

CIRCULAR OF INFORMATION

FOR THE USE OF CELLULAR THERAPY PRODUCTS

This circular was prepared jointly by the AABB, America's Blood Centers, American Association of Tissue Banks, American Red Cross, American Society for Apheresis, American Society for Blood and Marrow Transplantation, Foundation for the Accreditation of Cellular Therapy, International Council for Commonality in Blood Bank Automation, International Society for Cellular Therapy, and National Marrow Donor Program. Federal law prohibits dispensing the cellular therapy products described in this circular without a prescription.



Advancing Transfusion and
Cellular Therapies Worldwide



Foundation for the Accreditation
of Cellular Therapy



American Association of Tissue Banks



American Society for Blood
and Marrow Transplantation



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Notice to All Users

The *Circular of Information for the Use of Cellular Therapy Products* (hereafter referred to as the *Circular*) is an extension of container labels, as the space on those labels is limited. The scope of this *Circular* is restricted to cellular therapy products, such as hematopoietic progenitor cells (HPCs) and other leukocytes that are minimally manipulated. Cellular therapy products are biologic products that contain living human cells and are intended for use in patient treatment. Professional judgment based on clinical evaluation determines the selection of products, dosage, rate of administration, and decisions in situations not covered in this general statement.

WARNING: Because cellular therapy products are derived from human blood or tissues, they may carry a risk of transmitting infectious agents such as viruses, bacteria, and fungi. Donor screening and testing procedures are in place to minimize the risk of transmitting such infections but do not eliminate this risk. Also, serious life-threatening septic and toxic reactions can result from administration of products containing bacterial toxins. In addition, cellular therapy products may contain certain immunizing substances other than those indicated on the label, such as red cells, mature white cells, and platelets. Therefore, this *Circular*, as a whole or in part, cannot be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described products even when used for their intended purpose. Attention to the specific indications for cellular therapy products is needed to prevent inappropriate administration. This *Circular* is supplied to conform to applicable federal statutes and regulations of the Food and Drug Administration (FDA), US Department of Health and Human Services.

General Information

Donors

Cellular therapy products described in this *Circular* have been collected from human donors for autologous or allogeneic administration. Autologous HPC collection usually occurs after mobilization of the donor with growth factors, chemotherapy, or both. Donors for other cellular therapy products may or may not require growth factor stimulation depending on the protocol employed. Allogeneic HPC collection usually occurs after mobilization with growth factors alone.

Allogeneic donors have been screened through the use of questions designed to detect risk factors for infectious diseases transmissible by the cellular therapy product and have been tested for transmissible infectious diseases (see Table 1). The questions are based on criteria set forth by AABB, the American Association of Tissue Banks (AATB), the Foundation for the Accreditation of Cellular Therapy (FACT), the National Marrow Donor Program (NMDP), and the FDA. The provision of truthful and accurate information by a donor during health/risk assessment is essential for the exclusion of donors whose cellular therapy products may transmit diseases to recipients.

Table 1. Testing of Cellular Therapy Product Donors

	Peripheral Blood or Marrow Donors	Cord Blood Donors	Others (for example, donor lymphocyte infusion)
FDA-licensed, approved, or cleared donor screening tests for transmissible agents			
Timing of specimen collection	Up to 30 days before collection	Up to 7 days before or after delivery	Up to 7 days before or after collection
Human immunodeficiency virus, type 1 and 2 (HIV-1, HIV-2)	X	X (MS)	X
Hepatitis B virus (HBV)	X	X (MS)	X
Hepatitis C virus (HCV)	X	X (MS)	X
Human T-cell lymphotropic virus, type I and II (HTLV-I, HTLV-II)	X	X (MS)	X
Cytomegalovirus (CMV)	X (if allogeneic)	X (if allogeneic) (MS)	X
<i>Treponema pallidum</i> (syphilis)	X	X (MS)	X
Additional tests			
ABO group and Rh (D) type	X	X (CBU)	X
HLA typing	X (if allogeneic)	X (if allogeneic) (CBU)	X
Screening and/or testing for clinically significant hemoglobinopathies such as sickle cell disease and thalassemia	X	X (CBU)	

MS = maternal sample; CBU = cord blood unit

Cellular therapy products with abnormal test results may be administered to a recipient if the recipient has been advised of the risk, the recipient's physician has authorized the use of the product, and the product is appropriately labeled.

