

Guidance for Industry and FDA Review Staff

Collection of Platelets by Automated Methods

DRAFT GUIDANCE

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For questions on the content of this guidance contact Dr. Sharyn Orton, Division of Blood Applications, at 301-827-3524 or Dr. Jaroslav Vostal, Division of Hematology, at 301-496-2577.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Guidance for Industry and FDA Review Staff

Collection of Platelets by Automated Methods

Paperwork Reduction Act

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The information collection provisions in this guidance are under FDA's regulations at parts 211, 601, 606, 610, and 640 (21 CFR parts 211, 601, 606, 610, and 640). Part 211, subpart J (Records and Reports) was approved under OMB control number 0910-0139; part 606, subpart I (Records and Reports) was approved under OMB control numbers 0910-0116 and 0910-0458. Sections 606.100(b) and (c), 606.110(a), 606.121, 606.122, 640.25, and 640.27 were approved under OMB control number 0910-0116; §§ 211.22, 211.80, 211.100(b), and 211.160 were approved under OMB control number 0910-0139; § 610.2 was approved under OMB control number 0910-0206; and §§ 601.12 and 610.60 were approved under OMB Control No. 0910-0338.

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Collection of Platelets by Automated Methods

This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance provides to you, blood establishments, and FDA staff revised recommendations for the collection of Platelets by automated methods (plateletpheresis). It is intended to help you ensure donor safety and the safety, purity, and potency of Platelets collected by an automated blood cell separator device. For the purpose of this document, Platelets collected by automated methods will be referred to by the product name “Platelets, Pheresis.” We consider the recommendations in this guidance document to provide appropriate criteria for a biologics license application or supplement for manufacturing Platelets, Pheresis, and provide guidance on preparing a manufacturing supplement for Platelets, Pheresis under 21 Code of Federal Regulations (CFR) 601.12. When finalized, this draft guidance will replace the October 1988, “Revised Guideline for the Collection of Platelets, Pheresis” (Ref. 1).

This draft guidance applies only to Platelets, Pheresis components collected by automated methods and resuspended in plasma; this guidance does not pertain to plateletpheresis components collected concurrently during apheresis granulocyte collection procedures or plasma reduced apheresis platelets.

Platelets are no longer prepared from plasmapheresis as described in 21 CFR 640.22(b). Accordingly, the regulations applicable to platelets prepared from plasmapheresis (see, for example, 21 CFR 640.21(b), 640.22(b)) are not applicable to Platelets, Pheresis.

FDA’s guidance documents, in general, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA’s guidances means that something is suggested or recommended, but not required. Insofar as this guidance adjusts reporting categories for manufacturing changes pursuant to section 506A of the Federal Food, Drug, and Cosmetic Act and 21 CFR 601.12, it does have binding effect. If you have any questions about the effect of any portion of this guidance, contact Sharyn Orton, PhD, Center for Biologics Evaluation and Research, Office of Blood Research and Review, Division of Blood Applications, at 301-827-3524.

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II. DISCUSSION

A. Background

Plateletpheresis is the routine collection from a single donor of platelets using an automated blood cell separator device (device). Collection of Platelets by apheresis methods results in a high yield of platelets collected from a single donor. Transfusion of Platelets, Pheresis provides an effective component for treating thrombocytopenic patients while limiting the recipient's exposure to platelets from multiple donors. In recent years, many improvements have been made in automated blood cell separator technology and blood cell counting methods, including:

- Collection process efficiency;
- Storage container characteristics; and
- Accuracy of methods for determining a donor's pre-donation platelet count and component yields.

Automated blood cell separator devices are now capable of various plateletpheresis collection procedures including but not limited to the following:

- Collection of double and triple platelet components obtained during a single procedure;
- Use of in-process leukocyte reduction (Ref. 2);
- Collection of concurrent plasma components (Ref. 3); and
- Collection of concurrent Red Blood Cell components (Ref. 4).

We provide in this guidance recommendations for collecting components by these procedures. This guidance applies to collection by automated methods of the following components:

- Platelets, Pheresis (single, double, and triple collections)
- Platelets, Pheresis Leukocyte Reduced (single, double, and triple collections)
- Plasma (concurrent)
- Plasma, Leukocytes Reduced (concurrent)
- Source Plasma (concurrent)

We have new information since the issuance of our previous guidelines. Following are the changes from our prior recommendations:

- Published research indicates that there is poor recovery of viable platelets stored at a pH of less than 6.2 (Refs. 5 and 6). Therefore, in addition to the pH requirement as defined in 21 CFR 640.25(b)(2), you should include additional criteria at the time of process validation and quality control (QC) testing for Platelets, Pheresis to include evaluation of pH at 6.2.

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- You should include additional deferral of Platelets, Pheresis donors for medication use (Ref. 9).
- Because of similarities between plateletpheresis and Source Plasma donation, you should follow the weight requirements for Source Plasma donors under 21 CFR 640.63(c)(6).
- Quality control testing described in 21 CFR 640.25(b)(1)-(3) contains requirements that each month four units prepared from different donors be tested at the end of the storage period for the platelet count, pH of not less than 6.0 measured at the storage temperature of the unit, and the volume. In addition, 21 CFR 211.160(b) requires that laboratory controls include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. We identify the use of “scan statistics” as one method to comply with this regulation.

Because of the continuing problem of bacterial contamination of blood components and associated transfusion risks (Refs. 7 and 8), we continue to believe that bacterial contamination testing is a necessary part of process validation and quality assurance monitoring.

B. Definitions

For purpose of this guidance, the following definitions apply:

Automated blood cell separator device – A device operating on a centrifugal or a filtration separation principle that automatically removes whole blood from a donor, separates the blood into components (red blood cells, white blood cells, plasma, and platelets), retains one or more of the components, and returns the remainder of the blood to the donor (see 21 CFR 864.9245).

Actual platelet yield – The total platelet yield in the component, calculated by multiplying the platelet count of the sample times the volume of the component.

Apheresis – Automated blood collection in which a device repeatedly removes a small volume of whole blood, separates the components by centrifugation, and returns certain components to the donor.

