Recommendations for the Development of Blood Collection, Processing, and Storage Systems for the Manufacture of Blood Components Using the Buffy Coat Method

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research
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I. INTRODUCTION

The purpose of this guidance is to provide recommendations on the development of blood collection, processing, and storage systems (e.g., blood bags with anticoagulant and additive solutions, empty bags for platelet pooling) intended for the manufacture of blood and blood components for transfusion using the buffy coat (BC) method. This guidance is intended for manufacturers of blood collection, processing, and storage systems. The recommendations in this guidance do not apply to devices used to manufacture platelet rich plasma or similar products used for therapeutic purposes other than transfusion.

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II. BACKGROUND

Whole Blood (WB)-derived components for transfusion, including platelets, plasma, and red blood cells (RBCs), can be manufactured using methods that consist of different, sequential centrifugation steps. In the United States (U.S.), blood establishments currently prepare WB-derived blood components using the platelet rich plasma (PRP) method (Ref. 1). In this method, WB is centrifuged at a relatively low speed (i.e., a "soft spin") to yield RBCs and PRP. PRP is then separated from the RBCs, and the PRP undergoes a second centrifugation step (i.e., a "hard spin") to yield platelet and plasma components. Certain other countries prepare blood components from WB using the BC method (Ref. 2). In the BC method, WB is centrifuged at a high speed (i.e., a "hard spin") to yield RBCs, plasma and a zone between the RBCs and plasma,

which is the BC that contains platelets and white blood cells. The BC is then separated from the RBCs and plasma. Either a single BC or a pool of 4-6 BCs is then centrifuged at low speed (i.e., a "soft spin") to yield the supernatant-containing platelets which are separated, often leukoreduced, and then stored in plasma or additive solution, under defined conditions and duration before transfusion.

Blood establishments in the U.S. are interested in using the BC method to manufacture blood components for transfusion. Studies demonstrate that blood components prepared by using the BC method are comparable to blood components prepared using the PRP method, in terms of biochemical and physiological characteristics (Refs. 3-7). In addition, use of the BC method may offer logistical advantages, which could result in higher plasma and platelet recovery and increased platelet availability, when compared to the PRP method (Ref. 8).

Blood and blood components must be prepared in a manner consistent with the instructions provided by the manufacturer (Title 21 Code of Federal Regulations 606.65(e)), including the directions provided in the instructions for use of the approved or cleared collection, processing, and storage system. To prepare blood components using the BC method, blood establishments must use blood collection, processing and storage systems approved or cleared for such use. However, blood collection, processing, and storage systems currently marketed in the U.S. are only approved or cleared for the preparation of blood components from WB using the PRP method, and none are yet approved or cleared for the preparation of blood components using the BC method.

This guidance provides recommendations to manufacturers who wish to obtain FDA approval or clearance to market blood collection, processing, and storage systems intended for the manufacture of blood components for transfusion using the BC method. With the availability of such systems, blood establishments in the U.S. would have the option of manufacturing WB-derived blood components using the BC method.

III. RECOMMENDATIONS

Our recommendations for the development of blood collection, processing, and storage systems for the manufacture of blood components for transfusion using the BC method are as follows:

1. The regulatory pathway for a blood collection, processing, and storage system depends on whether the system consists of an empty bag alone or contains anticoagulant or storage solutions. Manufacturers should contact FDA to clarify the appropriate regulatory pathway (e.g., New Drug Application (NDA), Premarket Approval (PMA) or 510(k), Investigational New Drug (IND) or Investigational Device Exemption (IDE) submission) for their blood collection, processing, and storage systems.

2. When developing collection, processing, and storage systems that include anticoagulant or additive solutions for RBCs and platelets, manufacturers should consider using solutions already approved by FDA.

3. Regulatory submissions for blood collection, processing, and storage systems should include the following:

    a. The design of the collection, processing, and storage system, including materials used for construction.

    b. A description of the established methods, facilities and controls used for the manufacture of the blood collection, processing and storage system.

    c. Biocompatibility studies and toxicologic risk assessments:

        Biocompatibility testing should be performed on the sterilized finished product, using test conditions simulating clinical use. Biocompatibility tests should include extractables and leachable studies and a toxicological risk assessment of these chemicals. Manufacturers may refer to the latest version of the International Standard ISO 10993-1 (Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process), and applicable FDA guidance documents including "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'; Guidance for Industry and FDA Staff" (Ref. 9).

    d. Performance data that support sterility of the collection, processing and storage system including sterilization validation, endotoxin testing, and container closure integrity evaluation.

    e. Performance data that support maximum shelf life of the collection, processing, and storage system.

    f. Results of studies evaluating the quality of blood components using the BC method throughout the duration of storage.

