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January 14, 2000

Docket Management Branch
HFA 305
Food and Drug Administration
12420 Parklawn Dr. Rm 1-23
Rockville, MD 20857

Docket Number 97N-0497

RE: Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products: Request for Comments

To Whom It May Concern:

The American Association of Blood Banks (AABB) is the professional society for approximately 9,000 individuals involved in blood banking and transfusion medicine and represents roughly 2,200 institutional members, including community and Red Cross blood collection centers, hospital based blood banks, and transfusion services as they collect, process, distribute, and transfuse blood and blood components and hematopoietic stem cells.

Enclosed please find (1) the second edition of the *AABB Standards for Hematopoietic Progenitor Cell Services* and (2) the Circular of Information For the Use of Hematopoietic Progenitor Cell Products. These documents are submitted in response to the FDA request for proposed Standards.

The AABB has been a standard-setting organization since 1958 when the first edition of *Standards for Blood Banks and Transfusion Services* was published. Beginning in 1991 these *Standards* also addressed Hematopoietic Progenitor Cell Services. In 1996 these HPC Standards were separated out and the first edition of *Standards for Hematopoietic Progenitor Cells* (HPC Standards) was published. The second edition was published in 2000. The AABB accredits institutions by inspecting the institution and determining compliance with quality and technical requirements in these *HPC Standards*.

These *HPC Standards* have been developed on the basis of good medical practice, and when available, scientific data. Input has been obtained from recognized experts in the field of hematopoietic progenitor cell collection and processing as well as public members. The *HPC Standards* are first published as proposed standards, and both AABB

member and public comment is sought before they are finalized. We also call your attention to both the preface and the introduction which provide important explanatory information.

These *HPC Standards* are compatible with ISO 9000 requirements and address the items identified in the FDA request for Standards. However, they do not specifically identify the categories as noted by FDA. Elements of establishment controls, processing controls, and product standards are included throughout the twenty sections of the *HPC Standards*.

The Circular of Information is intended to be distributed to hematopoietic progenitor cell users to provide them with information including product description, action, indications, contraindications, dosage and administration, and storage. All accredited institutions are required by the *HPC Standards* to use this Circular. We are providing a copy of this required Circular of Information as additional information for your use in evaluating the *HPC Standards*.

If you have any questions or need additional information, please contact Kay Gregory, AABB Director of Regulatory Affairs at 301-215-6522 or kayg@aabb.org.

Yours truly,

A handwritten signature in black ink that reads "Paul Ness MD". The signature is written in a cursive, slightly slanted style.

Paul Ness, MD
President

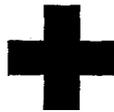
CIRCULAR OF INFORMATION

FOR THE USE OF HEMATOPOIETIC PROGENITOR CELL PRODUCTS

This circular was prepared jointly by the American Association of Blood Banks and the American Red Cross.



AMERICAN ASSOCIATION OF BLOOD BANKS



American Red Cross

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Notice to All Users

This *Circular*, as a whole or in part, cannot be considered or interpreted as an expressed or implied warranty for the safety or fitness of the described products when used for their intended purpose.

HPC products are biologic products in the form of living human tissue intended for use in the treatment of patients. The patient's physician will determine the choice of product, dosage, and rate of administration, and will make decisions in situations not covered in this *Circular*.

Warning: *Because this product is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.* In addition, if the product is bacterially contaminated, septic and toxic reactions may result. Such reactions are infrequent, but may be life-threatening. Other disease-causing agents may be present in these products.

This circular was prepared jointly by the American Association of Blood Banks and the American Red Cross.

Description

Hematopoietic progenitor cell (HPC) products can be prepared from donations by allogeneic or autologous donors. Collection usually occurs after mobilization with growth factors, the use of high-dose chemotherapy, or both.