Bacterial contamination testing – Testing conducted to determine whether a product is free from viable contaminating organisms in platelets collected using automated methods.

Component – A part of a single donor's blood, such as platelets, separated from whole blood by physical or mechanical means. For Platelets, a component is a transfusable

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product that may result from a single collection (resulting in one component), two components from a double collection, or three components from a triple collection.

Concurrent component – When a blood component, such as Platelets, is being collected during an apheresis procedure, a concurrent component is another blood component (i.e., Plasma, Red Blood Cells (RBCs)) that is collected at the same time.

Devices Cleared or Approved – Describes a device that has been approved or cleared by FDA pursuant to a 510(k) Premarket Notification (cleared device) or Premarket Approval Application (approved device).

Dedicated Donation – Platelets, Pheresis donated for a specific recipient.

Donation frequency – Interval between collection procedures.

Process Validation – Establishing by objective evidence that a process consistently produces components that meet predetermined specifications.

Qualification – A part of Process Validation that establishes confidence that a manufacturing activity is capable of operating consistently (equipment installation qualification) and can be performed effectively and reproducibly (process performance qualification), and that the finished product meets all of the release requirements for functionality and safety (product performance qualification).

Residual White Blood Cell (WBC) count – The number of WBCs remaining in a leukocyte reduced component, calculated by multiplying the WBC count from a sample of the component times the volume of the component.

Target platelet yield – The intended platelet yield programmed into an automated blood cell separator, which may be based on the donor's platelet count and other factors.

Tolerance values – Minimum and maximum values (i.e., container volume; platelet concentration) described by the manufacturer as being acceptable. These values may also be described as specifications.

Weight/volume conversion – The total weight of the component minus the tare weight of the empty container divided by the specific gravity of the component equals volume of the component.

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III. DONOR SELECTION AND MANAGEMENT

A. Donor Selection

Under 21 CFR 640.21(c), plateletpheresis donors must meet donor suitability criteria described in the biologics license application or supplement. At a minimum, donors should meet the requirements described in 21 CFR 640.3 (suitability of donors of whole blood) and guidance related to those provisions. In addition, we recommend that you follow these additional provisions:

- Donor weight of at least 110 pounds (currently required for Source Plasma donors under 21 CFR 640.63(c)(6))
- Prior to the first donation, test Platelets, Pheresis donors for levels of the following laboratory values that are acceptable under the manufacturer's directions for use:
 - WBC count
 - Platelet count
- If you cannot test the donor before the first donation (for example, because the donor presents at a mobile collection site), you should evaluate the donor's WBC and platelet counts after the first collection.

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)

B. Donor Management

1. Platelet Count

- You should perform a pre-donation platelet count (Ref. 10), which will allow the device operator to more accurately set the target platelet yield parameters for each collection of Platelets, Pheresis. This is consistent with the device manufacturer's directions for use.
- For any collection facility that cannot perform a pre-donation platelet count (for example, a mobile collection site), you should use a platelet count as specified by the device manufacturer, or a post-donation count from a previous collection to set the target platelet yield. You should collect only a single Platelets, Pheresis collection from first-time donors who do not have a pre-donation platelet count.

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- You should defer from donation donors whose platelet counts are less than 150,000/uL until a subsequent platelet count indicates that the donor's platelet count is at least 150,000/uL.

2. Donation Frequency

To protect the safety of the donor:

- A donor should undergo no more than 24 Platelet, Pheresis collections in a 12-month period.
- You should collect no more than 24 total Platelets, Pheresis components in a 12-month period. Two components collected from a double collection of Platelets, Pheresis and three components collected from a triple collection of Platelets, Pheresis would be counted as two components and three components respectively.
- The interval between each collection of Platelets, Pheresis should be at least two (2) days with no more than two procedures in a 7-day period.
- The interval between collection of a double Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 7 days.
- The interval between collection of a triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 14 days.
- A post-donation platelet count should be performed after each collection.

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

To protect the donor from significant RBC loss, we recommend that:

- You not allow a donor who has donated a unit of Whole Blood (450 mL) in the previous 8 weeks to donate Platelets, Pheresis, unless the extracorporeal red blood cell volume during the Platelets, Pheresis collection is expected to be less than 100 mL.
- A donor who donated a single unit of Red Blood Cells by apheresis may serve as a Platelets, Pheresis donor within 8 weeks if the extracorporeal red blood cell volume during the current procedure is expected to be less than 100 mL.
- You not allow a donor who has donated a single unit of Red Blood Cells plus platelets or plasma in the previous 8 weeks to donate Platelets, Pheresis, unless the extracorporeal volume during the current procedure is expected to be less than 100 mL (Ref. 4).
- You not perform any collection procedure on a donor who has donated two units of Red Blood Cells by apheresis within the previous 16 weeks (Ref. 4).

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4. Total volume loss per collection procedure

The total volume (excluding anticoagulant) of all blood components retained per collection of Platelets, Pheresis should not exceed 500 mL (600 mL for donors weighing 175 lbs or greater) or the volume described in the labeling for the device, whichever is less.

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 donor suitability requirements, provided that a licensed physician has determined that the recipient must be transfused with the platelets from that specific donor. The collection of Platelets, Pheresis must be performed under the supervision of a qualified licensed physician who is aware of the health status of the donor and the physician must certify in writing that the donor's health permits the collection of Platelets, Pheresis (see 21 CFR 640.27, 606.110(a)). You are not required to obtain a variance under 21 CFR 640.120. However, you must test the donor as specified in 21 CFR 610.40. Note that 21 CFR 610.40(c)(1) provides for periodic testing of repeat donors of dedicated units.

D. Medical Coverage

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

IV. INFORMATION PROVIDED TO THE DONOR

Under 21 CFR 640.22(c), the collection procedure, including the information provided to the donor, must conform to the standards described in the biologics license application or supplement. Platelets, Pheresis donors should receive information about the collection procedure and its associated risks. You should provide Platelets, Pheresis donors with the same information that you provide a Whole Blood donor, plus the following information specific to the platelet collection:

- A description of the procedure for collection of Platelets, Pheresis.

