Guidance for Industry

Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods

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GUIDANCE FOR INDUSTRY

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This guidance document represents FDA's current thinking on recommendations for collecting red blood cells by automated apheresis methods. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance document provides the recommendations of the Food and Drug Administration (FDA) for the use of FDA cleared automated blood cell separators in blood establishments for collecting single and double units of Red Blood Cells (RBC). This guidance also describes the information to be included in a license application or supplement. This final guidance document finalizes the draft guidance document entitled "Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods," dated July 1998.

II. BACKGROUND

The FDA has cleared devices that allow for the safe and effective collection of RBC using automated methods. The intended uses of those devices include use in the collection protocols for:

a) a single unit of Red Blood Cells and plasma,
b) a single unit of Red Blood Cells and platelets,
c) a single unit of Red Blood Cells, platelets and plasma, or
d) double units of Red Blood Cells only.

Other intended uses and other collection protocols are being evaluated by the Center for Biologics Evaluation and Research (CBER).

Blood establishments that currently manufacture licensed RBC products and intend to use these devices must notify FDA before implementing this change in their production process [21 CFR 601.12(b)]. Blood establishments that plan to apply for a license for RBC products using these devices must include a full description of manufacturing methods in their license application [21 CFR 601.2(a)]. This guidance document describes recommended donor selection criteria, product quality control protocol, and other criteria that should be addressed in license applications and supplements for automated RBC collections.

FDA regulations require that equipment used in the collection or processing of blood and blood components "shall perform in the manner for which it was designed." [21 CFR 606.60(a)]. An establishment must maintain written standard operating procedures for all steps in the collection and processing of blood and blood components [21 CFR 606.100(b)]. Accordingly, an establishment must incorporate the device manufacturer's instructions for use into its standard operating procedures for collecting red blood cells by automated apheresis methods. Regulations further require establishments to maintain records "concurrently with the performance of each significant step in the collection [and] processing... of blood and blood components." [21 CFR 606.160(a)(1)].

Blood establishments that use or intend to use FDA cleared devices to manufacture either double units of RBC or single unit of RBC plus platelets and/or plasma using automated methods should revise their SOP and records to include such methods. The procedures and records should include, at a minimum, all the donor selection criteria consistent with FDA regulations and the manufacturer's instructions for use, as specified in the device operator's manual, manufacturing procedures, recordkeeping requirements, information necessary for product tracking, lot numbers of all leukocyte reduction filters, disposables, and fluids (anticoagulants, saline and additive solutions), QC acceptance criteria and test results, and labeling.

III. CHANGES FROM THE DRAFT GUIDANCE

Several comments were received on the draft guidance document (Docket Number 98D-0545). The majority of the comments addressed the donor selection criteria for the double RBC protocol, the donation intervals, and the procedures for the quality control of the RBC product.

In the draft guidance, FDA identified suitability criteria, in addition to criteria identified in FDA regulations, for donors of two (2) units of RBC. Those additional criteria were identical to those included in the instructions for use of the only device cleared for the collection of two (2) units of RBC at the time the draft guidance was issued. In the future, FDA may clear devices intended to be used in the collection of RBC from donors identified by different selection criteria. The criteria identified in the draft guidance would not be appropriate for use in such devices. It is for this reason that FDA is not identifying additional criteria for donor suitability in this guidance document. Instead, FDA recommends that an establishment assure the safety of donors. Moreover, an establishment must use the collection device "in the manner for which it was designed." [21 CFR 606.60(a)]. Establishments should follow the donor selection criteria described in the device operator's manual. In addition, the donor must meet all FDA criteria for allogeneic Whole Blood donation [21 CFR 640.3 and 640.12]. Autologous donors should be selected following the procedures described in the device operator's manual and the establishment's SOP. Unless the weighing of donors is specified in the device operator's manual, FDA is not recommending the routine weighing of all donors who undergo double RBC collection. Since insufficient data is available to determine the effect of double RBC collection on donors of small stature, FDA is recommending that donors who are near the minimum weight be further evaluated (e.g., weighed, center physician assessment, etc.) to assure their eligibility to undergo double RBC collection. In addition, FDA is recommending that a quantitative method be used to determine the pre-donation

hemoglobin or hematocrit of donors undergoing double RBC collection, as this method is more accurate.

