process. RBC/hematocrit is not associated with any specification; therefore it should be dropped from the performance qualification.

Recommendation: Reword - “Qualification should include testing for the actual platelet yield, volume, residual WBC count and percent component recovery (if applicable), pH (performed at maximum storage), and bacterial contamination testing.”

General comments: SECTION VI. PROCESS VALIDATION

Page 9, PROCESS VALIDATION

Paragraph 3 with 5 bullets: *“In addition, you should perform Process Validation on the following devices used in the collection process:”*

Comment: 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. It is also unclear how various devices would be validated; for example, a Nageotte Chamber or similar device. We believe validation of a Class I device, per se, is not needed. Appropriate training and demonstration of proficiency of the technologist would apply. Even properly installed, calibrated and functioning devices, as the agency notes later in the document, will not assure the proper use. We believe the goal is better served with a focus not on the devices but on the entire process.

Recommendation: Reword - “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.”

Page 10, PROCESS VALIDATION, B. Validation Protocol Bullet #2, point 2

“Minimum/maximum acceptable values for the Platelets, Pheresis collection and/or component as specified by the device manufacturer ... Target platelet yield”.

Comment: Specifying a minimum/maximum value for a “Target platelet yield”, which is a fixed value, does not make sense in this context.

Recommendation: We suggest this be removed.

Page 11, D. Product Performance Qualification (Component Collection)

“For facilities using automated blood cell separators...”

Clarification requested: Please define the term “facility”. Does it refer to a collection center or to the blood establishment (i.e., the corporate establishment under which there may be multiple collection centers that use the same SOPs, training, and share the same management/medical structure).

Page 11, D. Product Performance Qualification (Component Collection)

Residual WBC count is performed within 24 hours of collection, or per the manufacturer’s directions for the cell counting methodology (Ref 2);

Comment: It is not clear whether the “within 24 hours of collection” is 24 hours from collection of product from the donor or from the collection of the sample from the product.

Recommendation: Suggested rewording: “Follow the manufacture’s directions or in house validation for maximum time window prior to testing.”

Page 11-12, PROCESS VALIDATION, D. Product Performance Qualification (Component Collection),

General comment:

The description provided on pages 11 and 12 of the collection performance qualification criteria are central to activities of the blood establishment, 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. We believe these criteria as described are confusing, sometimes overly burdensome, and in some cases incorrect. 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 some systems a single therapeutic dose can and at times must be held in more than one container to preserve the proper storage conditions.

Recommendation: We have presented some specific comments on the FDA text. A recommended format and criteria change are presented in Appendix B.

Text with comments:

“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.”*

Comment: There are no specifications for “visible RBCs” in the platelets; therefore, this should be dropped from the list of performance criteria. How this paragraph would be

implemented is confusing. AABB Standard 5.14.5 requires a crossmatch 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. In addition, we would like to stress that bacterial contamination testing on 500 collections is particularly burdensome. It would take smaller collection facilities a year or more to reach this number.

Recommendation: Replace this bullet as suggested in Appendix B.

Additional Comment: This example is confusing in that it is not clear exactly how many consecutive collections must be tested if single, double and triple products are being collected. Also, please clarify if the testing of 60 consecutive collection should be applied to each collection location or to products collected by the blood establishment (which might include several collection locations).

Recommendation: Suggested rewording: “If single, double and triple products are being collected, a minimum of 60 consecutive collections which include a representative sample of single, double, and triple products from each type of automated blood cell separator device used by the blood establishment, should be tested for actual platelet yield, volume, and concentration. See Attachment B for acceptance criteria.”

- *“For facilities using automated blood cell separators from a single manufacturer only, we recommend that:*
 - *All devices be included in the initial product performance qualification; and*
 - *Additional devices of the same model be included in monthly QC testing only.*
- *Product performance qualification should be completed for each automated blood cell separator used in your establishment.”*

Comment: The agency should clarify their meaning of facility. Does this refer to a collection center at one geographic location or to the blood establishment (i.e., the corporate establishment under which there may be multiple collection centers using the same SOPs, training, and share the same management/medical structure)?

Automated collection processes are defined by the device manufacturer, device model and software version. Therefore, initial performance qualification should be performed by device manufacturer, device model and software version. There are situations where a facility may have devices from only one manufacturer but 3 or 4 different device models and/or software versions (e.g., Trima Accel version 5.0 and 5.2).

The terms “facility” and “establishment” may not provide enough clarification. In the context of process validation, we believe this activity need not be performed for each fixed site provided that all sites operate under the same standard operating procedures, training program, etc.

Recommendation: Replace the above 4 bullets with “Product performance qualification should be completed for each automated blood cell separator (defined device manufacturer, device model and software version) used in your establishment. All devices should be included in the initial product performance qualification; and devices added following the initial qualification of the device manufacturer, device model and

software version should be included in monthly QC testing only. 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, products collected from the new devices would be immediately included in the monthly QC process.”

“Testing be conducted on both containers from double collection and on all three containers for triple collection;”

Comment: This statement is confusing in that it implies that a WBC count and test for bacterial contamination must be performed on both products from a double collection and all three products from a triple collection, rather than testing a single sample from the initial product. For pH testing, it implies that both products from a double collection and all three products from a triple collection must be tested, rather than testing a sample from one of the double products and one of the triple products respectively. Testing all of the products from a double and/or triple collection for WBC, bacterial contamination, and pH is not a reasonable test plan.