Cellular Therapy Product Labeling

Labels will contain the following information at the time of product distribution or issue:

- Unique identifier
- Proper name of the product, including an indication of any qualification or modification
- Date and time of collection
- Expiration date and time (if applicable)
- Approximate volume
- Name and volume of anticoagulant or other additives
- Recommended storage temperature
- Identity and address of collection facility or donor registry
- Identity and address of processing facility
- Statements regarding transmission of infectious diseases
- Statement indicating "Do Not Irradiate"
- Biohazard or other warning label(s) (if applicable)
- Statements regarding recipient identification
- Donor identifier and (if applicable) name
- Recipient name and identifier
- ABO group and Rh (D) type of donor [or in the case of a cord blood unit, the ABO group and Rh (D) type of the cord blood]
- RBC compatibility testing results (if applicable)

Biohazard and Warning Labels

The application of biohazard and warning labels on the cellular therapy product is summarized in Table 2. Questions about the interpretation of any label on a specific product should be directed to the service distributing the product.

Instructions for Storage and Administration of Cellular Therapy Products

The following instructions pertain to cellular therapy products described in this *Circular*:

- All products must be maintained in a controlled environment and stored under appropriate conditions as described in FDA regulations and applicable AABB, AATB, FACT, or NMDP standards
- The intended recipient and the product container must be properly identified before the product is administered, according to facility standard operating procedure
- Products must be inspected immediately before administration and any questions about

Table 2. Biohazard and Warning Labels

		Status				Product Labels				
	Title 21 CFR Citation	All Donor Screening and Testing Completed	Abnormal Results of Donor Screening	Abnormal Results of Donor Testing	Urgent Medical Need	Biohazard Legend [per 21 CFR 1271.3(h)]	For Autologous Use Only	Not Evaluated for Infectious Substances	WARNING: Advise patient of communicable disease risks	WARNING: Reactive test results for (name of disease agent or disease)
Donor Eligibility Determination Required [21 CFR 1271.45(b)]										
1	Allogeneic donors with incomplete donor eligibility determination ^{1,2}	1271.60	No	No	No	Yes			X	X
2	Allogeneic donors found ineligible									
	A first-degree or second-degree blood relative ³	1271.65 (b) 1. i	Yes	No/Yes	Yes	NA			X	X
	A first-degree or second-degree blood relative ³	1271.65 (b) 1. i	Yes	Yes	No	NA			X	
	Unrelated donor	1271.65 (b) 1. iii	Yes	No/Yes	Yes	Yes			X	X
	Unrelated donor	1271.65 (b) 1. iii	Yes	Yes	No	Yes			X	
Donor Eligibility Determination Not Required [21 CFR 1271.90(a)]										
3	Autologous donors ⁴	1271.90 (a)(b)								
	Autologous donor	1271.90 (a) (1)(2)	No	No	No	NA		X	X	
	Autologous donor	1271.90 (b) (1)(3)	Yes	No/Yes	Yes	NA	X	X		X
	Autologous donor	1271.90 (b) (1)(3)	Yes	Yes	No	NA	X	X		

1. The donor eligibility must be finalized during or after the use of the cellular therapy product. The results must be communicated to the treating physician [21 CFR 1271.60 (d)4].
2. Abnormal results of any screening or testing requires labeling as in item 2 in this table (21 CFR 1271.65 applies).
3. Notification of the recipient's and donor's physicians of abnormal screening and/or testing results is required.
4. Any abnormal donor screening or testing results (even though neither screening nor testing is mandated for this group of donors) require appropriate labeling [21 CFR 1271.90 (b)].