Donors

For allogeneic donors, truthful and accurate information during health assessment is essential in order to provide a safe product to the recipient. Prior to donation, the process used to determine donor eligibility will include:

- A health history evaluation for past and present illnesses, high-risk behaviors, and other practices and circumstances that would be causes for deferral from donation.
- An evaluation to meet minimum physiologic criteria as set forth in the American Association of Blood Banks (AABB) *Standards for Hematopoietic Progenitor Cell Services* and the standards of the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT).

Testing of Donor Blood

Allogeneic Donors

Within 30 days of each collection, a sample of the allogeneic donor blood must be tested in accordance with the AABB

Standards for Hematopoietic Progenitor Cell Services and the FAHCT standards for the following:

- Donor qualification testing
 - ABO group and Rh type
 - HLA-A, -B, and -DR antigens
 - If the donor has a history of transfusion or pregnancies, test for antibodies to red cell antigens
- Infectious disease testing (FDA-licensed tests for infectious diseases)
 - HBsAg
 - Anti-HTLV-I
 - Anti-HTLV-II
 - Anti-HIV-1
 - Anti-HIV-2
 - HIV-1-Ag
 - Anti-HCV
 - Anti-HBc
 - Anti-CMV
 - Serologic test for syphilis

Prior to testing, the donor must agree that abnormal results will be communicated to the recipient's physician in order to provide proper informed consent for the patient.

Note: Red cells from the cord blood collection of the infant donor will be tested for ABO, Rh, and HLA-A, -B, -DR antigens. A sample from the donor's mother shall be collected within 48 hours of collection from cord blood donors, and required tests will be performed on this sample to prevent disease transmission.

Autologous Donors

For units that will be processed or administered outside the collecting facility, intended for autologous use, the donor-patient will have been tested for the following:

- Infectious disease testing (FDA-licensed tests for infectious diseases)
 - HBsAg
 - Anti-HTLV-I
 - Anti-HTLV-II
 - Anti-HIV-1
 - Anti-HIV-2
 - HIV-1-Ag
 - Anti-HCV
 - Anti-HBc

Instructions for All Hematopoietic Progenitor Cell Products

Laboratory

1. Verification of the correct product for the recipient must occur before removing the product from storage.
2. When thawing frozen products in a waterbath, care must be taken to prevent contamination of entry ports. The use of watertight protective plastic overwrap is recommended.

3. The product container must NOT be vented.
4. HPC products must be inspected prior to issue.

Nursing/Administration

5. The intended recipient must be properly identified before the product is administered.
6. HPC products should be mixed thoroughly before administration.
7. HPC products must NOT be administered through a leukocyte reduction or microaggregate filter. HPC products may be filtered through a 150- to 200-micron clot filter.
8. HPC products must not be irradiated.
9. No medications or solutions may be added or infused through the same tubing with HPC products except 0.9% Sodium Chloride, Injection (USP).
10. Lactated Ringer's, Injection (USP) or other electrolyte solutions containing calcium should NEVER be added or administered concurrently with products collected in an anticoagulant containing citrate.
11. If questions are raised during the inspection of the HPC product, the issuing laboratory must be consulted.
12. The patient should be observed during the infusion and for an appropriate period thereafter.
13. Vital signs must be recorded before and after the infusion and more often when needed.
14. All adverse events related to infusion, including possible bacterial contamination of a product or suspected disease transmission, must be reported to the processing laboratory and the collection facility.

Hematopoietic Progenitor Cell Product Labeling

Labels should contain the following information:

1. Product name.
2. Date of collection.
3. Name of collection service/donor registry.
4. Name of contact person, name of institution, address and telephone number (including emergency number) of receiving HPC therapy service.
5. Expiration date.
6. The donation (unit) identification number.
7. The donor category.
8. ABO group and Rh type.
9. Preparation method.
10. Recommended storage temperature.
11. Name/volume of anticoagulants and other additives in the product.
12. Approximate volume of product.
13. The phrase "Do Not Irradiate."
14. Statements referring to this *Circular* or regarding recipient identification, infectious diseases risk, and prescription requirement.