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- Information about potential side effects of the procedure including possible effects as a result of solutions and/or treatment to reduce side effects such as treatment with a calcium replacement. Examples of side effects include anticoagulant effects (tingling and/or nausea), hypovolemia (decreased blood volume), and fainting.
- A statement that the long-term effects of repeated plateletpheresis on the donor's platelet and leukocyte count is not understood.
- A description of the number of Whole Blood, apheresis Red Blood Cells or plateletpheresis collection procedures and/or components that may be collected per year, and the donation interval for each.

V. COMPONENT COLLECTION AND MANAGEMENT

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

A. Collection

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

B. Target Platelet Yield

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

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

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

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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.

VI. PROCESS VALIDATION

Current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals described in 21 CFR Parts 210 and 211 contains minimum requirements to assure that drugs conform to the safety, quality and purity characteristics that they purport or are represented to possess. These cGMP regulations also apply to blood and blood components (21 CFR 210.2(a), 211.1(b)) (Ref 15). As an element of cGMP, Process Validation “establishes documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics” (Ref. 12). We believe that establishing documentation of Process Validation includes, but may not be limited to, validation protocol development, installation qualification, process operator performance qualification, and product performance component qualification (Ref. 12).

Each device intended for the routine collection of Platelets, Pheresis must be cleared by FDA for this purpose (see 21 CFR 864.9245). You should conduct Process Validation for each type of device used in your establishment prior to implementing routine collections.

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

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

A. Equipment Installation Qualification

21 CFR 606.60(a) requires that equipment be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual and must perform in the manner for which it was designed. Accordingly, upon initial installation, the automated blood cell separator must be qualified as described in the Operator’s Manual or manufacturer’s directions for use.

B. Validation Protocol

An integral element of the performance and documentation of Process Validation is the development of a validation protocol. You should refer to FDA’s “Guideline on General Principles of Process Validation,” issued May 1987 (Ref. 12) as an outline for

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developing your validation protocol. The validation protocol should include at least the following:

- A description of the equipment to be used
- Minimum/maximum acceptable values for the Platelets, Pheresis collection and/or component as specified by the device manufacturer (see 21 CFR 606.60(a)).
 - Total volume (after removal of samples for testing and bacterial contamination testing), including per component (container) from double and triple collections
 - Target platelet yield
 - Actual platelet yield, including count per container for double and triples
 - Residual WBC count for the collection (if leukocyte reduced) and percent recovery
 - Concurrent component volume (Plasma or Red Blood Cell), if applicable
 - pH measurement
 - Bacterial contamination testing
- Manufacturer's specifications or recommendations for processing parameters (i.e., platelet yield and concentration, weight or volume collected)
- Description of supplies used in the collection (e.g., collection/storage containers, anticoagulants, etc.)
- Failure investigation criteria including provisions for corrective action, follow-up (see 21 CFR 211.165(f); 211.192), and/or re-qualification if appropriate.
- Personnel training criteria
- Standard operating procedure(s) for performing each element of Process Validation
- Documentation of the validation protocol criteria (all of the above) (see 21 CFR 211.194(a)).

C. Process Performance Qualification (Operator)

Personnel performing collection of Platelets, Pheresis must have adequate training to assure their competent use of the devices involved (21 CFR 606.20(b); 211.25 (a) and (b)); they should demonstrate competency (Ref. 14).

Personnel training should include the successful, consecutive performance, under supervision, of an appropriate number of procedures, as defined by your facility. These procedures should result in the collection of Platelets, Pheresis meeting relevant component specifications.

D. Product Performance Qualification (Component Collection)

Various mechanical and biological factors may influence the plateletpheresis collection process, (i.e., the optical qualities of a donor's plasma, the donor's platelet count and platelet size, vascular access, and procedure duration) (Ref. 15). The objective of collection performance qualification is to verify that the device performs according to the manufacturer's claims when used by a collection facility, and through appropriate testing establishes confidence that the finished product produced by the specified process

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meets all release requirements for functionality and safety (Ref. 12). All components collected during the validation process can be released for transfusion provided that they meet minimum component specifications.

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).

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.
 - 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.
- Testing be conducted on both containers from double collection and on all three containers for triple collection;
- Qualification include Platelets, Pheresis collection by all trained personnel;
- Residual WBC count be performed within 24 hours of collection, or per the manufacturer's directions for the cell counting methodology (Ref. 2);
- An RBC count/hematocrit be performed on Platelets, Pheresis or concurrent Plasma (when collected) containing visibly apparent RBCs to determine total packed RBC volume. You should hold Platelets, Pheresis containing more than 2 mL of RBCs until the residual WBC count has been determined and found to be less than 5.0×10^6 for platelet or plasma components labeled as leukocyte reduced;
- Test one third of the components collected for qualification during the first third of the dating period; one third during the second third of the dating period, and one third the day of outdate. For example, for Platelets, Pheresis with a 5-day dating period, test one third at 1-2 days, one third at 3-4 days and the final third on day 5 after collection. Components that expire may be used for qualification if tested

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within 12 hours after expiration. You should not release such outdated components for transfusion, however.

- Perform bacterial contamination testing using a CBER cleared or approved bacterial detection system specifically labeled for testing of plateletpheresis components (Refs. 16, 17, 18, and 19), used in the manner for which it was cleared or approved.
- 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.

Table 1. Collection Performance Qualification Criteria

Test	Acceptance Criteria	Target ¹	Allowable Process Failures ²	
			N= 20 (triple) 30 (double) 60 (single)	N= 31 (triple) 47 (double) 93 (single)
Actual Platelet yield ³	Minimum: 3.0×10^{11}	95% / 95%	0	1
	Maximum: per manufacturer ³			
pH	≥6.0	100%		
	≥6.2	95% / 95%		
Volume	Minimum/maximum per manufacturer Double collections: each container contains 50% +/- 5%. ⁵ Triple collections: each container contains 33% +/- 3%. ⁵	100%	All adjusted to correct volume	
Residual WBC count; component recovery	< 5.0×10^6 per collection <u>and</u> per component for double and triple collections; ≥ 85% component retention ⁵	95% / 95%	0	1
Red blood cell count ⁴	RBC/hematocrit for visible RBCs	NA	NA	
			N=500	
Bacterial contamination testing	No growth	99% / 99%	0	

¹Binomial distribution: 95% confidence that 95%, or 99% confidence that 99% of the components meet the acceptance criteria.