the product should be directed to the facility distributing or issuing the product

- Aseptic technique must be employed
- Products must NOT be administered through a filter designed to remove leukocytes
- Products may be filtered through a 170- to 260-micron filter designed to remove clots
- Products should be mixed thoroughly before use
- Products must NOT be irradiated
- No medications or solutions may be added to or infused through the same tubing with products with the exception of 0.9% Sodium Chloride, Injection (USP)
- Periodic observation of the patient is required during and after administration to detect adverse reactions
- Vital signs must be recorded at a minimum before and after administration or more often if required by facility standard operating procedure

Reporting of Deviations and Adverse Reactions

Any adverse event including suspected microbial contamination of a product or suspected disease transmission during or after product administration must be documented and reported in accordance with the facility's policies or applicable laws and regulations. At a minimum any such event must be reported to the patient's physician and the medical director of the facility that issued the product.

Certain deviations and adverse reactions related to cellular therapy product manufacturing and administration are required to be reported to the Center for Biologics Evaluations and Research (CBER), Food and Drug Administration, Rockville, MD. The definitions of reportable deviations and adverse reactions and the requirements for their reporting are specified in 21 CFR 1271.350. Updated information about CBER reporting requirements may be found at www.fda.gov/cber/biodev/biodev.htm or by calling (301) 827-6220.

Side Effects and Hazards

The following side effects and hazards pertain to administration of cellular therapy products:

Immunologic Complications, Immediate

1. *Acute Hemolytic Reaction* is one of the most severe complications of cellular therapy product administration and is usually caused by donor-recipient major ABO incompatibility. 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, with the direction and magnitude of change depending upon the phase of the antigen-antibody event and the magnitude of compensatory mechanisms. In anesthetized patients, hypotension and evidence of disseminated intravascular

coagulopathy (DIC) may be the first signs of incompatibility. Laboratory findings can include hemoglobinemia and/or hemoglobinuria, followed by elevation of serum bilirubin. Treatment includes measures to maintain or correct the blood pressure; correct the coagulopathy, if present; and promote and maintain urine flow.

Signs and symptoms of acute hemolytic reactions may be immediate and include:

- Burning sensation along the vein
- Low back pain
- Facial flushing
- Chills, fever [temperature may be 40.5 C (105 F) or higher]
- Chest pain; rapid, labored respirations
- Headache
- Shock

2. *Febrile, Nonhemolytic Reactions* are typically manifested by a temperature elevation of at least 1 C (2 F) occurring during, shortly after, or up to 2 hours following product administration and in the absence of any other pyretic stimulus. This may reflect the action of antibodies against white cells or the action of cytokines, either present in the infused product or generated by the recipient after product administration. Febrile reactions may accompany product administration and they occur more frequently in patients previously alloimmunized by transfusion or pregnancy. No routinely available tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief.

Signs and symptoms of febrile, nonhemolytic reactions include:

- Temperature elevation of 1 C (2 F) or more
- Chills

3. *Allergic Reactions* usually occur as urticaria, but may also include wheezing or angioedema. These reactions are thought to be related to the presence of atopic substances capable of interacting with antibodies present in the donor or recipient plasma. In rare cases, anaphylaxis may occur. Allergic reactions to hydroxyethyl starch (HES) or dimethylsulfoxide (DMSO) used in cellular therapy product processing or cryopreservation may occur in sensitized patients. No laboratory procedures are available to predict or prevent these reactions, which usually respond to antihistamines or, in severe cases, corticosteroids or epinephrine.

