

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Bethesda MO 20892

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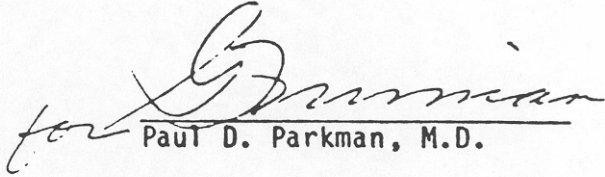
FROM: Director, Center for Biologics Evaluation and Research

SUBJECT: Revised Guideline for the Collection of Platelets, Pheresis

TO: Facilities Preparing Platelets, Pheresis

In August, 1981, the Food and Drug Administration issued a guideline for the collection of Platelets, Pheresis. Since that time, we have received comments on the guideline, new instrumentation has appeared, and considerable experience with platelet collection and storage has been accumulated. All of these factors were considered when the revised guideline was proposed and distributed for comment in March, 1984. The comments received were discussed along with the proposed revisions at a public meeting held in Bethesda, MD, on May 22, 1984. The most significant changes that resulted are explained in the guideline introduction.

Since then, new instrumentation and separation techniques have been approved and additional testing for disease transmission potential have been proposed and included in donor screening. Informed consent forms have been modified to include this testing as well as donor self-exclusion policies. These changes have been reflected in the current revision of the guideline. It should be noted, however, that a guideline establishes principles of general applicability and does not include advice on particular situations. A guideline is not a legal requirement, but a person may rely upon a guideline with assurance that it is acceptable to the FDA (21 CFR 10.90). When different procedures or standards are chosen, a person may, but is not required to, discuss the matter in advance with FDA.



for Paul D. Parkman, M.D.

Enclosure

**Guideline for the Collection of Platelets,
Pheresis Prepared by Automated Methods**

October 1988

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REVISED GUIDELINE FOR COLLECTION OF PLATELETS, PHERESIS

INTRODUCTION

The first edition of this guideline appeared in August, 1981. Since that time, we have received comments on the guideline, new instrumentation has appeared, and considerable experience with collection and storage has been accumulated. All of these factors were considered when the revised guideline was proposed and distributed for comment in March, 1984. Comments were received and discussed along with the proposed revisions at a public meeting held in Bethesda, MD on May 22, 1984.

This process has resulted in the current version of the guideline that incorporates many changes as compared to the March, 1984 version. The following is a partial list of such changes. Included in this list are items that were the subject of many comments, as well as some for which we do not believe a clear consensus yet exists.

1. The outline format has been revised so that reference can be made to unique paragraphs.
2. (I.B) Donor deferral interval after aspirin ingestion. Published data support the contention that a 36 hour interval is sufficient to yield platelets with satisfactory function. The American Association of Blood Banks (AABB) requires a 3 day interval. The present version of the guideline reflects this uncertainty with more flexible language.
3. (I.E) The suggested maximum number of collections from a donor in one year has been increased to 24. The magnitude of the potential risks, especially lymphocyte depletion, is still unclear. However, newer collection techniques decrease these risks, and experience has revealed no clinically apparent adverse side effects. Further study in this area is needed.
4. (I.F) Tests for disease transmission (STS, HBsAg and HIV antibody testing) and ABO and Rh groups need be performed only once at the beginning of a 30 day period of donation by a dedicated donor for a single recipient. There was not a clear consensus on this point among those who offered comments. The policy proposal reflects the fact that this portion of the guideline is to be applied only in certain specific clinical situations. We believe that the risk benefit analysis in such situations supports this exemption from routinely applied requirements.
5. (I.H) Plateletpheresis donor deferral after whole blood donation previously had been recommended at 8 weeks to reflect the potential danger of losing a significant number of red blood cells during the pheresis procedure. Newer instruments now limit the potential red blood cell loss and, therefore, the guideline has been made more flexible.
6. The recommended total volume of collected plateletpheresis product is limited to 500 mL (600 mL for donors 175 lb), rather than the 1,000 mL limitation listed in the AABB Standards.

Collection of plasma by products (Source Plasma, Fresh Frozen Plasma, etc) from plateletpheresis procedures will be considered upon receipt of amendments to establishment and product applications. We have reviewed data that support removal of total volumes larger than recommended by the current guideline. Such data should be obtained first on an ambulatory donor population in the setting of typical collection facilities. In addition, such plasma obtained by plateletpheresis procedures shall be collected as prescribed in 21 CFR 640.62, 640.64 (except that paragraph (c) (3) of 640.64 shall not apply), and 640.65.