Labels will contain the following information when applicable:

1. Collection time.
2. Expiration time.
3. For patient-specific product, name or identifier of intended recipient.
4. The phrase "For Autologous Use Only," or "For Use by Intended Recipient Only."
5. Biohazard label.

Side Effects and Hazards

Immunologic Complications, Immediate

1. *Acute hemolytic reactions* are usually caused by the destruction of ABO incompatible donor red cells. Hemolytic reactions may occur due to blood type discrepancies. ABO incompatibility is not a contraindication to transplantation of HPCs from an HLA-matched donor. In cases of ABO or other major red cell incompatibility, methods of red cell depletion are available and should be employed to reduce the risk of a severe hemolytic reaction. Acute hemolytic reactions characteristically begin with an increase in temperature and pulse rate. Symptoms may include chills, dyspnea, chest or back pain, abnormal bleeding, or shock. Instability of blood pressure is frequent, the direction and magnitude of change depending upon the phase of the antigen-antibody event and the magnitude of compensatory mechanisms. Laboratory findings can include hemoglobinemia and/or hemoglobinuria, followed by elevation of serum bilirubin. In less catastrophic acute hemolytic reactions, a positive direct antiglobulin test result is commonly found. Treatments include measures to maintain or correct arterial blood pressure; to correct coagulopathy, if present; and to promote and maintain urine flow.
2. *Febrile nonhemolytic reactions* are typically manifested by a temperature elevation of $\geq 1\text{ C}$ or $\geq 2\text{ F}$ occurring during or shortly after an infusion and in the absence of any other cause. This may reflect the action of antibodies against white cells or the action of cytokines, either present in the infused component or generated by the recipient in response to infused elements. Febrile reactions occur more frequently in patients previously alloimmunized by transfusion or pregnancy, and in patients with immune dysfunction due to neoplasm or autoimmunity. No routinely available tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief.
3. *Allergic reactions* mostly occur as urticaria, but may also include wheezing or angioedema. No laboratory

procedures are available to predict or prevent these reactions, which usually respond to antihistamines or, in severe cases, corticosteroids or epinephrine.

4. *Anaphylactic reactions*, characterized by autonomic dysregulation, severe dyspnea, pulmonary and/or laryngeal edema, and bronchospasm and/or laryngospasm, are a rare but dangerous complication requiring immediate treatment with epinephrine, diphenhydramine, and/or corticosteroids.
5. *Allergic/anaphylactic reactions* to hydroxyethyl starch products of HPC cryoprotectants may occur in sensitized patients.

Immunologic Complications, Delayed

1. *Delayed hemolytic reactions* may occur when 1) antibodies remaining in the host attack donor red cells of an incompatible ABO type 2) transplanted immune cells attack residual ABO-incompatible recipient red cells after engraftment. Signs may include unexplained fever, development of a positive direct antiglobulin test, and unexplained decrease in hemoglobin/hematocrit. Hemoglobinemia and hemoglobinuria are uncommon, but elevation of lactic dehydrogenase or bilirubin may be noted. These delayed hemolytic reactions can occur within days or weeks of infusion.
2. *Alloimmunization* to antigens of red cells, white cells, platelets, or plasma proteins may occur usually after repeated transfusions. If products that express the relevant antigen are subsequently transfused, there may be accelerated removal of cellular elements from the circulation and/or systemic symptoms. Antibodies to red cell antigens will usually be detected by pretransfusion testing but there are no routinely performed pretransfusion tests for other antigen systems.
3. *Graft-vs-host disease* occurs when viable T lymphocytes in the infused product engraft and react against tissue antigens of the recipient.