        The study results should demonstrate that blood components prepared using the BC method are comparable to blood components prepared using approved or cleared collection, processing, and storage systems. If the collection, processing, and storage system includes pooling of BC to prepare platelets, study results should represent the maximum pool size.

        Manufacturers should conduct in vitro studies that evaluate key parameters representing the quality of blood components prepared with their collection, processing and storage systems developed for the BC method. This includes parameters tested as a primary endpoint and other parameters as secondary endpoints. Some suggested parameters for the secondary endpoints for platelets, plasma and RBC components to demonstrate comparability with blood components prepared in approved or cleared blood collection, processing and storage systems are listed in

Appendix A. While the list is not comprehensive nor exhaustive, we view these measurements or some combination thereof as an adequate demonstration of the quality of the blood components for transfusion.

Manufacturers should use standard summary statistics (e.g., mean, standard deviation, minimum, median, and maximum values) to report the results of the in vitro studies. Study acceptance criteria for each blood component type should include the following:

i. Platelet components (evaluated for single units or pools):

- Primary endpoints:
  - Platelet pH at end of storage: 95% confidence that greater than 95% of components have a pH ≥6.2 (22°C).
  - Platelet yield at end of storage: 95% confidence that greater than 75% of components have a platelet yield of ≥ 5.5 $x10^{10}$ platelets per unit or 3.0 x 10^{11} for pooled BC platelet units.
- Secondary endpoints at end of storage: The averages of the differences between test and control should be less than 20%. We recommend a sample size of at least 60 single units or 60 pools in the test and control arms.

ii. Plasma components:

Biochemical and functional parameters of plasma components manufactured using BC method should be compared to control plasma after at least 30 days of frozen storage. The averages of the differences between test and control should be less than 20%. We recommend a sample size of at least 60 units in the test and control arms.

iii. RBC components:

- Primary endpoint: 95% confidence that greater than 95% of components show ≤1.0% hemolysis at the end of storage.
- Secondary endpoints at the end of storage: The averages of the differences between test and control should be less than 20%. We recommend a sample size of at least 60 units in the test and control arms.

g. If the collection, processing, and storage system includes a leukocyte reduction filter, you should provide results on the performance of the leukoreduction filter. We recommend the following acceptance criteria:

i. Residual white blood cell (WBC) content: 95% confidence that greater than 95% of RBC components have < 5.0×10^6 residual WBCs. For platelet units: < 8.3×10^5 residual WBCs or < 5.0×10^6 residual WBCs for a platelet pool.

ii. Percent recovery of the original component: The acceptance criteria for RBC or platelets is at least an 85 percent recovery of the original component.

h. Manufacturers should conduct appropriate clinical studies or submit existing clinical data to demonstrate the safety and efficacy of blood components prepared using the BC method.

IV. COMMUNICATION WITH FDA

We recommend manufacturers engage CBER's Office of Blood Research and Review (OBRR) early in product development and before submission of a drug or device application. The meeting type for such discussions depends on the regulatory pathway and the stage of product development. These include pre-submission meetings for devices or type C meetings for NDAs. Contact OBRR with any questions regarding the appropriate meeting type.

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APPENDIX

Recommended in-vitro parameters for evaluation of platelets, plasma and RBC components at the end of storage.

1. **Platelets**

Item	In-vitro Parameters
1	Mean platelet volume (MPV)
2	Glucose *
3	Lactate *
4	pO_2
5	pCO_2
6	Bicarbonate (HCO_3^-), extracellular
7	Lactate dehydrogenase (LDH)*
8	Morphology score
9	Hypotonic stress response (HSR)
10	Extent of platelets shape change (ESC)
11	CD62P
12	PS exposure by annexin V binding or lactadherin

You should report the parameters shown with "*"as normalized values to the platelet content for glucose and lactate. For LDH, normalize the result to total cellular LDH content thus calculate relative LDH release.

2. **Plasma**

Item	In-vitro Parameters
1	Total protein
2	Albumin
3	IgG
4	Fibrinogen
5	PT
6	APTT
7	Prothrombin fragment 1,2 (PF1,2)
8	Factor V activity
9	Factor VII activity
10	Factor VIII activity
11	Factor IX activity
12	Factor X activity
13	Factor XI activity
14	Protein C
15	Protein S
16	ADAMTS 13 activity
17	vWF:Ag and activity
18	Alpha 2-antiplasmin activity

3. RBCs

Item	In-vitro Parameters
1	pH
2	pO_2
3	pCO_2
4	HCO_3^-
5	ATP conc. *
6	Sodium (Na^+), extracellular
7	Potassium (K^+), extracellular
8	Glucose
9	Lactate *
10	Hemoglobin conc. (Hgb)*
11	Hemoglobin content/unit
12	Mean corpuscular volume (MCV)
13	RBC morphology score
14	Hematocrit

You should report the parameters shown with "*" as normalized values to the RBC content.