Recommendation: See the proposed Table 1 in Appendix B.

“Qualification include Platelets, Pheresis collection by all trained personnel;”

Comment: This phrase does not clearly express the intent of the agency.

Recommendation: Move this bullet to section “C. Process Performance Qualification (Operator)” competency.

“Residual WBC count be performed within 24 hours of collection, or per the manufacturer’s direction for the cell counting methodology (Ref. 2);”

Comment: No manufacturer currently requires processing within 24 hours. As stated, 24 hours will be interpreted as the maximum time, and will impose an undue burden on some blood establishments.

Recommendation: Maintain the wording from Ref. 2, “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.”

“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;”

Comment: There are no specifications associated with residual RBC in platelet products; therefore, 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.

Recommendation See the proposed Table 1 in Appendix B.

“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.”

Comment: Storage characteristics with pH outcomes have been well studied and described by manufactures during FDA clearance/approval processes. As reported in Reference #6, 1 pH failure out of 24 might be expected at outdate. Therefore, the target criteria for process validation should not impose too strict of a burden on the blood establishment.

Recommendation: We recommend the AABB standard of pH (22°C) ≥ 6.2 in 90% of samples tested or pH (22°C) ≥ 6.2 in 90% of samples tested with a 90% confidence. Furthermore, we believe pH monitoring for qualification purposes may be conducted concurrently with implementation of the preparation method. See the proposed Table 1 in Appendix B.

*“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.”*

Comment: Interpretation of a positive bacterial test that may be from a transient bacteremic donor may prove to be difficult.

Recommendation: We suggest that additional specific examples of “non-process failures” would be helpful in interpreting and applying this concept in concrete terms.

Yield-

Comment: As is well known in the industry and to the agency, 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. Therefore, the state-of-the-art inter-laboratory accuracy of this outcome over the entire country 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 call out 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.

Recommendation: We propose the criteria for a therapeutic dose be 90% $\geq 3.0 \times 10^{11}$ (reflecting the industry approach to platelet yield in AABB Standards) or 90% $\geq 3.0 \times 10^{11}$ with a 90% confidence. See the proposed Table 1 in Appendix B.

Volume -

“Double collections: each container contains 50% +/- 5%. Triple collections: each container contains 33% +/- 3%.”

Comment: It is not clear what the agency intends with the volume criteria. Perhaps the agency means that the net volume of the 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? The agency has not clarified its rationale for the tolerances given. 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.

Recommendation: We propose there should be no volume specification for divided products beyond the manufacturer's criteria for storage containers and minimum therapeutic dose for products with 3×10^{11} platelets. We further recommend the target criteria be 90% compliance with 90% confidence. See the proposed Table 1 in Appendix B.

RBC Content –

Comment: Red blood cell count is not associated with any specification.

Recommendation: Drop from the qualification testing criteria.

pH -

Comment: Storage characteristics with pH outcomes have been well studied and 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.

Recommendation: We recommend 90% pH (22°C) ≥ 6.2 (as currently required by AABB Standards) or 90% pH (22°C) ≥ 6.2 with a 90% confidence. Furthermore, we believe pH monitoring for qualification purposes may be conducted concurrently with implementation of the preparation method. pH should be evaluated over the first 2 months of use. See the proposed Table 1 in Appendix B.

Bacterial Contamination -

Comment Bacterial contamination risk has been described, and industry standards (AABB) have provided clear direction on prevention and detection strategies. Therefore, we believe bacterial testing for qualification purposes may be conducted concurrently with implementation of the preparation method. Bacterial testing should be conducted according to industry standard. 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: See the proposed Table 1 in Appendix B.

**(Page 11) PROCESS VALIDATION, D. Product Performance Qualification
(Component Collection)**

“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 (Table 1).

Comment: Some of these outcomes should be evaluated by collection and others by therapeutic dose as indicated in the Table 1 in Appendix B.

“Product performance qualification should be completed for each automated blood cell separator used in you establishment.”

Recommendation: “Product performance qualification should be completed for each automated blood cell separator (defined as device manufacturer, device model, and software version) used in your establishment. All devices in use at the time of qualification should be included in the initial product performance qualification; and

products from new devices from the same manufacturer and of the same device model/software version that are added following the initial qualification, should be included in monthly testing only.”

*“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.”*

Recommendation: See the proposed Table 1 in Appendix B.

VII. QUALITY ASSURANCE (QA) AND MONITORING

A. Standard Operating Procedures (SOPs) and Record Keeping

2. Additional Provisions Applicable to SOPs

Page 13, E. Re-qualification/Re-validation

“Exceeding the allowable process failures of the collection process qualification may indicate that the process is not in control. You must investigate and correct the source of the failure and complete the collection process qualification in its entirety.”

Comment: If the root cause of the nonconformance cannot be identified, making a change may not solve the problem & may compound the problem. Also, please standardize the terms used to describe the various sections of process validation, (i.e., *collection process qualification* does not coincide with the previous wording - *Product Performance Qualification (Component Collection)*).

Recommendation: re-word: “Exceeding the allowable process failure rate limit of the Product Performance Qualification may indicate that the process is not in control. Document the investigation, the actions taken to identify the root cause of the failure, and your findings. If the root cause is identified, document the actions taken to correct the issue. Repeat the Product Performance Qualification.”