²Process failures only; non-process failures should be excluded.

³All actual platelet yield values that exceed the manufacturer's specifications must be handled appropriately.

⁴When applicable and including plasmapheresis components.

⁵Or per the container/cell separator manufacturer's specifications

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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 this failure and complete the collection process qualification in its entirety (see 21 CFR 211.192).
- As long as the collection process operates in a state of control and you make no changes to the collection process or the collected components, you do not need to re-qualify or re-validate the process. However, you are required to conduct periodic performance checks of equipment (see 21 CFR 606.160(b)(5)(ii), 606.100(b)(15), 606.60(a), 211.160(b)(4), 211.194(d)).
- Deviations from the written procedures must be recorded and justified (21 CFR 211.100(b)). You should review and evaluate changes or deviations from the collection process, and perform re-qualification if determined to be appropriate (Ref. 12).
- The manufacturer may specify re-qualification requirements for the device, which you must follow (21 CFR 606.60(a), 606.65(e)).

VII. QUALITY ASSURANCE (QA) AND MONITORING

Quality assurance is the sum of activities planned and performed to provide confidence that all systems and their elements that influence the quality of the component are functioning as expected (Ref. 14). When this is demonstrated, the process is considered to be in a state of control. Whether a process is operating in a state of control is determined by analyzing the day-to-day process and the data for conformance with the manufacturer's specifications and for variability. You must have an appropriate QA program for platelet component production (see, for example, 21 CFR 211.22, 211.80, 211.192, 211.198, 606.100). You should refer to FDA's "Guideline for Quality Assurance in Blood Establishments," issued July 1995 for developing a QA and Monitoring program (Ref. 14). Your QA unit is responsible for oversight of component manufacturing (21 CFR 211.22(a)), and should report to management (Ref. 14).

A. Standard Operating Procedures (SOPs) and Record Keeping

1. Requirements for SOPs
 - You must ensure that the automated blood cell separator "perform[s] in the manner for which it was designed" (21 CFR 606.60(a)) during the collection or processing of apheresis components. Written SOPs must be maintained and must include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components (21 CFR 606.100(b)). Therefore, you must have written SOPs for each function in the collection of Platelets, Pheresis, including all of the sections described in this guidance.

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- 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)).
 - Your written SOPs must include procedures for investigating adverse donor and recipient reactions (21 CFR 606.100(b)(9)).
2. Additional Provisions Applicable to SOPs
- **Equipment/devices, supplies or reagents:** Supplies and reagents must be used in a manner consistent with the instructions provided by the manufacturer (21 CFR 606.65(e)).
 - **Adverse reactions:** You must have a written SOP for investigating adverse donor and recipient reactions (21 CFR 606.100(b)(9)). In addition, you should have a written SOP for managing a cardiopulmonary emergency or any other adverse reactions associated with donation, containing steps (including phone numbers) for contacting physicians, obtaining an emergency rescue squad, and transporting the donor to the hospital.
 - **Sample handling:** There must be adequate identification and handling of all test samples so that they are accurately related to the specific unit of product (component) being tested, or to its donor, or to the specific recipient, where applicable (21 CFR 606.140(c)).
 - **Hematocrit:** If the final platelet or plasma component contains more than 2 mL of packed RBCs, you should attach a sample of donor blood to the platelet storage container for compatibility testing to prevent the possibility of an adverse reaction during transfusion.
 - **Bacterial contamination testing:** Containers must be opened, sampled and resealed in a manner designed to prevent contamination of the contents using sterile equipment and aseptic sampling techniques when necessary (21 CFR 211.84(c)(2) and (3)); any closure must maintain a hermetic seal and prevent contamination of the contents (21 CFR 640.24(e)).
 - The instruction circular must state that, if the storage container is entered, transfusion of the component must be initiated as soon as possible, and no more than 4 hours later (21 CFR 606.122(1)(2)).
 - Components that fail bacterial contamination testing are adulterated (21 U.S.C. 351(c)). You should discard them.
 - **Component volume:** You should describe how to process components if the volume exceeds the automated blood cell separator manufacturer's specifications.

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- **Actual platelet yield:** The platelet yield from each collection of Platelets, Pheresis should be provided to the transfusion facility.
- **Residual WBC counts:** Your SOP should state the maximum acceptable WBC limits for each automated blood cell separator device in use.
- **pH measurement:**
 - Accurate pH measurement is time dependent, and samples should be tested within 1 hour of sampling. If you choose to determine pH measurements with nitrazine paper, the selected paper should read in increments of one-tenth units, or it may provide inaccurate measurements.
 - Components with a pH < 6.0 are adulterated (21 U.S.C. 351(c)). You should discard them.
- **RBC loss:** (see 21 CFR 606.100(b)) Using the information about extracorporeal red blood cell volume supplied by the manufacturer of the automated blood cell separator, you should calculate the volume of RBCs remaining in the apheresis collection set after a collection of Platelets, Pheresis and record it in the donor's record. (The total extracorporeal red blood cell volume of each device is described in the Operator's Manual or manufacturer's directions for use.)
- **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 donors weighing more than 175 lbs) (Ref. 3).
- **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.
- **QC failures:** (see 21 CFR 211.165(f); 211.192) Define appropriate criteria for retesting of components, testing of additional components, final labeling, and disposition of components that fail to meet specifications.
- **Failure investigations:** (see 21 CFR 211.192] The criteria to assess in the performance of a thorough failure investigation may include, but not be limited to: donor characteristics or specifications; operation and or performance of the collection device; adherence to SOPs; lot numbers of reagents or supplies; sample collection, storage or shipping; operator performance, training or competency; and cell counting instrument performance including shifts or trends in controls.
- **Performance specifications:** (see 21 CFR 606.140(a); 21 CFR 211.165(d), (f)) State the acceptable tolerance specifications for the volumes, platelet concentration, and/or actual platelet yield for each component collected

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(single, double or triple collection) as described by the manufacturer. You should have a procedure addressing the handling of components that exceed the manufacturer's limitations.