Nonimmunologic Complications

1. *Transmission of infectious disease* may occur despite careful selection and testing of donors. Donor selection criteria are designed to screen out potential donors with increased risk of infection.
 - a. *Cytomegalovirus (CMV)* may, unpredictably, be present in leukocyte-containing products from donors previously infected with this virus. Infusion of products from seropositive donors has resulted in fatal CMV disease in some seronegative allogeneic transplant patients.
 - b. *For other infectious agents*, there are no routinely available tests to predict or prevent disease transmission.
2. *Bacterial contamination* occurs rarely but can cause acute, severe, sometimes life-threatening effects. On-

set of high fever (>2 C or >3.5 F rise in temperature), severe chills, hypotension, or circulatory collapse during or immediately after transfusion should suggest the possibility of bacterial contamination and/or endotoxin reaction. Prompt recognition of a possible septic reaction is essential and aggressive therapy with broad-spectrum antimicrobials and vasopressor agents increases the chances for a patient's survival if they are administered promptly. Investigation of a possible septic reaction should include a Gram's stain of the product and cultures of the product and the patient's blood.

3. *Circulatory overload*, leading to pulmonary edema, can occur after transfusion of excessive volumes or at excessively rapid rates. Pulmonary edema should be promptly and aggressively treated, and infusion of colloid preparations, including plasma products and the suspended plasma in cellular products, should be reduced to a minimum.
4. *Hypothermia* carries a risk of cardiac arrhythmia or cardiac arrest. Rapid infusion of large volumes of cold products can depress body temperature. *Do NOT use blood warming devices with HPC products.*
5. *Nonimmunologic hemolysis* can result from: 1) injury and lysis of red cells in the HPC freezing and thawing process; 2) effects of drugs co-administered with transfusion; 3) effects of bacterial toxins; 4) metabolic damage to cells, as from hemoglobinopathies or enzyme deficiencies.
6. *Hypertension* may occur in response to the cryoprotectant dimethyl sulfoxide (DMSO) or to volume overload. *Bradycardia* and *tachycardia* have also been observed in conjunction with hypertension and may be secondary to DMSO. These effects may be ameliorated by slowing the infusion or removal of DMSO.
7. Marrow products contain varying amounts of fat. Fat emboli may block capillary perfusion, causing dyspnea, chest tightness, and coughing. Supplemental oxygen may be required during and immediately after infusion.
8. Breakdown products of DMSO are excreted by the lungs, producing a strong, garlic-like odor that can be detected on the breath of the recipient of a cryopreserved product for 24 to 48 hours after the infusion.
9. *Nausea and vomiting* may occur with the infusion of thawed products containing DMSO. Premedication with antihistamines and/or antiemetics may be effective in preventing or reducing this response.
10. Flushing, rash, chest tightness, and other related symptoms may occur after infusion of products containing DMSO, and are due to histamine release. They are prevented by premedication with antihistamines.

Hematopoietic Progenitor Cell Products

Description

HPC products contain lymphohematopoietic cells capable of providing hematopoietic and immune reconstitution in a myeloablated recipient. The products contain varying numbers of pluripotent and lineage-committed hematopoietic progenitors. Procedures have been developed for depletion of plasma and of various cell populations from these products. HPC products can be broadly categorized by the extent of manipulation to which they have been subjected.

Actions

HPCs administered intravenously migrate to the marrow where they divide and mature. The mature cells are released into the bloodstream, restoring blood counts and immunity. The time from the infusion of HPCs to recovery of blood counts is variable. Allogeneic transplantation sometimes induces a graft-vs-tumor effect that is beneficial in recipients who receive a transplant for treatment of malignancies.

Indications

Allogeneic HPC infusions are performed to provide hematopoietic reconstitution for individuals with marrow aplasia or chemotherapy-induced marrow ablation. This therapy may be indicated for certain malignancies, immune deficiencies, hematologic diseases, and congenital diseases. *Autologous* HPCs are collected and stored for use as rescue from myeloablative therapy and as vehicles for some types of immune therapy and gene therapy.

Contraindications

Institutional policies and protocols will dictate specific contraindications for HPC transplantation.