In the draft guidance document, FDA recommended a sixteen (16) week donation interval between double RBC collection and any other type of donation procedure. Some comments complained that a 16 week interval was too long. At present there are insufficient data available to demonstrate that donation at a more frequent interval (less than 16 weeks) would not adversely affect donor safety. Therefore, FDA is continuing to recommend that donors be deferred for 16 weeks after undergoing double RBC collection before participating in any other type of donation protocol, including plateletpheresis and plasmapheresis.

FDA has revised the product quality control section in the draft guidance document and is now recommending a two-phase process for RBC product QC. During the first phase of the QC process, the manufacturer should test each unit for the parameters described in the device operator's manual. If an evaluation of the data obtained from these tests demonstrates that at least 95% of the RBC units meet the manufacturing specifications defined in the device operator's manual and the establishment's SOP, the manufacturer may proceed to the second phase and test a representative sampling of products manufactured each month. The revised QC process is described in section IV. of this final guidance document.

Questions may be directed to the Division of Blood Applications, CBER at 301-827-3543 (fax: 301-827-3534) or Division of Hematology, CBER at 301-496-2577 (fax: 301-402-2780).

IV. RECOMMENDED DONOR SELECTION CRITERIA FOR THE AUTOMATED RED BLOOD CELL COLLECTION PROTOCOLS

Automated RBC collections are unlike plateletpheresis collections. While plateletpheresis and plateletpheresis with plasma by-products donors may undergo no more than 24 procedures during a calendar year and no more than two procedures within a seven-day period with at least 48 hours between procedures, the donation intervals for RBC collections are much longer. (See the FDA Guideline for the Collection of Platelets, Pheresis by Automated Methods, October 7, 1988. Obtain the document from the CBER fax information system: 1-888-223-7329.) Establishments should follow the instructions for use described in the device operator's manual, including the donor suitability criteria. In addition, FDA makes the following recommendations:

A. Donor Selection

1. Hematocrit/Hemoglobin – A donor should have an adequate hemoglobin level. FDA recommends that a quantitative method be used for determining the pre-donation hemoglobin or hematocrit of donors who will undergo the double RBC collection protocol. Use of copper sulfate ($CuSO_4$) is not recommended.

2. Donor weight – FDA recommends that donors of small stature who are near the minimum weight be further evaluated (e.g., weighed, center physician assessment, etc.) to assure their eligibility to undergo double RBC collection.

3. Selection Criteria –

   a. Allogeneic donors: The donor selection criteria described in the device operator's manual should be followed. The donor must also meet all FDA criteria for allogeneic Whole Blood donation [21 CFR 640.3 and 640.12].

   b. Autologous donors: The donor selection criteria described in the device operator's manual and the establishment's SOP should be followed.

B. Donation Interval

1. Donors who donate a single unit of RBC plus platelets and/or plasma, like Whole Blood donors, should be deferred from all collections (including plateletpheresis and plasmapheresis) for at least 8 weeks [21 CFR 640.3(b) and 640.12] except:

   After donating a single unit of RBC, a donor may serve as a plateletpheresis or plateletpheresis with plasma by-products donor within eight weeks if the extracorporeal red blood cell volume during the procedure is less than 100 mL., provided all the required donor suitability criteria are met.

2. All donors should be deferred for at least sixteen (16) weeks after undergoing a double RBC collection procedure. No manual or automated collection procedures, including plateletpheresis or plasmapheresis, should be performed prior to 16 weeks.

3. RBC loss during an incomplete procedure –

   a. If an apheresis procedure is discontinued before completion and the absolute RBC loss is less than 200 mL, the donor may return to donate within 8 weeks provided all the required donor suitability criteria are met.

      i) If there is a second RBC loss of less than 100 mL during a subsequent donation within 8 weeks (total RBC loss within an 8 week period is less than 300 mL), the donor should be deferred for 8 weeks from the date of the second RBC loss.

      ii) If the total absolute RBC loss within 8 weeks is equal to or greater than 300 mL, the donor should be deferred for 16 weeks from the date of the last RBC loss.

b. If an apheresis procedure is discontinued before completion and the absolute RBC loss is equal to or greater than 200 mL but less than 300 mL, the donor should be deferred for 8 weeks.

c. If an apheresis procedure is discontinued before completion and the total absolute RBC loss is equal to or greater than 300 mL, the donor should be deferred for 16 weeks.