- **Labeling:**
 - For Platelets, the volume range reported on the label must be within reasonable limits (21 CFR 606.121(c)(6)). You should determine the final component volume to be stated on the label after removal of samples for platelet count determination, QC and/or bacterial contamination testing.
 - Platelets, Pheresis routinely should contain no less than 3.0×10^{11} platelets per storage container. When special circumstances warrant their use, Platelets, Pheresis components containing less than 3.0×10^{11} platelets per storage container should be labeled with the actual platelet content.

- **Component Storage and Shipping:**
 - If Platelets, Pheresis are stored at 20-24 °C, you must maintain a continuous gentle agitation throughout the storage period. Agitation is optional if platelets are stored at a temperature between 1 and 6 °C (21 CFR 640.25(a)). You should describe how temperature and agitation will be monitored, and the disposition of platelet components that are not stored properly.
 - You must follow the automated blood cell separator manufacturer's directions for use (21 CFR 606.60(a), 606.65(e)) and have provisions for the disposition of Platelets, Pheresis that have actual platelet yield or volumes that are outside of the limits of the automated blood cell separator manufacturer's specifications. If sterile docking of an additional container(s) is necessary, use a container(s) designed to achieve and protect a sterile conduit. You should use containers from the same manufacturer.
 - You should include the recommended shipping procedure including temperature and time for Platelets, Pheresis.

- **Deviations:** 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.

3. Record-keeping:

All record-keeping requirements of 21 CFR Part 606, Current Good Manufacturing Practice for Blood and Blood Components, Subpart I (Records and Reports), Part 211, Current Good Manufacturing Practice for Finished

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Pharmaceuticals, Subpart J (Records and Reports), and applicable provisions of 21 CFR 640.20-640.27 must be met.

B. Donor Monitoring

1. Platelet counts

You should notify your Medical Director when a donor has a post collection platelet count less than 100,000/uL, and you should defer the donor until his/her platelet count has returned to at least 150,000/uL.

Transient decreases in platelet counts have been reported in donors undergoing multiple collections of Platelets, Pheresis (Ref. 21). Although the effect of long-term regular collection of Platelets, Pheresis on donor platelet counts is unknown, clinically significant thrombocytopenia in these donors is unusual. You should review a donor's records before each donation to monitor the donor's ability to recover his/her baseline platelet count.

2. Adverse reactions in donors

Records must be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion (21 CFR 606.170(a)). In particular, before a subsequent donation by a donor who reported an adverse reaction, including red blood cell losses in the previous 8 weeks (Ref. 10), total volume loss, and low donor platelet counts, you should have a qualified physician or designee (i.e., a medical professional working under a physician's supervision) review the records of that adverse reaction report and subsequent investigation (see 21 CFR 606.170). In addition, you should monitor donors undergoing frequent multiple component collection of Platelets, Pheresis for platelet recovery (Ref. 21).

3. Red blood cell loss

- **Per collection:**

- If the collection procedure needs to be discontinued for any reason before completion, and if the Operator's Manual allows, you should attempt to return RBCs to the donor. If the RBCs cannot be returned to the donor, you should determine the absolute RBC loss. Donor eligibility based on RBC loss is described in Table 2 (Ref. 4).

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Table 2: RBC loss per collection

Donor's <u>Initial</u> packed RBC loss	Donor's <u>Second</u> packed RBC loss within 8 weeks	Eligibility
Less than 200 mL	No donation or none lost	Donor is eligible to donate within 8 weeks
Less than 200 mL	< 100 mL (total loss is < 300 mL)	Donor is not 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

- Donors who donate a single concurrent RBC unit with the Platelets, Pheresis should be deferred from all collections for at least 8 weeks unless the extracorporeal red blood cell volume during a subsequent collection of Platelets, Pheresis is expected to be less than 100 mL (Ref. 4).
- Donors who donate a double RBC by apheresis should be deferred from any type of collection for 16 weeks.

- **Per 12 months:**

Under 21 CFR 640.3(b), a person may not serve as a source of Whole Blood more than once in 8 weeks. In any such assessment, and in assessing a donor's RBC loss during the past rolling 12-month period, the RBC loss associated with the collection of Platelets, Pheresis must also be considered.

- **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

C. 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.
 - Weight/volume conversion: A weight/volume conversion is necessary to determine the volume.

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- Residual WBC count on all collections that do not utilize an automated leukocyte reduction methodology.
- Hematocrit: You should perform a RBC count/hematocrit on Platelets, Pheresis or concurrent Plasma components (when collected) containing visibly apparent RBCs to determine total packed RBC volume. Platelets, Pheresis containing more than 2 mL of RBCs should be held 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.
- Bacterial contamination testing: as specified by the collection device manufacturer.

2. QC monitoring

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

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

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

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

As part of your QC protocol you should:

- Define a plan for non-selectively identifying collections to be tested. Testing should be conducted on a regularly scheduled basis (i.e., daily, weekly).
- Include testing of components collected on each individual automated blood cell separator device.
- Allow for testing at the maximum allowable storage time for the container system used (or representing the dating period). 21 CFR 640.25(b) specifies that QC testing be performed at the end of the storage period. Components that expire or are returned to the collection facility may be used for QC. We interpret “at the end of the storage period” to include testing within 12 hours of expiration.
- Include the residual WBC count (Ref. 2) for automated leukocyte reduced components, and RBC count/hematocrit (when RBCs are observable).