Signs and symptoms of allergic reactions include:

- Urticaria (hives), pruritus (itching)
- Facial or glottal edema (rare)

4. *Anaphylactoid or Anaphylactic Reactions* are characterized by autonomic dysregulation, severe dyspnea, pulmonary and/or laryngeal edema, and bronchospasm and/or laryngospasm. They are rare but dangerous and potentially life-threatening complications of product administration. Many of these reactions have been reported in IgA-deficient patients who have IgA-specific antibodies of the IgE class. Such patients may develop symptoms after administration of very small amounts of IgA-containing plasma in any cellular therapy product. Anaphylactoid and anaphylactic reactions to HES or DMSO used in cellular therapy product processing or cryopreservation may occur in sensitized patients. Patients tend to respond to fluids, corticosteroids, and epinephrine, and may require attention to cardiorespiratory support.

Signs and symptoms of anaphylactoid reactions include:

- Autonomic dysregulation
- Severe dyspnea
- Pulmonary and/or laryngeal edema
- Bronchospasm and/or laryngospasm
- Hypotension

5. *Transfusion-Related Acute Lung Injury (TRALI)* occurs when an acutely increased permeability of the pulmonary microcirculation allows the massive leakage of fluids and protein into the alveolar spaces and interstitium. In many cases, the occurrence of TRALI is associated with the presence of leukocyte antibodies in the donor or recipient. Treatment consists of aggressive respiratory support.

In the absence of evidence for cardiac failure, circulatory overload or preexisting lung injury, signs and symptoms of TRALI include:

- Acute respiratory distress within 6 hours of administration
- Hypoxemia (oxygen saturation <90% on room air)
- Bilateral pulmonary infiltrates on frontal chest x-ray

Immunologic Complications, Delayed

1. *Delayed Hemolytic Reactions* may occur in two different allogeneic settings. In previously alloimmunized patients, antigens on infused red cells can stimulate anamnestic production of antibody from residual recipient B cells. The antibody levels may reach a significant circulating level while the infused cells are still present in the circulation. The activity of the native recipient B cells will decrease as they are replaced with the donor's immune system. The usual timeframe for reappearance of antibody is 2 to 14 days after product administration. The relatively small volume of red cells infused with cellular therapy products will typically limit this type of delayed hemolytic reaction. The potentially more serious delayed hemolytic reaction may occur in recipients who receive antibodies incompatible with ABO or other red cell antigens to the remaining recipient red cells. The relative small volume of plasma in the HPC product will usually limit this immediate reaction. In this setting, the infused donor's B lymphocytes may produce antibodies to red cell antigen isohemagglutinins thus destroying the recipient's own remaining red cells in the 1 to 3 weeks after HPC product administration. This reaction may be sudden, severe, and life-threatening, so at-risk recipients should be monitored for this occurrence. Treatment usually includes Group O or affected antigen-negative red cell transfusion beginning at the time of transplantation as needed to support the patient and to begin replacement of at-risk red cells. More rapid antigen-negative red cell replacement, fluid administration, and perhaps red cell exchange may be required in more severe cases.

Signs and symptoms of delayed hemolytic reactions may include:

- Unexplained low-grade fever
- Unexplained decrease in hemoglobin/hematocrit
- Mild jaundice
- Development of a positive direct antiglobulin test (DAT)
- Elevation of lactic dehydrogenase (LDH) or bilirubin

- Hemoglobinemia and hemoglobinuria (rare)
2. *Alloimmunization to Antigens* of red cells, white cells, platelets, or plasma proteins may occur unpredictably after product administration. Primary immunization does not become apparent until days or weeks after the immunizing event and does not usually cause symptoms or physiologic changes. If cellular therapy products that express the relevant antigens are subsequently administered, there may be accelerated removal of cellular elements from the circulation and/or systemic symptoms. Clinically significant antibodies to red cell antigens are usually detected by preadministration testing. Alloimmunization to antigens of white cells, platelets, or plasma proteins can be detected only by specialized testing.
 3. *Graft-vs-Host Disease (GVHD)* is an extremely serious condition that occurs frequently in recipients of allogeneic cellular therapy products. GVHD occurs when viable T lymphocytes in the infused product engraft in the recipient and react against tissue antigens in the recipient. GVHD can follow administration of any product that contains even small numbers of viable T lymphocytes. Severely immunocompromised recipients receiving allogeneic cellular therapy products are at greatest risk.