7. (IV.E) Sterility testing need be done only during establishment of the technique.
8. (IV.F) Quality control testing (pH and platelet count) may be done on units at the time of issue. Many comments addressed the fact that units of product rarely reach the outdate time, and testing at the maximum storage time would be impractical and not representative.
9. (IV.G) Platelet content of each unit should be determined, but the value may be kept in records and need not go on the container label. Platelet counts on samples may therefore be done after the units have been issued.
10. (V.) Labeling is revised to conform with the Guidelines for Uniform Labeling of Blood Products, developed by the American Blood Commission Labeling Subcommittee. The product name, Platelets, Pheresis, is the designation contained in those guidelines and adopted by the FDA in the final rule for Uniform Labeling of Blood Products.

REVISED GUIDELINE FOR THE COLLECTION OF PLATELETS, PHERESIS

UPDATED OCTOBER 1988

This Food and Drug Administration (FDA) guideline applies to all registered blood collecting facilities which prepare Platelets, Pheresis by mechanical means using a currently approved instrument.

I. DONOR SELECTION

- A. The same general criteria used to select donors for whole blood apply to donors selected for pheresis procedures. These include the health history, temperature, pulse, blood pressure, and weight. In addition, a hemoglobin or hematocrit should be determined. All AIDS related deferral procedures shall be followed.
- B. Persons who have recently ingested medication containing aspirin, especially within 36 hours, may not be suitable donors for Platelets, Pheresis.
- C. If pheresis procedures are performed at the same frequency and interval allowed for whole blood, the donor should meet the whole blood suitability criteria. No additional laboratory testing is required for this frequency and interval.
- D. If pheresis procedures are to be performed at a greater frequency or shorter interval than allowed for whole blood, then, in addition to meeting the whole blood donor suitability criteria, a blood sample should be drawn from the donor prior to the start of the initial plateletpheresis procedure. A platelet count should be performed and the results reviewed prior to the donor's undergoing each subsequent procedure. Counts obtained after the previous procedure may serve this purpose. The platelet count should be greater than 150,000. Donors whose counts are less than those stated above should be deferred until the counts have returned to normal.
- E. A donor should not generally undergo a total of more than 24 platelet pheresis procedures during a calendar year. With intervals of 48 hours between procedures, a donor should not undergo more than two procedures within a seven day period.
- F. Platelets, Pheresis collected repeatedly from a single donor and intended for a single recipient, i.e., dedicated or family donor, may be collected as often as necessary for a period not to exceed 30 days (21 CFR 606.110).

The donor should be examined as for whole blood donation prior to each plateletpheresis in order to ascertain his/her health status. The testing of the dedicated donor for disease transmission potential, i.e., serological test for syphilis (STS), hepatitis testing (HBsAg), HIV antibody testing, and ABO and Rh grouping, need be done only once at the beginning of the donation period. Other recommendations as described under Processing and Testing apply to every unit of Platelets, Pheresis collected from a single donor intended for a single recipient.

- G. Donors undergoing plateletpheresis procedures with greater frequency than mentioned in paragraph I.E., who do not meet the criteria of I.F., will be considered by the Center for Biologics Evaluation and Research to be undergoing an investigational procedure. If the product is to be shipped interstate, an "Investigational New Drug Application" must be filed. The conditions that should be met prior to the performance of each investigational procedure are as follows:

1. There should be an investigational protocol describing the information that will be obtained at each donation. At minimum, a white blood cell count, differential, and platelet count should be performed prior to each donation procedure. These data should be maintained cumulatively for each donor and reviewed periodically by a physician for any adverse effect. The accumulation of other data (especially that pertaining to donor cellular immunity) is encouraged.
 2. The medical director or designated physician should certify in writing that the need to collect the component from this particular donor to support a patient outweighs the potential risks as they are known.
 3. There should be an investigational procedure consent form in addition to the routine informed consent form to be signed by the donor and a witness. The responsible physician should obtain this consent.
- H. Any person who has donated 1 unit of whole blood or who has lost the equivalent amount of whole blood (450 mL) during a pheresis procedure should not serve as a pheresis donor for eight weeks if extracorporeal red blood cell volume during the procedure is greater than 100 mL. In the event of exceptions for plateletpheresis procedures, the responsible physician should certify in writing the need to collect this component as described in paragraph I.G.2.
- I. Maximum total red blood cell loss (whole blood donations, red blood cell loss during pheresis, and laboratory samples) for one calendar year should not exceed the loss of red blood cells permitted by FDA regulations for whole blood collection.
- J. Red blood cell loss noted for pheresis procedures that exceeds the frequency limit stated for whole blood in paragraph I.D. should be monitored by means of a hematocrit determination performed on products containing visibly apparent red blood cells. Complete and accurate donor records should be maintained.
- K. The total volume (excluding anticoagulant) of all blood products retained per plateletpheresis procedure should not exceed 500 ml (600 ml for donors weighing more than 175 pounds). Collection of plasma by products (Source Plasma, Fresh Frozen Plasma, Plasma, etc.) from plateletpheresis procedures (resulting in a larger total volume) will be considered upon receipt of amendments to establishment and product applications. In addition, plasma obtained by plateletpheresis shall be collected as prescribed in 21 CFR 640.64, 640.64 (except that (c)(3) of 640.64 shall not apply), and 640.65.
- L. The accumulated laboratory data for donors should be monitored by qualified personnel and reviewed every four months by a licensed physician. The minimum acceptable values should be included in the center's protocol and exceptions to these criteria approved in writing by the physician responsible for the pheresis program. A statement should be signed for exceptions made where laboratory values for a donor are at variance with accepted standards.
- M. Donors should be questioned about adverse reactions during or after previous pheresis or other blood donations. The determination of suitability to serve as a pheresis donor should take into account such reactions. A notation about the moderate to severe reactions should be made in the donor record file if a reaction has any bearing on future donations and/or applicable restrictions.