Page 13

...determined by analyzing the day-to-day process and the data for conformance with the manufacturer’s specifications and for variability.”

Comment: Conformance to manufacturer’s specifications is only part of the expectations for a process. Conformance to federal, state and local regulations, and facility defined limits and ranges should also be taken into account.

Recommendation: re-word - Quality Assurance and Monitoring -determined by analyzing the day-to-day process and the data for conformance with federal, state, and local regulations; facility defined limits and ranges; as well as manufacturer’s specifications and for unexpected variability.

Page 14, A. Standard Operating Procedures (SOPs) and Record Keeping, Additional Provisions

Your written SOPs must include minimum and maximum values for a test or procedure when it is a factor in determining donor acceptability (21 CFR 606.100(b)(2)).

Comment: To date, there have never been minimum values for donor temperature, maximum donor weight or minimum/maximum height.

Recommendation: 21 CFR 606.100(b)(2) be updated to reflect current practice.

Page 15. Actual platelet yield:

“The platelet yield from each collection of Platelets, Pheresis should be provided to the transfusion facility.”

Comment: This is an example of the inconsistency presented by the agency when describing product(s) per collection or per therapeutic dose. We assume the agency intends to state per therapeutic dose. 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 the care given the patient. The platelet content is available upon request of the clinical facility. We agree that the actual platelet yield should be recorded on the product if it is labeled with the “variable content” label.

Recommendation: Suggested rewording: “The platelet yield should be recorded on the label of each apheresis platelet product with ‘variable’ contents. The platelet yield should also be available for each apheresis platelet product upon request.”

Page 15. Residual WBC counts:

“Your SOP should state the maximum acceptable WBC limits for each automated blood cell separator device in use.”

Comment: The maximum acceptable residual WBC limit for apheresis platelets as established by AABB standards and is 5×10^6 per unit or transfusable dose. (13) The device manufacture claim of the instrument capability should have no relevance in how the final product is labeled. Stating the device claim in a blood establishment SOP would only cause confusion.

Recommendation: Change to “Your SOP should state the maximum acceptable WBC limits for the blood component collected.”

Page 15. Leukocyte reduction filters:

“CBER clears filters used to reduce leukocytes in Platelets, Pheresis for the filtration of specific components. You should use in-line or in-process leukocyte reduction filters.”

Comment: We recognize that the agency is attempting to clarify the need to use the correct filter for leukocyte reduction. However, we find this statement confusing.

Recommendation: Reword these sentences: “CBER clears filters used to reduce the number of leukocytes in Platelets, Pheresis. If filtration is required to leukoreduce an apheresis platelet product, use only leukoreduction filters cleared for this purpose.”

**Page 15, A. Standard Operating Procedures (SOPs) and Record Keeping,
Additional Provisions**

“Total volume loss: 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 donor weighing more than 175 lbs.”

Comment: We assume that this section is referring to plasma loss.

Recommendation: re-word: “Total *plasma* volume loss: Annual *plasma* volume loss for an ‘infrequent’ donor 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 donor 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 plasma volume loss.”

Page 15 - 16, A. Standard Operating Procedures (SOPs) and Record Keeping, Additional Provisions

Performance specifications: State the acceptable tolerance specifications for the volumes, platelet concentration, and/or actual platelet yield for each component collected (single, double, triple) as described by the manufacturer. You should have a procedure addressing the handling of components that exceed the manufacturer’s limitations.

Comment: 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 specification for the component collection/storage container. Specifications for the actual component are regulated by federal, state and local agencies. It would be helpful to modify the section title to clarify the intent.

Recommendation: re-word- “Collection/storage container specifications: 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.”

Page 16, A. Standard Operating Procedures (SOPs) and Record Keeping, Additional Provisions

Component Storage and Shipping: 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 manufacture.

Comment: 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 standard component being provided to the consumer, and allows for a standard 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, because 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 manufacture 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: re-word- “If sterile docking of an additional container is necessary, use a container designed to achieve and protect a sterile conduit. Use containers designed for storage of the blood component.”

**Page 16, A. Standard Operating Procedures (SOPs) and Record Keeping,
Additional Provisions**

Deviation: Deviations associated with the manufacturing, testing, processing, packing, labeling or storage, holding or distribution must be reported for distributed products as described in 21 CFR 606.171(b)(1)(i) and (ii). FDA has issued a draft guidance on deviation reporting (Ref 20). You should consult the guidance when it is finalized.

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

Recommendation: re-word: 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.

Page 16, Component Storage and Shipping:

“You should include the recommended shipping procedure including temperature and time for Platelets, Pheresis.”

Comment: This is unclear.

Recommendation: Perhaps the agency intends to say; “You should include the recommended shipping procedure which includes the acceptable temperature range and allowable transit time (i.e., time off of the agitator) for Platelets, Pheresis?”

Page 17, B. Donor Monitoring

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

Comment: This review can be effectively performed using the pre-donation platelet counts of the donor platelet count. We disagree that donation platelet counts should be performed after donation. The agency has not presented any data to support this extra step and how it would correct a demonstrated health risk to the donor, as discussed previously.

Recommendation: We Recommend the following wording, “Determination of donor post donation platelet counts is not required. However, if a post donation platelet count is

suspected 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.”