Nonimmunologic Complications

1. *DMSO Toxicity* is the most common complication of cellular therapy product administration and is caused by DMSO in thawed products that were cryopreserved with it. Symptoms result from histamine release and include flushing, rash, chest tightness, nausea and vomiting, and cardiovascular instability. Slowing the administration rate or removal of DMSO from the product by washing the cells before administration may reduce the risk of these symptoms. Premedication with antihistamines are usually effective in preventing or reducing the response. A garlic-like odor on the breath of cellular therapy product recipients may persist for 24 to 48 hours after product administration.

Signs and symptoms of DMSO toxicity include:

 - Cough
 - Flushing
 - Rash
 - Chest tightness and wheezing
 - Nausea and vomiting
 - Bradycardia and tachycardia
 - Hypertension
2. *Bacterial Contamination* of cellular therapy products may occur, but rarely causes acute, severe, or life-threatening effects. However, the onset of high fever (>2 C or >3.5 F rise in temperature), severe chills, hypotension, or circulatory collapse during or immediately after product administration should suggest the possibility of bacterial contamination and/or the presence of endotoxin in the product. Prompt recognition of a possible septic reaction is essential. Measures should be taken to maintain adequate blood pressure, followed by blood cultures and aggressive therapy with broad-spectrum antimicrobials. The remaining product in the container should be evaluated promptly by Gram's stain and microbial cultures.

Signs and symptoms of bacterial contamination reactions include:

- Fever with chills
 - Severe hypotension
 - Dry, flushed skin
 - Pain in abdomen and extremities
 - Vomiting
 - Bloody diarrhea
3. *Fat Emboli*, which are small fat droplets in marrow products, may block capillary perfusion and cause respiratory distress. Supplemental oxygen may be required during and immediately after infusion.
- Signs and symptoms of fat emboli include:
- Dyspnea
 - Tightness of the chest
 - Coughing
4. *Transmission of Infectious Disease* may occur because cellular therapy products are collected from human blood and/or tissues. This may be due to known agents, such as viruses, or unknown agents. Donor selection criteria are designed to screen out potential donors with increased risk of infection with HIV, HTLV, HBV, HCV, and syphilis, as well as other agents (see section on Donors). These measures do not totally eliminate the risk of transmitting these agents. Cytomegalovirus may, unpredictably, be present in white-cell-containing products from donors previously infected with this virus, which can persist lifelong despite the presence of serum antibodies. Up to 70% of donors may be CMV-seropositive. Transmission of CMV may be of concern in low birthweight infants born to CMV-seronegative mothers and in immunocompromised transplant recipients if they are CMV seronegative. Administering CMV seronegative products reduces the risk of CMV transmission by cellular therapy products. Testing for West Nile virus (WNV), available for investigational use only, may reduce the risk for WNV transmission. For some infectious agents, there are no routine tests to predict or prevent disease transmission. Examples of these organisms include *Babesia* spp., *Leishmania* spp., Parvovirus spp., *Plasmodium* spp., the coronavirus associated with severe acute respiratory syndrome (SARS), the agents of human transmissible spongiform encephalopathies (TSEs), and certain trypanosomes. All potential cellular therapy product donors are subjected to stringent screening procedures intended to reduce to a minimum the risk of infectious agent transmission.
5. *Bleeding Due to Excessive Anticoagulation* can occur if heparin (often 10,000-20,000 IU) was added to the product during collection and/or processing and remains in the cellular therapy product when administered.
6. *Circulatory Overload* leading to pulmonary edema can occur after infusion of excessive volumes or at excessively rapid rates. Pulmonary edema should be promptly and aggressively treated. In patients at risk, the infusion of colloid preparations (including plasma products and the suspending plasma in cellular therapy products) should be reduced to a minimum.
7. *Hypothermia* can be caused by rapid infusion of large volumes of cold products. Hypothermia carries a risk of cardiac arrhythmia or cardiac arrest. The use of a blood-warming device is not indicated for infusion of cellular therapy products.