- N. The pheresis instrument employed should be approved by the Center for Biologics Evaluation and Research (see appendix).

II. INFORMED CONSENT

The elements of informed consent as stated here are not applicable to investigational procedures. Full consent should be obtained from new donors. On subsequent donations the signing of simple consent statements will suffice. For investigational procedures, the Investigational New Drug Application (IND) informed consent requirements (21 CFR 50.25) would apply.

- A. Appropriate consent should be obtained by a physician or an allied health person experienced in the procedure to be performed. A copy should be offered to the person signing the form.
- B. In seeking informed consent, the following information should be provided each donor:
1. A description of the procedures to be followed should be given in language understandable to the donor.
 2. A description of any reasonable foreseeable risks or discomforts that may occur. Information as to the side effects of the procedure and the hazards of solutions and/or drugs the donor will receive should be given.
 3. An explanation of the procedure should consist of such disclosure and be made in such a manner that a clear opportunity to refuse is presented.
 4. A statement that participation is voluntary and that donors may withdraw their consent at anytime.
 5. A statement informing the donor of his/her right to ask questions of and discuss the procedure with a physician.
 6. A statement that the long term effect of the reduction of lymphocytes is not clear.
 7. A statement that the donor has reviewed and understands the information provided to him/her regarding the spread of AIDS virus by donated blood and plasma. It should also state that if the donor considers him/herself to be at risk for spreading the virus known to cause AIDS, that he/she will agree not to donate blood or plasma products for transfusion to another person or for further manufacturing.

III. PROCEDURAL PROTOCOLS

- A. A qualified physician who is familiar with the procedure should be available to attend the donor within 15 minutes when a pheresis procedure is being performed and should be available for consultation and management of donor adverse reactions.
- B. Personnel engaged in plateletpheresis should obtain specialized training for the use of the instruments involved. This training should include periodic refresher courses that include updated information on product preparation and machine maintenance.

- C. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis that conforms with 21 CFR 606.60.
- D. During the course of the procedure the separated plasma should be visually inspected for hemolysis. A red tinge to the plasma in the return line is cause for evaluation (prior to the reinfusion to donor) to determine whether this results from red blood cell contamination of plasma or to hemolysis.
- E. There should be a written procedure for management of a cardiopulmonary emergency which contains steps (including phone numbers) for contacting physicians, obtaining an emergency rescue squad, and transport of the donor to the hospital.
- F. The Center for Biologics Evaluation and Research requests that each establishment seeking licensure of Platelets, Pheresis prepared by approved instruments submit two units of freshly prepared Platelets, Pheresis from each approved instrument. An establishment may submit two whole units or two hermetically sealed aliquots (30-40 mL). A tie tag should be attached to each unit identifying the machine manufacturer, the PH, the platelet count, the white blood cell count, the total volume of product, and the packed red blood cell volume.

Processing and labeling should be completed prior to shipment, including preliminary HBSAg and HIV antibody test results. The same care should be taken in collecting, packing, and shipping as that taken for products intended for transfusion. Shipping arrangements should insure that samples arrive at the Center for Biologics Evaluation and Research prior to product expiration time. The products should not expire on the weekend.

Scheduled shipments should arrive prepaid at the following address between 8:30 a.m. and 4:00 p.m. Monday through Friday:

Center for Biologics Evaluation and Research
Food and Drug Administration
8800 Rockville Pike
Building 29, Room 323
Bethesda, MD 20892

IV. PROCESSING AND TESTING

- A. Platelets, Pheresis should be processed as a whole blood donation. Testing is performed on a pilot samples) drawn at the time of the procedure and should include ABO/Rh grouping, and all required testing for transfusion associated infections. HBsAg testing should conform to 21 CFR 610.40 and HIV antibody testing should conform to 21 CFR 610.45 and be completed prior to transfusion of plateletpheresis products. For Platelets, Pheresis collected repeatedly over a 30 day period from a single donor and intended for a single recipient, these tests need be done only once at the beginning of the donation period (see I.F.).
- B. A hematocrit should be performed on final products containing visibly apparent red blood cells to determine total packed red blood cell volume. If the final product contains more than 2 ml of packed red blood cells, a sample of donor blood should be attached to the container for compatibility testing. The possibility of adverse reactions due to ABO incompatible red blood cells should be stated in the product's circular of information.