Page 17, B. Standard Operating Procedures (SOPs) and Record Keeping, Donor Monitoring

Red Blood Cell Loss – Per Collection: - *If the RBCs cannot be returned to the donor, you should determine the absolute RBC loss.*

Comment: The title (RBC loss - Per Collection) implies that the RBC loss must be calculated for both successful and incomplete procedures. The actual text in the Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods, Feb 2001, (which this table appears to be summarizing) refers only to incomplete procedures. It will cause great confusion if the two documents differ in what they require.

Recommendation: re-word – “Red Blood Cell Loss – Discontinued Collection Procedures: - If the RBCs cannot be returned to the donor, you should determine the absolute RBC loss for the discontinued procedure.”

Page 17, B. Standard Operating Procedures (SOPs) and Record Keeping, Donor Monitoring, Table 2: RBC loss per collection

Donor’s <u>Initial</u> packed RBC loss	Donor’s <u>Second</u> packed RBC loss	Elibility
Less than 200 mL	No donation or none lost	Donor eligible to donate within 8 weeks
Less than 200 mL	<100 mL (total loss is <300 mL)	Donor eligible to donate for 8 weeks from 2 nd loss
More than 200 mL but less than 300 mL	NA	Donor is not eligible to donate for 8 weeks
300 mL or more of RBCs	NA	Donor is not eligible to donate for 16 weeks

Comment: The title implies that the RBC loss must be calculated for both successful and incomplete procedures. The actual text in the Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods, Feb 2001, (which this table appears to be summarizing) refers only to incomplete procedures. It will cause great confusion if the two documents differ in what they require.

Recommendation: Revise the table:

Table 2: RBC loss due to an incomplete apheresis platelet procedure

Donor’s <u>Initial</u> packed RBC loss due to an incomplete procedure	Donor’s <u>Second</u> packed RBC loss due to an incomplete procedure within 8 weeks	Elibility
Less than 200 mL	No donation or successful subsequent apheresis platelet donations for 8 weeks from date of initial loss	Donor eligible to donate within 8 weeks
Less than 200 mL	<100 mL (total loss is <300 mL)	Donor eligible to donate

		for 8 weeks from 2 nd loss
More than 200 mL but less than 300 mL	NA	Donor is not eligible to donate for 8 weeks
300 mL or more of RBCs	NA	Donor is not eligible to donate for 16 weeks

Page 18, Total plasma volume loss per 12 months:

”The maximum volume (excluding anticoagulant) collected from a donor during a 12-month period should not exceed (Ref. 3): 12 liters (12,000 mL) for donors weighing 110 – 175 lbs; 14.4 liters (14,400 mL) for donors weighing more than 175 lbs”

Comment: We assume that these limits include the plasma volume in the platelet product.

Recommendation: re-word: *”The maximum plasma volume (excluding anticoagulant) collected from an ‘infrequent’ donor during a 12-month period should not exceed (Ref. 3): 12 liters (12,000 mL) for donors weighing 110 – 175 lbs; 14.4 liters (14,400 mL) for donors weighing more than 175 lbs. Plasma in both the apheresis platelet components as well as the concurrent plasma components should be included in this total volume loss.”*

Page 18, Component Testing, 1. Daily component specification check

“Actual platelet yield after collection: Actual yields (volume x platelet count) must be determined at the conclusion of each appropriate phase of manufacturing (21 CFR 211.103), and should be determined prior to issue.”

Comment: 21 CFR 211.103 specifically refers to finished pharmaceuticals. Platelets, Pheresis are a biologic product. We believe this requirement is misplaced 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 resource. We do agree that the yield of the product should be determined prior to issue.

Recommendation: We recommend rewording this statement to *“Actual yields (volume x platelet count) should be determined prior to issue.”*

Bullet: *“Weight/volume conversion: A weight/volume conversion is necessary to determine the volume.”*

Comment: This statement may be overly restrictive for new technologies.

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

Page 19, “Residual WBC counts on all collections that do not utilize an automated leukocyte reduction methodology.”

Comment: We disagree that this should be required. Universal leukocyte-reduction is not required either by statute, rule or industry standard in the United States. Therefore, there could be a method (and currently are methods) to produce platelets, pheresis and co-

products that do not employ an automated leukocyte reduction methodology. There should not be a requirement to determine WBC content of each of these products. This will negatively impact platelet availability. Further, there are instances of platelets, pheresis and co-products 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. Would the agency also then apply this requirement (100% testing) for all blood products that are leukocyte-reduced by non-automated methods?

Recommendation: We recommend this requirement be deleted.

Page 19, *“Bacterial contamination testing: as specified by the collection device manufacturer.”*

Comment: Collection device manufacturers do not require bacterial contamination testing (e.g., method and frequency). Bacterial testing is required by industry standard (AABB), and in some instances (e.g., 7-day platelet storage) specified by the device manufacture. However, this is not universal and not a requirement for device approvals/clearances. This statement is also unclear as to which components it applies – platelets and all co-components?

Recommendation: We recommend this statement be modified to “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 manufactures.”

Page 20, Acceptance criteria:

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

Comment: This rate is based on dated surveillance data. Current methods employed in the United States will be using specified sample volumes and anaerobic and aerobic culture methods. The baseline positive rates for these testing schemes have not yet been determined; therefore it is inappropriate to specify an action level for the blood center.