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- Test for percent component retention.
- Test for the residual WBC count (when applicable) within 24 hours after collection to reduce aberrant results due to cellular deterioration and clumping, or per the manufacturer's directions for the counting device or method used.
- Calculate the volume of the component on day of QC testing.
- Describe in your SOP the criteria for investigation of failures during QC, including the criteria that will categorize a failure as process or non-process.
- Include assessment of shifts/trends in the collection and/or leukocyte reduction process.
- Have a method to document all test results and calculations used in the QC process.
- Test the same component for the actual platelet yield and pH, because these parameters may be correlated. Actual platelet yield and pH may be done on one container of a double or triple collection. Tests for residual WBC count may be performed on a different set of components, and may be performed on the parent container.

Acceptance criteria:

- Actual platelet yield should be $\geq 3.0 \times 10^{11}$; and in conformance with the manufacturer's specifications.
- pH must be ≥ 6.0 (21 CFR 640.25(b)(2)) and should be ≥ 6.2 (Refs. 5 and 6).
- Residual WBC count should be $< 5.0 \times 10^6$ per collection; percent component recovery should be $\geq 85\%$ or per the manufacturer's specifications.
- The volume in each container for double collections should be $50\% \pm 5\%$; for triple collections $33 \pm 3\%$, or per the manufacturer's specifications.
- If one component from a double or triple collection procedure is found to have unacceptable results (less than 3.0×10^{11} platelets, $\text{pH} < 6.2$, or a volume discrepancy), the corresponding component(s) from the collection should be quarantined until they are tested and found to be acceptable.

D. Equipment/Supplies QA

Equipment must be observed, standardized, and calibrated on a regularly scheduled basis as prescribed in the Standard Operating Procedures Manual (21 CFR 606.60(a)). Such equipment includes, but may not be limited to, the automated blood cell separator, cell counting instrument(s), pH meter, scales and sterile tubing welder.

Supplies (including containers) and reagents must meet all of the requirements described in 21 CFR 606.65.

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E. Operator QA

Operators must receive adequate training, education and/or experience to assure competent performance of their assigned functions (21 CFR 606.20(b)). Performance qualification should include acceptable completion of scheduled competency assessment and proficiency testing. You must maintain records of proficiency test results (21 CFR 606.160(b)(5)(v)). In addition, you should develop and document appropriate training on component preparation and/or machine maintenance as updated information becomes available (Ref. 14).

F. Quality System Audits

At a minimum, the systems included in a quality audit program should be those described in FDA's "Guideline for Quality Assurance in Blood Establishments," issued July 1995 (Ref. 14).

You should conduct audits to assess the following:

- Completion and documentation of training and competency assessment
- Total component volume and equal distribution of volume in double and triple component collection containers. This audit should include checking the performance of the scale; the tare weight of the empty containers/tubing; performing an actual tared weight and the weight/volume conversion.
- Component bacterial contamination testing: Rates of bacterial contamination of plateletpheresis should be monitored, and rates that exceed 1:3000 (Ref. 7) should be considered potentially non-conforming, and an investigation be initiated.
- Documentation of record completion

VIII. PROCESSING AND TESTING

A. Processing

Platelets, Pheresis must be processed as described in 21 CFR 640.20-640.27.

B. Testing

Platelets, Pheresis must be tested in compliance with the Testing Requirements for Communicable Disease Agents described in 21 CFR 610.40 and the general testing requirements for Whole Blood donation (21 CFR 640.5(a)-(c)) and Platelets (21 CFR 640.23). Platelets, Pheresis may be released or shipped prior to completion of testing only in accordance with 21 CFR 610.40(g).

You must test donations of human blood and blood components from a donor whose donations are dedicated to be used solely by a single identified recipient except that, if the

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donor makes multiple donations for a single identified recipient, you may perform such testing only on the first donation in each 30-day period (21 CFR 610.40(c)(1)).

C. Expiration Date

The dating period for Platelets, Pheresis collected using an FDA cleared collection container under a closed or functionally closed system will be specified by the collection container manufacturer. Platelets, Pheresis components expire 24 hours from the termination of the procedure if the integrity of the hermetic seal is broken during processing. If the integrity of the hermetic seal is broken after collection, the Platelets, Pheresis expire 24 hours from the time of the integrity violation, or at the original expiration date, whichever is earlier.

IX. LABELING

The *Circular of Information for the Use of Human Blood and Blood Components (The Circular)* (Ref. 22) describes in detail the indications, contraindications, side effects, hazards, dosages, and administration of Platelets. An instruction circular must be available for distribution if the product is intended for transfusion (21 CFR 606.122).

Your container labels must comply with 21 CFR 606.121 and 610.60.

In addition:

- The label should include the estimated amount of anticoagulant in the component container.
- Platelets, Pheresis components containing less than 3.0×10^{11} platelets per storage container should be labeled with the actual platelet content.
- The actual platelet yield of each component should be made available to the transfusion service.

X. REPORTING CHANGES TO AN APPROVED BIOLOGICS LICENSE APPLICATION (BLA)

Licensed establishments must report changes to their approved application(s) in accordance with 21 CFR 601.12. For assistance in reporting your changes see FDA's "Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture," issued August 2001 (Ref. 23). The information below is intended to assist you in determining which reporting mechanism is appropriate for a change to your approved BLA, as it applies to the manufacture of Platelets, Pheresis. You should prominently label each submission with the reporting category under which you are reporting your change, e.g., "Prior Approval Supplement", "Supplement - Changes Being Effectuated in 30 Days", "Supplement - Changes Being Effectuated" or "Annual Report."

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A. Prior Approval Supplement (PAS): Changes requiring supplement submission and approval prior to distribution of the product made using the change (major changes) (21 CFR 601.12(b)).

Under 21 CFR 601.12(b), changes that have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be reported to FDA in a prior approval supplement.

The following kinds of manufacturing changes fall within this category. Accordingly, you must submit your request to implement the following changes to your approved BLA as a Prior Approval Supplement (PAS) under 21 CFR 601.12(b).