V. RECOMMENDED RED BLOOD CELL PRODUCT QUALITY CONTROL

FDA regulations require blood establishments to perform appropriate tests before release of their products [21 CFR 211.110, 606.100, 606.140, 610.1, 610.10]. FDA believes that the quality control test program described below would satisfy this regulatory requirement.

A. Phase One Quality Control – Testing each product:

1. Evaluate 100 consecutive RBC units in the following manner:

   a. Determine the expected or target RBC volume (either total RBC product volume or absolute RBC mass volume, as determined by the device operator's manual (usually based on the donor's gender, weight, and hematocrit or hemoglobin)). Determine any other target parameters specified in the device operator's manual.

   b. After the collection procedure, calculate the total RBC product volume or absolute RBC mass volume and any other parameters, if applicable, using a method described in the device operator's manual or a validated method developed by the establishment. (Total red blood cell product volume = weight of the RBC divided by the appropriate specific gravity. Absolute red blood cell mass volume = total RBC volume X product hematocrit. NOTE: Specific gravity of product with additive solution is 1.06 g/mL and without additive solution is 1.08 g/mL.[1])

   c. Compare the target values and the actual values to determine product acceptability. Use the product acceptability ranges described in the device operator's manual to determine if the product meets the volume specifications. If ranges are not available in the operator's manual, the product must at least meet the volume range described in the labeling [21 CFR 606.121(c)(6)].

2. Retrospective data accumulated from prior units may be used to qualify the collection process, but the data should represent consecutively collected units.

[1] Mollison PL, Engelfriet CP, Contreras M. Blood Transfusion in Clinical Medicine. 10th ed. London: Blackwell Scientific Publications, 1997:560.

3. The 100 consecutive units should represent units collected from each device in use at the collection center and from all collection protocols (e.g., single RBC and double RBC).

4. Both units collected during a double RBC collection protocol should be included and may count as two units in the QC process.

5. If the evaluation of the data collected during this initial phase indicates that the collection procedure can be performed with at least 95% of the units meeting the product specifications described in the device operator's manual or on the product labeling (95 of the 100 units tested meet the specifications), the establishment may proceed to Phase Two.

6. If more than 5% of the units fail to meet the product specifications, the cause of the deviations should be investigated and corrected as part of the overall quality assurance program and the Phase One qualification process should be repeated. Units that do not meet the acceptable ranges specified in the device operator's manual or in the product labeling should be evaluated to determine their suitability for distribution. Biological product deviations (formerly known as errors and accidents) in manufacturing that may affect the safety, purity and potency of distributed product, must be reported to CBER, in accordance with the current reporting requirements [21 CFR 600.14 and 606.171].

B. Phase Two Quality Control – Monthly testing of a representative sampling of manufactured product:

1. Each month, test a minimum of 50 units at each collection center for the total RBC product volume or absolute RBC mass volume (as determined by the device operator's manual) and any other parameters described in the device operator's manual. If fewer than 50 units were manufactured at the center during the month, all units should be tested. Include RBC products from all collection protocols performed on all devices in use at the center.

2. Include at least one unit from the single RBC protocol and both units from the double RBC protocol collected on each device in use at the center, regardless of the manufacturer of the device, in the Phase Two sampling.

3. At least 95% of the product tested in the sampling should meet the product specifications described in the device operator's manual or on the product labeling.

4. If more than 5% fail to meet the product specifications, the cause of the deviations should be investigated and corrected as part of the overall quality assurance program and the process should be repeated. Units that do not meet the product specifications

should be evaluated to determine their suitability for use. Biological product deviations (formerly known as errors and accidents) in manufacturing that may affect the safety, purity and potency of distributed product, must be reported to CBER in accordance with the current reporting requirements [21 CFR 600.14 and 606.171].

VI. REGISTRATION AND LICENSING PROCEDURES FOR THE MANUFACTURE OF RED BLOOD CELLS COLLECTED BY AUTOMATED METHODS

All blood establishments must update their blood establishment registration and product listing form (FDA Form 2830) to report changes in blood product handling activity to FDA [21 CFR 607.7 and 607.26]. Establishments should update their product listing at the time they implement automated RBC collections, the subsequent June, or during the subsequent annual registration in December.