Recommendation: Reword - “Product bacterial contamination testing: Rates of bacterial contamination of platelet pheresis should be monitored. The facility should set alert and action levels for positive rates based their detection methods. There should be a plan established for investigation of rates exceeding expected levels.”

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13. California Blood Bank Forum E Network

If a CBC before plateletpheresis reveals an abnormal WBC count, should the donor be deferred?

Ira Schulman

<http://www.cbbsweb.org/enf/2001/wbcpltppher.html>

June 2001

APPENDIX A

CHANGES IN PLATELET COUNTS FOR FREQUENT APHERESIS PLATELET DONORS

We examined electronic donation records from one large blood center for the period December 5, 2004, through December 5, 2005. All personal identifiers had been removed from the database. In this 12 month period, 1535 donors sat for 6371 donation sessions resulting in 10,621 therapeutic doses of apheresis platelets; therapeutic dose being defined as Trima predicted final yield $3.0\text{-}5.9 \times 10^{11}$ platelets. The number of donation sessions resulting in various quantities of therapeutic doses were: triple platelet products 992 (15.6%), double platelet products 2743 (43.1%), single platelet product 2199 (33.9%) and less than 3×10^{11} platelets in 477 sessions (7.5%). Maximum donation sessions per year was 24 for any given donor.

We examined donors presenting for 8 or more donation sessions in the 12 month period to determine the effect frequent donation of apheresis platelets has on pre-donation platelet counts. Two hundred eighty-five (285, 18.6%) individuals had at least 8 donation sessions over the one year period as shown in Table 1.

Platelet counts over time for individual donors are shown for donation frequencies of 18 and 23 sessions in the period (Figures 1 and 2). To test the hypothesis that platelet count changed over the period, we fit platelet count to a mixed linear model with time, sessions per year, products per donation as fixed effects. Donor and time were random effects. The change in platelet count over the donation interval was tested by examining the slope shown as the estimated coefficient for DAYS in Table 2. As shown in Tables 2 and 3, there is no significant change in donor platelet count over this period when adjusted for the number of platelet products per donation and the number of donations in a year ($p=0.5386$).

While the overall average donor platelet counts for frequent donors did not change over the 12 month period, we were also interested in the effects in specific donors. We examined the data set for individual donors whose platelet counts either significantly decreased or increased over the period ($p > 0.1$). Six out of 285 donors (2.1%) had estimated decreases of 40,900 platelets over a 365day period. Ten (10) donors (3.5%) had increasing platelet counts over the period averaging 65,500 platelets/ μL over 365 days. These donors' donation histories are summarized in Table 4, and platelet counts are shown in the Figures 3 and 4.

Therefore, we conclude donor platelet counts may increase or decrease over a period of frequent donation history for a small percentage of donors, 5.6% in this data set. The change in platelet count over time is independent of both donation frequency and the number of therapeutic doses donated per session. The changes are small and are easily monitored using the pre-donation platelet count.

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Table 1: Donors having at least 8 donation sessions over the 12 month period are shown by the number of sessions and average number of therapeutic doses per donation. Six individuals had decreasing platelet counts and 10 had increasing counts over the period.

Donor Sessions in 12 months	Number of donors	Average therapeutic platelet doses per session	Donors with decreasing platelet count	Donors with increasing platelet count
8	39	1.7		2
9	49	1.6		1
10	28	1.5		
11	36	1.6		1
12	27	1.6		1
13	19	1.8		
14	13	2.0	2	
15	8	1.7		
16	10	2.2		1
17	9	2.0		
18	11	2.2	2	1
19	5	1.9		
20	10	2.2	1	1
21	5	2.1		
22	7	2.2		1
23	5	2.4	1	1
24	4	2.5		

Table 2: Regression solution for the effect of time in days, number of donations (donations) and number of platelet products per donation (NoProducts) on donor platelet count over a 12 month period. The interaction effects of donations*days and noproducts*days were insignificant and eliminated from the final model. There is no overall effect on donor platelet count over the 12 month period as shown by p=0.5386 for days. Zero (0) platelet products are for sessions which resulted in total yield less than 3×10^{11} platelets.

Effect	Platelet Products per Session	Estimate	SE	DF	P
Intercept		246.3	8.9	283	<.0001
DAYS		-0.0026	0.0041	284	0.5386
DONATIONS		1.9	0.6	2981	0.0027
NoProducts	0	-34.8	7.0	2981	<.0001
NoProducts	1	-27.9	5.5	2981	<.0001
NoProducts	2	-6.3	4.1	2981	0.1285
NoProducts	3	0			
Donations*NoProducts	0	0.36	0.48	2981	0.4566
Donations*NoProducts	1	-0.50	0.36	2981	0.1594
Donations*NoProducts	2	-0.66	0.25	2981	0.0071
Donations*NoProducts	3	0			

SE – standard error

DF – degree of freedom

Table 3: Test of significance for the effects of the regression model independent variables on donor platelet count. The interaction effects of donations*days and noproducts*days were insignificant and eliminated from the final model. There is no overall effect on donor platelet count over the 12 month period as shown by p=0.5386 for days. The significant effects of the other variables indicate only a difference in the initial (day 0) platelet count of the donor and not changes over time.