Dosage and Administration

The minimum number of HPCs necessary for engraftment in a myeloablated recipient has not been established. However, eligibility criteria for institutional protocols may dictate a minimum number of cells to be collected and infused. The number of cells in a collection is determined using various methods of graft evaluation. Some preparations may require filtration using a 150- to 200-micron red cell filter to remove clumps or aggregates. The initial portion of each HPC infusion should be administered slowly and with sufficient observation to detect onset of acute immunologic or infectious complications. Thereafter, the rate of infusion should be as rapid as can be tolerated. Information for administration of specific HPC products are found elsewhere in this *Circular*.

Storage

Hematopoietic progenitor cell products are stored using different methods and at different temperatures depending on the duration of storage required.

Hematopoietic Progenitor Cell Sources

Hematopoietic Progenitor Cells, Marrow

HPCs from marrow are obtained through multiple needle aspirations from the posterior iliac crests and occasionally from the anterior iliac crests or sternum of an autologous or allogeneic donor. The marrow is placed in a sterile container with an electrolyte solution and an appropriate anticoagulant. The cell suspension is run through a series of sterile filters of decreasing pore size to remove fat, bone particles, and cellular debris. The volume collected varies with the weight of the recipient, but generally ranges from 500 to 1500 mL. Human marrow contains mature red and white cells, platelets, committed precursors of all lineages, mast cells, fat cells, plasma cells, and pluripotent hematopoietic cells. Some of these cells are capable of reconstituting the hematologic and lymphoid systems of an autologous or allogeneic recipient. These cells are usually processed before infusion, but are sometimes infused in an unmodified state.

Hematopoietic Progenitor Cells, Apheresis

HPCs may also be obtained from the blood by apheresis, usually after recombinant hematopoietic growth factor administration. Autologous donors may also have undergone chemotherapy mobilization. Allogeneic peripheral blood HPCs are frequently infused in an unmodified state. The most common modification of hematopoietic progenitor cells, apheresis is to decrease the number of T lymphocytes in the graft.

Hematopoietic Progenitor Cells, Cord

HPCs can be obtained from the umbilical cord and, occasionally, placental vessels at the time of delivery and immediately placed in an anticoagulant solution. These cells are almost always cryopreserved.

Minimally Manipulated Hematopoietic Progenitor Cell Products

Collection procedures should be performed according to the manufacturer's instructions for the devices approved for such use. FDA-approved reagents or devices are used when available.

Plasma-Depleted Hematopoietic Progenitor Cells

**Hematopoietic Progenitor Cells, Marrow,
(Plasma Depleted)**

**Hematopoietic Progenitor Cells, Apheresis
(Plasma Depleted)**

**Hematopoietic Progenitor Cells, Cord
(Plasma Depleted)**

Description

These products contain the cellular elements of the HPCs that remain after the plasma is removed by centrifugation.

Indications

A plasma-depleted HPC graft is indicated 1) in cases of ABO or other red cell *minor* incompatibility where the *donor has antibody* to one or more recipient red cell antigens and 2) as a means of volume reduction for recipients who are small, fluid-sensitive, or have preexisting fluid overload, cardiac compromise, or renal dysfunction. Autologous HPCs collected by apheresis may be plasma-depleted to reduce volume prior to cryopreservation.

Administration

The product should be administered or cryopreserved immediately after processing. Filtration at the bedside is unnecessary. The infusion should be completed within 4 hours of initiation.

Red-Cell-Depleted Hematopoietic Progenitor Cells

**Hematopoietic Progenitor Cells, Marrow
(Red Cell Depleted)**

**Hematopoietic Progenitor Cells, Apheresis
(Red Cell Depleted)**

Hematopoietic Progenitor Cells, Cord (Red Cell Depleted)

Description

These are the HPCs remaining after the mature red cells have been depleted by a validated method of sedimentation, centrifugation or lysis.