- If you currently hold an unsuspended, unrevoked BLA to manufacture blood components other than Platelets, Pheresis, and you intend to manufacture and distribute Platelets, Pheresis under that license.
- If you are currently approved to manufacture Platelets, Pheresis at a specific facility, and you intend to manufacture Platelets, Pheresis at a different facility (not under an approved Comparability Protocol). To submit a request for a Comparability Protocol see below.
- If you are approved to manufacture Platelets, Pheresis, but intend to change your manufacturing process in a manner that presents a substantial potential for an adverse effect on the product. 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.
- If you are requesting approval for a Comparability Protocol. The Comparability Protocol described in 21 CFR 601.12(e) is a supplement that describes the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specific manufacturing changes on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. A new Comparability Protocol, or a change to an existing one, requires approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

A Comparability Protocol is appropriate, but not required, if you wish to add multiple collection facilities under your direction and control, using the same process to manufacture Platelets, Pheresis. If you request approval for a Comparability Protocol, you must describe the procedures and processes that each new collection facility will implement to ensure conformance with the Comparability Protocol. You may identify one or more collection facilities for the purpose of validation and submission of the Comparability Protocol and supporting data to CBER for review. Approval of such a Comparability Protocol for future collection facilities justifies a

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reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

If you are using an approved Comparability Protocol, you should routinely review the procedures and specifications in the Comparability Protocol to assure that they remain current and consistent with the applicable application and current guidance. If modifications are required, you should contact FDA to discuss the change and to determine the appropriate reporting category.

- We consider the recommendations in this guidance document to provide appropriate criteria for a biologics license application or supplement for Platelets, Pheresis. You may use an alternative approach if such approach satisfies the requirements of the applicable statutes and regulations. Your alternative procedure(s) may be acceptable if you demonstrate that the resulting Platelets, Pheresis components meet applicable standards.

You must not distribute in interstate commerce blood components made using the above changes requested in your PAS until you have received our approval (21 CFR 601.12(b)(3)).

B. Changes Being Effected in 30 Days (CBE-30) Supplement: Changes requiring supplement submission at least 30 days prior to distribution of the product made using the change (21 CFR 601.12(c)).

Under 21 CFR 601.12(c), changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product must be reported to FDA in a Changes Being Effected in 30 days (CBE-30) supplement.

The manufacturing changes described below fall within this category. Accordingly, you must submit your request to implement the following changes to your approved BLA as a Changes Being Effected in 30 Days supplement under 21 CFR 601.12(c):

- Upgrades provided by the manufacturer to your cleared apheresis device
- Addition of concurrent plasma collection
- Implementation of a new collection facility under an approved Comparability Protocol

You may distribute your blood components made using the change requested in your CBE-30 supplement in interstate commerce 30 days after we receive your supplement, unless we notify you otherwise.

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C. Submission Inclusion Documents

1. PAS: To comply with the requirements in 21 CFR 601.12(b)(3), the following must be included in the supplement:
 - A cover letter and FDA Form 356h. You must identify the components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and facility location(s), and provide a detailed description of the manufacturing change (including device collection technology and the collection protocol(s)) (21 CFR 601.12(b)(3)(i)-(iii)). To permit assessment of the manufacturing change, include copies of the following SOPs:
 - Collection
 - Informed consent
 - Labeling including labels
 - Donor qualification, deferral and adverse event follow-up
 - A description of training (or an example of training documents)
 - Component manufacturing
 - Monitoring donor RBC and plasma loss
 - Failure investigation
 - Quality Control including sampling scheme, sample handling, tracking and trending
 - Equipment standardization/calibration
 - Quarantine and disposition of unsuitable products
 - Form FDA 2567 including Circular (unless already on file at FDA). You must include product labeling for each component (21 CFR 601.12(f))
 - Relevant validation protocols and data (21 CFR 601.12(b)(3)(vi)). A summary of the validation protocol, including failure investigations, is acceptable.
 - A description of the methods used and studies performed to evaluate the effect of the change and the data derived from such studies (21 CFR 601.12(b)(3)(iv)-(v)). These include:
 - Two months of QC data including the device manufacturer, the device type, blood unit number, component description (i.e., leukocyte reduced), date of collection, date of testing, component volume, actual platelet yield, residual WBC count per component, pH, result interpretation(s), the identity of the person performing the QC, and the identity of the collection facility.
 - Evidence of quality assurance oversight
 - The expected component specifications
 - A reference list of relevant SOPs (21 CFR 601.12(b)(3)(vii)). We believe that the following SOPs, if already approved for other blood collection activities and unrevised, would be relevant:
 - Donor arm preparation
 - Sample preparation
 - Component storage and shipping

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2. Comparability Protocol (21 CFR 601.12(e)). In addition to the information listed in Section X.C.1 above, you must include the following:
 - Implementation plan
 - Proposed reporting category for changes made under proposed Comparability Protocol
3. CBE-30 submissions (excluding new facilities under an approved Comparability Protocol): To comply with the requirements listed in 21 CFR 601.12(c)(3), which includes 21 CFR 601.12(b)(3)(i)-(vii) requirements, the following information must be included in your CBE-30 submission:
 - A cover letter and FDA Form 356h. You must identify the components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and facility location(s), and provide a detailed description of the manufacturing change (including device collection technology and the collection protocol(s)) (21 CFR 601.12(b)(3)(i)-(iii)). To permit assessment of the manufacturing change, include copies of any new or previously approved but revised SOPs (21 CFR 601.12(b)(3)(iv)).
 - A summary of validation failure investigations (see 21 CFR 601.12(b)(3)(iv)-(vi)).
 - Two months of QC data (21 CFR 601.12(b)(3)(iv), (v))
4. CBE-30 submissions for new facilities under an approved Comparability Protocol: To comply with the requirements listed in 21 CFR 601.12(c)(3), which includes 21 CFR 601.12(b)(3)(i)-(vii) requirements, the following information must be included:
 - A cover letter and FDA Form 356h. You must identify the components involved (e.g., single plateletpheresis component, double plateletpheresis components, and/or triple plateletpheresis components) and new facility location(s), and provide a detailed description of the manufacturing change (including device collection technology and the collection protocol(s)) (21 CFR 601.12(b)(3)(i)-(iii)).
 - A summary of validation failure investigations (see 21 CFR 601.12(b)(3)(iv)-(vi)).
 - Two months of QC data (21 CFR 601.12(b)(3)(iv), (v)).