Effect	ndf	ddf	F Value	p
DAYS	1	284	0.38	0.5386
DONATIONS	1	2981	7.86	0.0051
NoProducts	3	2981	16.33	<.0001
Donations*NoProducts	3	2981	3.83	0.0095

Table 4: Donation history of donors with significant increase or decrease in platelet counts over the 12 month period. The change in platelet count is from linear regression solution for the donor times a period of 365 days.

Donor	Sessions in period	Average platelet products per session	Platelet count change (x1000/ μ L per 365 days)
3302031	16	2.9	+ 63
3606461	8	1.5	+ 64
4733347	12	2.7	+ 63
11717620	9	2.7	+ 63
12661511	18	2.9	+ 73
41735677	20	1.9	+ 50
45066765	23	2.4	+ 69
55314716	8	3.0	+ 68
72411160	11	3.0	+ 72
76500631	22	2.9	+ 70
366043	23	1.9	- 40.9
3200104	18	1.6	- 40.9
12211775	14	2.9	- 40.9
15114244	20	2.6	- 40.9
41564021	14	2.1	- 40.9
55667611	18	2.5	- 40.9

Figure 1: Platelet count for 11 donors with 18 donation sessions in a 12 month period. Day 0 is the donor's first session of the period. Platelet counts are x1000/ μ L. Donor 12661511 had an increasing platelet count. Donors 3200104 and 55667611 had decreasing platelet counts. These 3 donors are also presented in Figures 3&4.

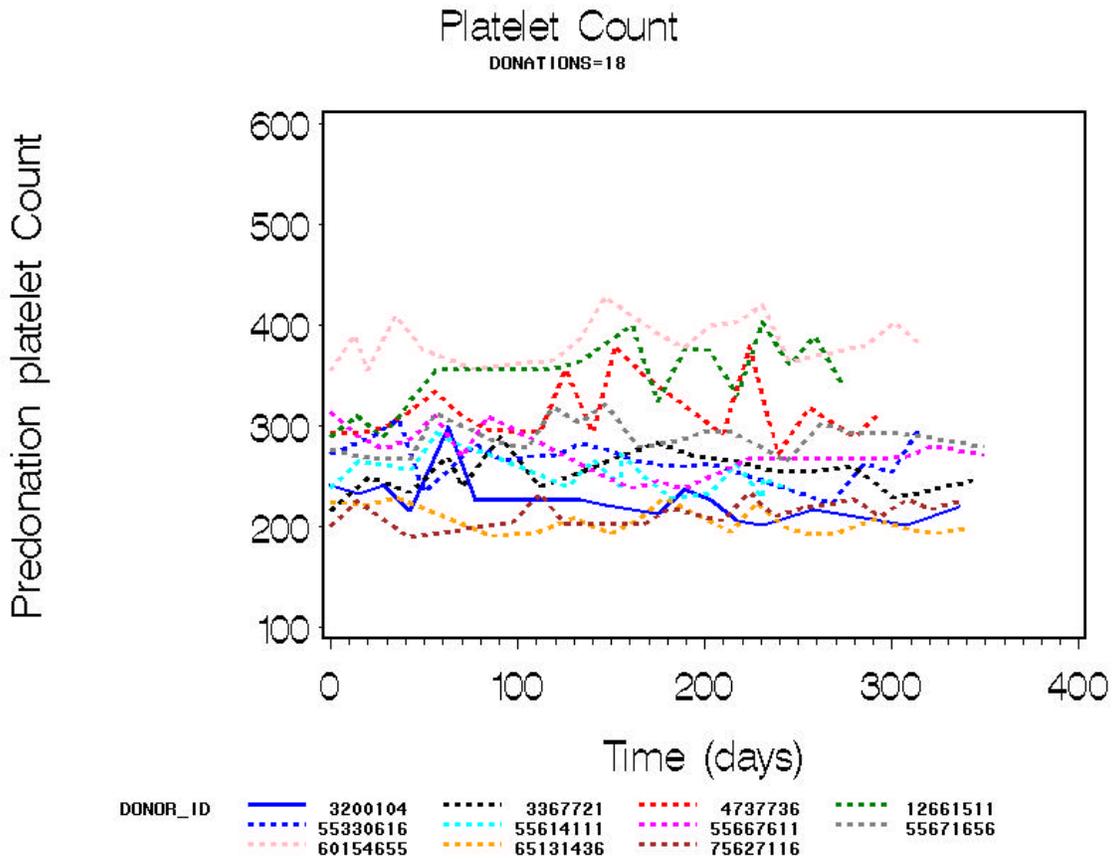


Figure 2: Platelet count for 5 donors with 23 donation sessions in a 12 month period. Day 0 is the donor's first session of the period. Platelet counts are x1000/ μ L. Donor 45066765 had an increasing platelet count. Donor 366043 had decreasing platelet counts. These 2 donors are also presented in Figures 3&4.