8. *Nonimmunologic Hemolysis* can result from lysis of red cells in the product, which may occur at any time during processing, cryopreservation, thawing, and administration. This lysis may be caused by a number of factors. Some examples are osmotic stress, mechanical injury, shear stress, co-administration with incompatible fluids, and intrinsic red cell abnormalities such as hemoglobinopathies or enzyme deficiencies.

Hematopoietic Progenitor Cell Sources

HPC, Marrow

HPC, Marrow (HPC-M) preparations contain HPCs obtained by 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 passed through sterile filters to remove fat, bone particles, and cellular debris. The volume collected varies with the weight of the recipient, but generally ranges from 10 to 15 mL/kg of donor weight. Marrow contains mature red cells, white cells, platelets, committed progenitors 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. The most common modifications of allogeneic HPC-M are to decrease the volume of ABO-incompatible red cells, remove ABO-incompatible plasma, isolate CD34+ progenitor cells, and remove donor T lymphocytes. The most common modification of autologous HPC-M is to reduce the volume by removing plasma and red cells before cryopreservation.

HPC, Apheresis

HPC, Apheresis (HPC-A) preparations contain HPCs collected from the peripheral blood by an apheresis procedure, usually after recombinant hematopoietic growth factor administration. Autologous donors may also have undergone chemotherapy mobilization. Allogeneic HPC-A collections are frequently infused in an unmodified state, but may be processed. The most common modifications of allogeneic HPC-A are to decrease the volume of ABO-incompatible red cells, remove ABO-incompatible plasma, isolate CD34+ progenitor cells, and remove donor T lymphocytes. The most common modifications of autologous HPC-A are to reduce the volume by removing plasma before cryopreservation, to isolate CD34+ progenitor cells, and to wash the cells to remove DMSO after thawing.

HPC, Cord

HPC, Cord (HPC-C) preparations contain HPCs obtained from the umbilical cord at the time of delivery and immediately placed in an anticoagulant solution. Initial processing

may include removal of red cells and plasma. The HPC-C products are usually cryopreserved after collection and initial processing.

Hematopoietic Progenitor Cell Products

Description

HPC products contain hematopoietic stem and progenitor cells capable of providing hematopoietic and immune reconstitution after myeloablative or nonmyeloablative preparative regimens. The products contain pluripotent and lineage-committed hematopoietic progenitors. Procedures have been developed for depletion of plasma and of various cell populations from these products.

Cellular therapy products can be broadly categorized as being minimally manipulated products and more than minimally manipulated products.

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 administration of HPCs to recovery of adequate or normal 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 products are intended to provide hematopoietic reconstitution after myeloablative or nonmyeloablative preparative regimens for a wide range of disease states. For patients with certain malignancies the product is also intended to provide immune reconstitution, known as graft-vs-tumor effect. Autologous HPCs are collected and stored for use as “rescue” following myeloablative or myelotoxic therapy. The therapy is intended to treat the patient’s underlying malignancy and autologous HPC products are administered to minimize morbidity and mortality due to the myelotoxic effects of the therapy.

Contraindications

Institutional policies, protocols, and federal regulations 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 some protocols may dictate a

minimum number of cells to be collected and infused. Several methods are used to measure the number of cells in an HPC collection. Some preparations may require filtration using a 170- to 260-micron filter to remove clumps or aggregates. HPC infusion should begin slowly and with sufficient observation to detect symptoms and/or signs suggestive of acute immunologic or infectious complications. Thereafter, the rate of infusion may be as rapid as tolerated. Information for administration of specific HPC products is found elsewhere in this *Circular*.

Storage

HPC products are stored using various methods and temperatures depending on the required duration of storage. Institutional policies and protocols dictate specific storage requirements for HPCs.