Indications

This product is indicated 1) in cases where the *recipient has antibody* to one or more antigens on the donor red cells, 2) for concentration of an autologous HPC graft prior to cryopreservation, and 3) for return of the red cells back to the donor.

Administration

The product should be administered or cryopreserved immediately after processing. Filtration at the bedside is unnecessary. The infusion should be completed within 4 hours of initiation.

Buffy Coat Preparation

**Hematopoietic Progenitor Cells, Marrow
(Buffy Coat Preparation)**

**Hematopoietic Progenitor Cells, Apheresis
(Buffy Coat Preparation)**

**Hematopoietic Progenitor Cells, Cord
(Buffy Coat Preparation)**

Description

The buffy coat is the portion of an HPC product containing the bulk of the nucleated cells after plasma and mature red cells have been removed by sedimentation or centrifugation technique.

Indications

This procedure is indicated when a concentrated HPC product is required for further manipulation such as purging and/or cryopreservation. It may also be used when greater volume reduction is desired than can be obtained with plasma reduction alone.

Administration

The product should be administered or further manipulated immediately after processing. If not cryopreserved, the infusion should be completed within 4 hours of starting the buffy coat procedure. *Buffy coat preparations should not be filtered through a microaggregate filter.*

Density Separated Hematopoietic Progenitor Cells**Hematopoietic Progenitor Cells, Bone
(Density Separated)****Hematopoietic Progenitor Cells, Apheresis
(Density Separated)****Hematopoietic Progenitor Cells, Cord
(Density Separated)*****Description***

These are the HPCs that remain after the depletion of mature red cells, polymorphonuclear leukocytes, and plasma through the use of validated materials for separation of the cells on the basis of their density.

Indications

Density separation is indicated when there is a need for an HPC preparation enriched for mononuclear cells and depleted of the majority of red cells and polymorphonuclear leukocytes. This component is usually an initial step in a manipulated preparation.

Administration

Density separated HPCs are generally not administered until further processing has been performed.

Cryopreserved Hematopoietic Progenitor Cells**Hematopoietic Progenitor Cells, Marrow
(Cryopreserved)****Hematopoietic Progenitor Cells, Apheresis
(Cryopreserved)****Hematopoietic Progenitor Cells, Cord
(Cryopreserved)*****Description***

These are HPCs frozen using cryoprotectant solutions, containers, and techniques validated for the procedure.

Indications

Cryopreservation of cells is indicated when the product is to be stored for a prolonged period before infusion.

Administration

The product must be thawed and prepared for infusion using validated materials, equipment, and techniques.

Further Manipulated Products

After minimal manipulation by one or more of the previously described procedures, HPCs may be further processed or manipulated. The purpose of further manipulation may be to enrich, expand, or change the function of one or more of the nucleated cell populations in the HPC product. Preparation and administration of these products may be considered experimental; therefore, they require appropriate institutional and federal approval for their use. Information regarding actions, indications, contraindications, side effects, hazards, dosage, and administration of these products should be supplied by the individual facility.

References

American Association of Blood Banks, America's Blood Centers, American Red Cross. Circular of Information for the Use of Human Blood and Blood Components. Bethesda, MD: American Association of Blood Banks, 1997.

Circular of information for use with human peripheral blood progenitor cells. Dallas, TX: Parkland Health and Hospital System, 1999.

Circular of information—progenitor cell components. Sacramento, CA: Sacramento Medical Foundation Blood Center, 1992.

Instruction circular for human progenitor cell components. New Haven, CT: Yale New Haven Hospital, 1997.

Standards for hematopoietic progenitor cell collection, processing and transplantation, 1st ed. Omaha, NE: Foundation for the Accreditation of Hematopoietic Cell Therapy, 1996.

Standards for hematopoietic progenitor cell services, 2nd ed. Bethesda, MD: American Association of Blood Banks, 2000.

**The Second Edition can be viewed in the Dockets
Management Public Reading Room
5600 fishers Lane, Room 1061**