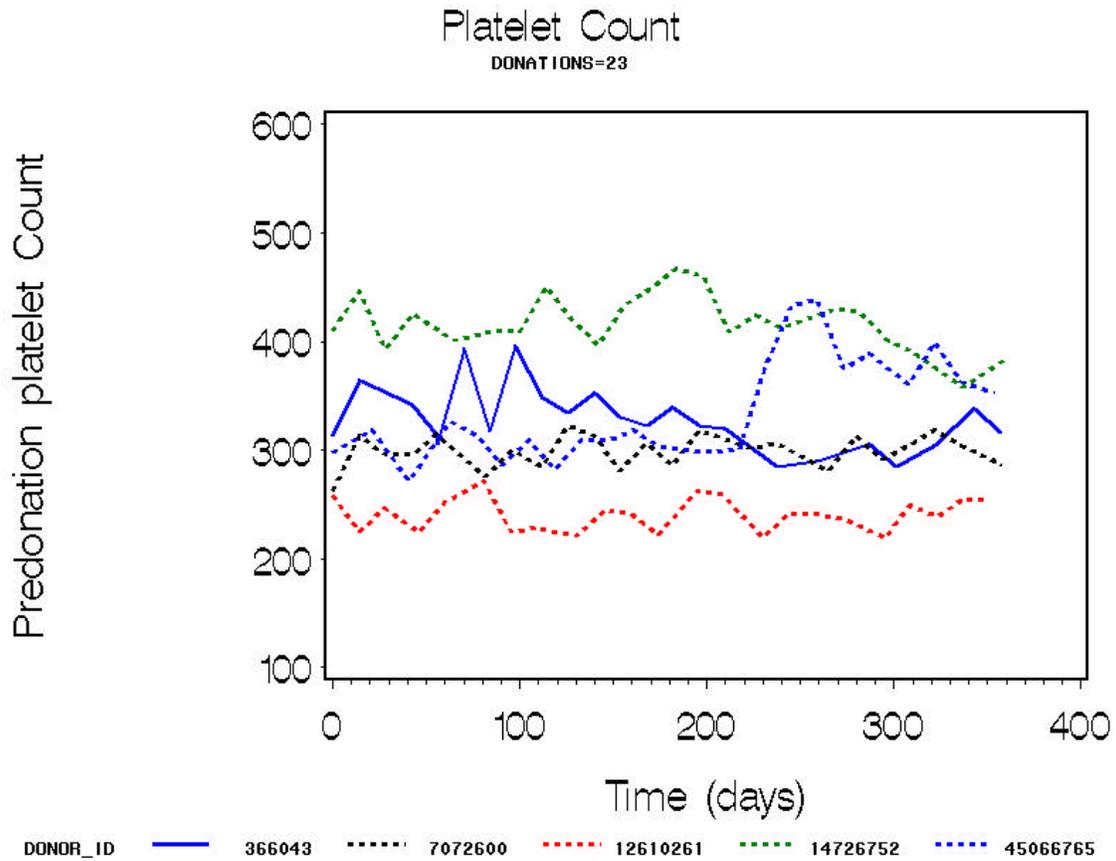


Figure 3: Six donors (2.1%) with significant platelet count decrease over the 12 month period. Overall average of 40,900 platelets/ μL for 365 days. Day 0 is the donor's first session of the period. Platelet counts are $\times 1000/\mu\text{L}$.