- C. The dating period for Platelets, Pheresis collected with an approved instrument is 24 hours from the termination of the procedure, unless the system used for collection has been specifically approved for longer storage (see appendix).
- D. Platelets, Pheresis should be stored at 20-24°C with gentle agitation.
- E. During the establishment phase of the procedure, the following determinations should be made for each unit: hematocrit or red blood cell count, platelet count, white blood cell count, pH determination, and total product volume. The total number of platelets and the volume of red blood cells obtained from each plateletpheresis should be calculated. During this period sterility tests should be performed as described in 21 CFR 610.12 on outdated units, or on 30 ml of the product separated at the time of preparation and stored at 20-24°C for the duration of the dating period. The procedure may be considered established when all operators have been trained and several consecutive procedures yield consistently satisfactory products meeting all requirements.
- F. Once the procedure is operating satisfactorily, at least 75% of the units tested should contain a minimum of 3.0×10^{11} platelets unless the equipment has been approved by the FDA for collection of a product having a lower minimum limit (see appendix). In addition, four units per month should be tested at the time of issue (or the maximum storage time allowable for bag system used) to provide additional quality control information. All of these units should have a pH of greater than 6.0. A white blood cell count should be done as a quality control indicator for the automated plateletpheresis instruments. The Standard Operating Procedures Manual should state maximum acceptable limits for instruments in use. A weight/volume conversion should be done for calculation purposes. A hematocrit should be performed on the final products containing visibly apparent red blood cells to determine total packed red blood cell volume.
- G. The actual platelet content of product (volume X platelet count) should be determined on every unit. These data should be a part of the issue records.

V. LABELING INSTRUCTIONS:

NOTE: The following instructions fulfill requirements in 21 CFR, Part 606 only when the guideline for uniform labeling is met. The container label should bear the following information:

- A. The proper name of the product, Platelets, Pheresis.
- B. The appropriate donor classification statement, i.e., "paid donor" or "volunteer donor" as prescribed in 21 CFR 606.121 (c)(5).
- C. The volume of the product, accurate to within $\pm 10\%$ or a volume range with reasonable limits.
- D. A statement indicating the kind and volume of anticoagulant solution present. The estimated amount of anticoagulant added to blood during processing is satisfactory.
- E. The donor's ABO and Rh blood groups.
- F. Donor unit number.

G. The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, the hour of expiration.

H. Recommended storage temperature of 20 to 24 °C.

I. The statement: "See circular of information for indications, contraindications, cautions, and methods of infusion."

J. The statement: "Properly identify intended recipient."

K. The statement: "This product may transmit infectious agents."

L. The statement: Caution: " Federal Law prohibits dispensing without prescription."

M. Name, address, registration number, and if applicable, the license number of the manufacturer.

The package insert should include the following specific information in addition to the general requirements for all blood products:

- (1) Instructions to use a filter (other than a microaggregate filter) in the administration equipment.
- (2) Instructions to begin administration as soon as possible but not more than 4 hours after entering the container.
- (3) A statement indicating that the actual platelet content is available from the manufacturer upon request.
- (4) Instructions to maintain continuous gentle agitation during storage.

Appendix to Guideline for the Collection of Platelets, Pheresis Prepared by Automated Methods

Currently approved instruments for automated collection of Platelets, Pheresis:			
Minimum Storage	Platelet Concentration (maximum)	Manufacturer Instrument	Per Unit Storage
Haemonetics	H-30	H-30S 3.0×10^{11}	24 hours
Haemonetics	V-50 (without surge)	2.0×10^{11}	24 hours
Haemonetics	V-50 (with surge)	3.0×10^{11}	24 hours
Haemonetics	V-50 (with surge)	3.0×10^{11}	5 days in functionally closed system using CLX
Baxter	Fenwal CS-3000	3.0×10^{11}	24 hours
Baxter	Fenwal CS-3000	3.0×10^{11}	5 days in functionally closed system using PL-732
COBE/IBM	IBM-2997 (dual/stage)	3.0×10^{11}	24 hours
COBE/IBM	Spectra	3.0×10^{11}	5 days in functionally closed system
Dideco	Progress 790/A	3.0×10^{11}	24 hours

Currently approved instruments for automated plasmapheresis:			
Haemonetics	V-50		
Haemonetics	PCS		
Baxter	Autopheresis C		
Baxter	Fenwal CS-3000		

Note: This appendix will be revised periodically and copies of the latest revision of this appendix will be available upon request from the Center for Biologics Evaluation and Research (HFB-480).