In addition, you should include the submission tracking number (STN) of the approved Comparability Protocol, or the STN(s) of changes to the SOPs associated with an approved Comparability Protocol.

D. Component Submission for CBER QC Testing

To obtain a biologics license under Section 351 of the Public Health Service Act for any biological product, a sample(s) representative of the product must be provided with the application (21 CFR 601.2(a)). Samples of any lot of any licensed product may at any time be required to be sent to CBER (21 CFR 610.2(a)).

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In compliance with these regulations:

- 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.

You must investigate the cause of the failure when CBER reports that components have failed CBER QC testing (21 CFR 211.192, 211.198).

E. Shipping Information

Within 30 days of receiving your STN assignment and filing notification letter, if CBER has requested you to submit Platelets, Pheresis to CBER for testing, you should contact CBER Division of Hematology, Laboratory of Cellular Hematology at (301) 496-2577 to schedule delivery of your components to arrive prepaid. We recommend that you submit freshly prepared components collected from two collection procedures for each single, double and/or triple collection of Platelets, Pheresis or Platelets, Pheresis Leukocyte Reduced, prepared by each cleared device, to the following address between 8:30 a.m. and 4:00 p.m. Monday through Friday, excluding federal holidays:

Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
8800 Rockville Pike
Building 29, Room 323
Bethesda, Maryland 20892

You should attach a tie tag to each component identifying the location of the collection facility, the STN, the device manufacturer, the cell separator type, the pH, the actual platelet yield, residual WBC count, the total component volume, and the hematocrit/packed red cell volume (if visibly apparent). We recommend that you enclose a pre-paid, self-addressed shipping label to allow return of shipping boxes and coolants, if desired.

We recommend that you ensure that components arrive at CBER prior to component expiration time. The components should not expire on Friday or Saturday at midnight, or at midnight on the day before a federal holiday.

Labeling and processing, including required testing for evidence of infection due to communicable disease agents (21 CFR 610.40(a)), should be complete prior to shipment.

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You should follow your SOPs for collecting, packing, and shipping components intended for transfusion.

XII. CONTACT INFORMATION

You may direct questions specific to Platelets, Pheresis application submissions to the Division of Blood Applications (DBA). You may also direct questions to the Office of Communications, Training, and Manufacturers Assistance (OCTMA) as an initial general point of contact. Submit all registration forms (Form FDA 2830) and licensure applications/supplements to the Director, Center for Biologics Evaluation and Research (CBER).

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Table 3: FDA Contact Information

<p>Submissions: Registrations License Applications</p>	<p>Director, Division of Blood Applications Center for Biologics Evaluation and Research, HFM-370, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.</p>
<p>General Questions</p>	<p>Director, OCTMA, HFM-40, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Voice (301) 827-2000; Fax (301) 827-3843.</p>
<p>Application Submission</p>	<p>Director, Division of Blood Applications, Center for Biologics Evaluation and Research, HFM-370, Food and Drug Administration, c/o Document Control Center, HFM-99, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, Voice (301) 827-3543; Fax (301) 827-3534.</p>
<p>Platelets, Pheresis Samples to CBER</p>	<p>Center for Biologics Evaluation and Research (CBER) Food and Drug Administration 8800 Rockville Pike Building 29, Room 323 Bethesda, Maryland 20892</p>

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APPENDIX A: Scan statistics^(Ref. 24)

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 observed rate of failed tests. To assess non-conformance, the samples tested for QC are evaluated in a rolling “window” of test results. A “trigger” value is determined that alerts you to the potential for an unacceptable level of non-conformance for a process as a whole.

The accepted rate of nonconformance for automated methods is estimated to be 0.1%, and is the basis for the figures in Table 4. Figures in the table were generated by considering the power to detect a 5% nonconformance rate (i.e., a 50-fold increase), a false positive rate < 5%, and the number of “windows” per year that would be evaluated (approximately ~ 1 per month). We recommend that you define a plan for the random selection of 10% of your annual collections to be tested.

N = number of samples to be tested per year (this should represent 10% of total collections)

m= sample size of the assessment “window”

Trigger = failure level that when reached, can be interpreted as a potentially unacceptable non-conformance rate, and initiates a complete investigation

FP = the probability that the interpretation of an unacceptable non-conformance rate is incorrect

Power = the power to detect a failure rate of 5% (i.e., 50-fold increase in non-conformance) from the expected rate of 0.1%

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

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

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

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The rolling “window” works in the following way: Following Process Validation as described in Section VI, start the testing of the sample “window” (for this example, use weekly testing). Each week you continue your QC testing until you have completed the selected number of samples in the “window.” As long as you have fewer failures than described as the trigger, your process is considered to be at an acceptable level of conformance. As you move to the next week, you add the next set of test results as part of a test “window” and drop the set from the first week of that window. For example, if your window includes testing for weeks 1 – 4, at week 5 you drop the results from week 1, and the current window of assessment now includes weeks 2, 3, 4 and the new data from week 5, and so on.

Each QC failure should be evaluated for an attributable cause. Non-process failures (i.e., donors with hemoglobin S (Hgb-S) trait) may be removed from contributing to the “trigger” value. Failures that have attributable causes (i.e., incorrect donor parameters used, incorrect operation of device, error in cell counting or pH determination) should have corrective action initiated with follow-up. In this case, these may also be removed from contributing to the “trigger” value, but should be tracked and trended to ensure that corrective action was successful. Failure rates that initiate a “trigger” indicate that your process may have an unacceptable level of non-conformance. We recommend that further investigation be done which may include contact with the manufacturer, evaluation by the Medical Director as to the appropriateness of continued production, necessity of re-validation (as described in Section VI) and/or appropriateness of continuation of QC monitoring. After this evaluation and when QC monitoring resumes, the sample “window” begins as if it were week one again, and the failures that initiated the investigation are not reconsidered in the sampling plan.

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