The implementation of automated RBC collection is a change that has substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a product. Blood establishments holding a biologics license application that intend to manufacture double RBC units and/or single unit of RBC plus platelets and/or plasma by automated methods must submit a supplement to their biologics license application and receive approval by FDA for each of these products prior to interstate distribution of the product [21 CFR 601.12(b)]. Blood establishments that are approved to manufacture RBC using one manufacturer's device and wish to change to another manufacturer's device must also submit a supplement and receive approval prior to distribution of the product manufactured on the new device [21 CFR 601.12(b)]. These supplements should include:

A. FDA Form 356h ("Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use") describing the products for which the applicant is requesting licensure (e.g., single RBC and two (2) units of Fresh Frozen Plasma, double RBC, etc.). Include the name(s) of the anticoagulant(s) and device(s) that will be used to manufacture the products and list the manufacturing site(s) that will be collecting RBC by automated methods.

B. Standard Operating Procedures [21 CFR 606.100] related to the collection of two (2) units of RBC and/or one (1) unit of RBC plus platelets and/or plasma by automated apheresis. The SOP should include methods for determining allogeneic and autologous donor eligibility and product acceptability and should be consistent with device operator's manual, FDA regulations and labeling requirements, where applicable. All blood establishments performing the double RBC collection procedure must include in their SOP methods to accurately track multiple units collected from each donation [21 CFR 606.160(b)(1)(vii), 606.160(c), and 606.165(a)].

C. Records and Forms [21 CFR 606.160, 606.165 and 606.170], including:

1. Informed Consent Form [21 CFR 606.160(b)(1)(i)] describing the procedure, donation frequency, and any reasonable risks or discomforts that might occur. The form should include, but not be limited to the following:

   a. Complications at the venipuncture site, e.g., bruising, hematoma formation or local infection.

   b. Tingling of fingers or lips, or tremor due to a reaction to the anticoagulant.

   c. Nausea, vomiting, light-headedness, fainting, dyspnea, dizziness, pallor, feeling of warmth, chills, excessive tiredness, or convulsions related to change in blood volume.

   d. Frequency of donation procedures and intervals between donations.

2. Donor Suitability [21 CFR 606.160(b)(1)(i)].

3. Product Collection [21 CFR 606.160(b)(1)(vi)].

4. Quality Control for the product [21 CFR 606.140].

D. Quality Control

Submit two (2) months of quality control data for products collected after the Phase I qualification process, using the automated device. Include units collected from all devices in use and from all collection protocols being applied for (e.g., single RBC and double RBC). Separate QC data should be submitted for each collection center.

E. Labeling

1. Submit labels with FDA Form 2567 ("Transmittal of Labels and Circulars").

2. The labels must meet the applicable requirements set forth in 21 CFR 606.121 for Red Blood Cells, Platelets, Pheresis, and Fresh Frozen Plasma and in 21 CFR 640.70 for Source Plasma.

3. Labels should display the proper product codes for the product being collected.

VII. ADDITIONAL REQUIREMENTS

Pursuant to FDA regulations, all blood establishments must also maintain the following records. These records do not need to be submitted, but should be available for review during FDA inspections.

- Records related to instrument and disposable equipment failures and reporting of failures to device manufacturers. Establishments should follow the device operator's manual for corrective action for any adverse or unexpected event, e.g., evidence of product hemolysis [21 CFR 606.60(a)].

- Documentation of observation, standardization and calibration of the automated equipment on a regularly scheduled basis, consistent with 21 CFR 606.60(b) and the device operator's manual [21 CFR 606.60(a), 606.160(b)(5)(i) and 606.160(b)(7)(iv)].

- Documentation of installation, operation and performance qualification tests, as applicable, performed on the automated device prior to implementing routine collections, in accordance with the device operator's manual [21 CFR 606.60(a), 606.160(b)(5)(i), 606.160(b)(5)(ii)].

- Documentation of a thorough investigation, including the conclusions and follow up, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications [21 CFR 606.100(c)].

- Records of any donor adverse reaction complaints and reports, including results of all investigations and follow up [21 CFR 606.160(b)(1)(iii)].

- Personnel training for the collection of RBC by automated apheresis [21 CFR 606.20(b), 606.160(b)(7)(ii), and 606.160(b)(5)(v)]. FDA recommends that complete product QC testing be performed on all RBC units collected by an operator during the training period.