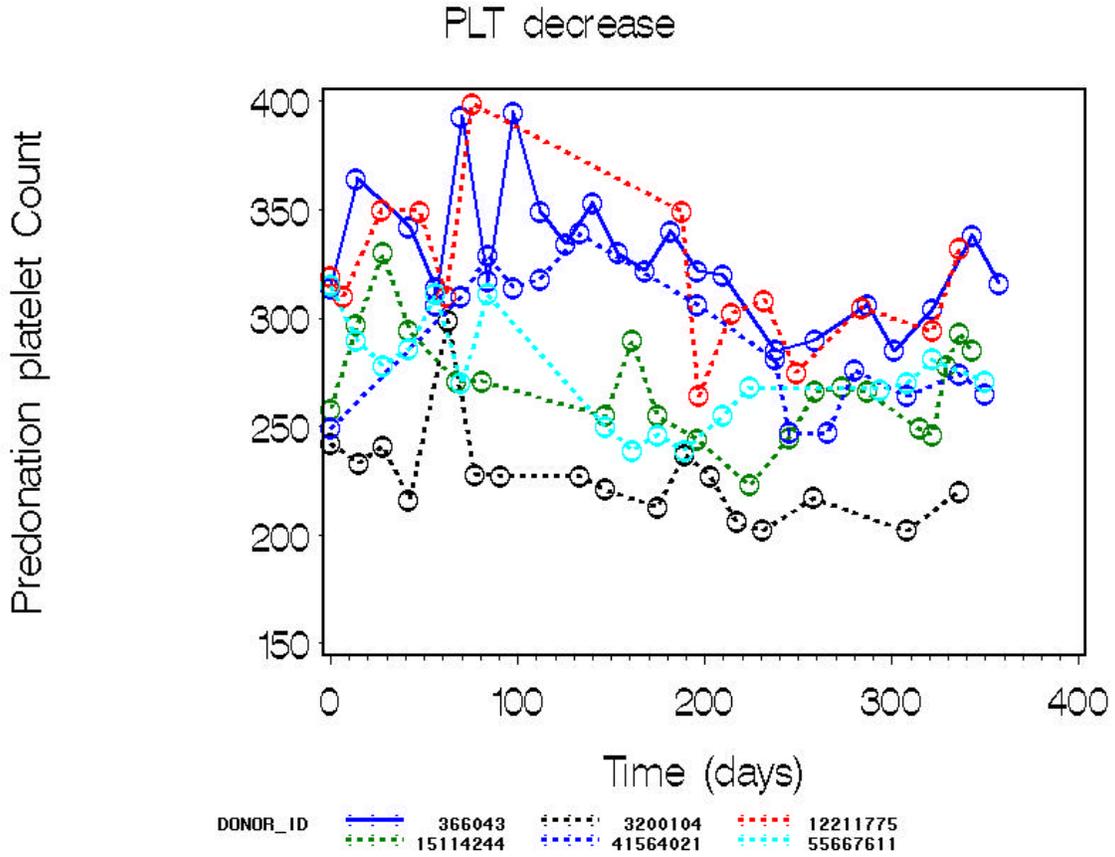
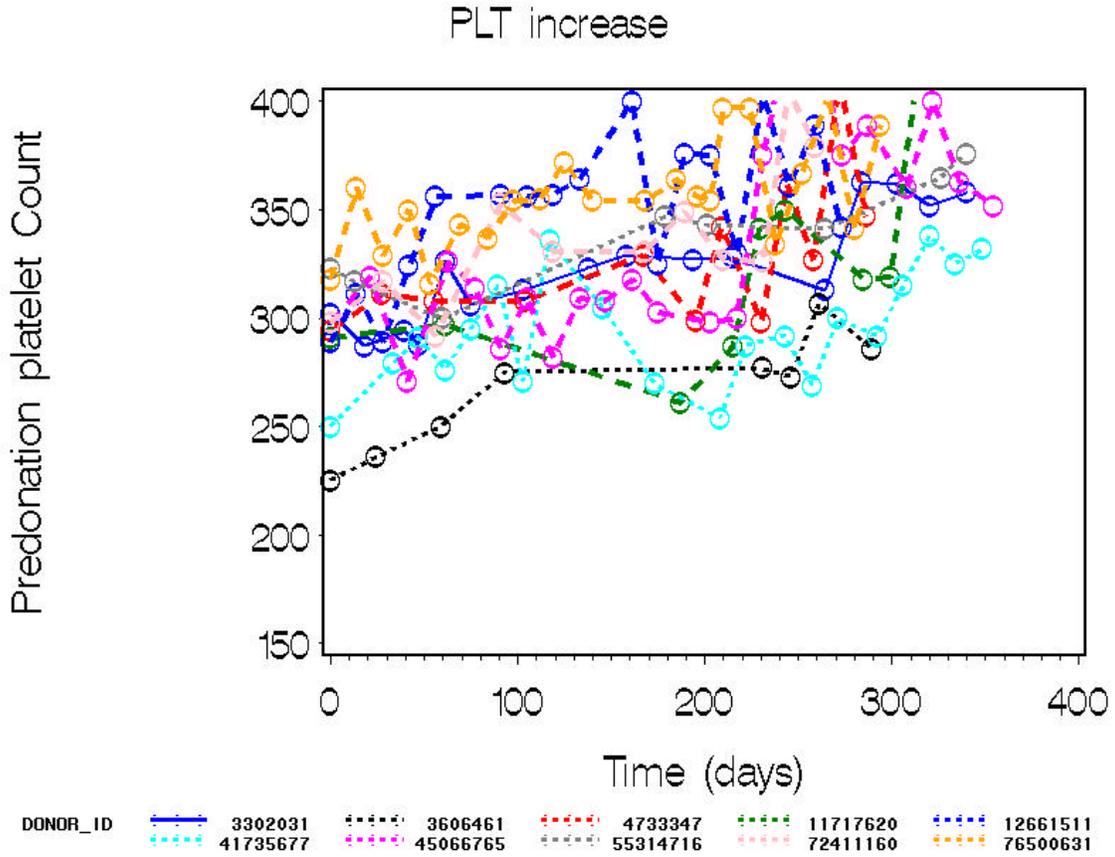


Figure 4: Ten donors (3.5%) with significant platelet count increase over the 12 month period. Overall average of 65,500 platelets/ μL for 365 days. Day 0 is the donor's first session of the period. Platelet counts are $\times 1000/\mu\text{L}$.



APPENDIX B

Table 1. Collection Performance Qualification Criteria

Outcome	Unit of Evaluation	Performance Criteria	Target	Acceptance Criteria^{1, 2} (# Products / # failure)	
Platelet yield	Per therapeutic dose	> 3x 10¹¹ 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 content³	Per therapeutic dose	£ 5 x 10⁶	95/95	60/0	93/1
% recovery following leukocyte-reduction⁴	Per therapeutic dose	≅ 85% original component retention	95/95	60/0	93/1
pH_{22°C}	Per therapeutic dose	100% [≅] 6.0 and 90% [≅] 6.2 (per AABB) or 90%/90% [≅] 6.2		2 month QC 10/1 22/0	2 month QC 10/1 38/1
Bacterial contamination	Per collection	No growth	See note	2 month testing⁶	

1. Samples should be stratified over single, double, and triple collection procedures as applicable. Total sample size and acceptance criteria should be selected prior to initiation of validation (e.g., 60 collections 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 or 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 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 therapeutic dose would be stratified over single, double and triple collections.
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 and reported for the first 2 months of use. Action limits to initiate an investigation of component qualification failure should be based on current industry reported positive rates for the testing method used.