Minimally Manipulated Cellular Therapy Products

HPC, (Plasma reduced)

- **HPC, Marrow (Plasma reduced)**
- **HPC, Apheresis (Plasma reduced)**
- **HPC, Cord (Plasma reduced)**

Description

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

Indications

A plasma-reduced HPC graft is indicated 1) when the donor has a high-titer 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-reduced to decrease volume prior to cryopreservation.

Administration

The product should be administered or cryopreserved immediately after processing. Filtration of a fresh or previously frozen product at the bedside is not required. In the presence of aggregates the product should be filtered using a 170- to 260-micron filter. The infusion should be started slowly to observe for reactions and completed as quickly as tolerated. However, the administration time will be determined by the total volume to be infused and whether the cells are fresh or previously frozen.

HPC, (RBC reduced)

- **HPC, Marrow (RBC reduced)**
- **HPC, Apheresis (RBC reduced)**
- **HPC, Cord (RBC reduced)**

Description

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

Indications

This product is indicated 1) when the recipient has a high-titer antibody to one or more antigens on the donor red cells, and 2) for concentration of an autologous HPC product before cryopreservation.

Administration

The product should be administered or cryopreserved immediately after processing. Filtration of a fresh or previously frozen product at the bedside is not required. In the presence of aggregates the product should be filtered using a 170- to 260-micron filter. The infusion should be started slowly to observe for reactions and completed as quickly as tolerated. However, the administration time will be determined by the total volume to be infused and whether the cells are fresh or previously frozen.

HPC, (Buffy coat enriched)

- **HPC, Marrow (Buffy coat enriched)**
- **HPC, Apheresis (Buffy coat enriched)**
- **HPC, Cord (Buffy coat enriched)**

Description

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

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 cryopreserved immediately after processing. Filtration of a fresh or previously frozen product at the bedside is not required. In the presence of aggregates the product should be filtered using a 170- to 260-micron filter. The infusion should be started slowly to observe for reactions and completed as quickly as tolerated. However, the administration time will be determined by the total volume to be infused and whether the cells are fresh or previously frozen.

HPC, (Density enriched)

- **HPC, Marrow (Density enriched)**
- **HPC, Apheresis (Density enriched)**
- **HPC, Cord (Density enriched)**

Description

These are primarily mononuclear cells that remain after the depletion of mature red cells, polymorphonuclear leukocytes, and plasma by separation of the cells on the basis of their density. This is achieved using devices or density gradient solutions.

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.

Administration

The product should be administered or cryopreserved immediately after processing. Filtration of a fresh or previously frozen product at the bedside is not required. In the presence of aggregates the product should be filtered using a 170- to 260-micron filter. The infusion should be started slowly to observe for reactions and completed as quickly as tolerated. However, the administration time will be determined by the total volume to be infused and whether the cells are fresh or previously frozen.

Cryopreserved HPC

- **Cryopreserved HPC, Marrow**
- **Cryopreserved HPC, Apheresis**
- **Cryopreserved HPC, Cord**

Description

These are HPCs that have been frozen using cryoprotectant solutions and containers.

Indications

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

Administration

The product must be thawed before administration. The product should be administered immediately after thawing and/or processing. Filtration of the product at the bedside is not required. In the presence of aggregates the product should be filtered using a 170- to 260-micron filter. The infusion should be started slowly to observe for reactions and completed as quickly as tolerated. However, the administration time will be determined by the total volume to be infused and whether the cells are fresh or previously frozen. If the thawed products have not been washed to remove DMSO, care should be taken not to exceed 1 mL of DMSO per kilogram of recipient weight per day administration (eg, 100 mL of 10% solution contains 10 mL of DMSO).

HPC, (CD34 enriched)

- **HPC, Marrow (CD34 enriched)**
- **HPC, Apheresis (CD34 enriched)**
- **HPC, Cord (CD34 enriched)**

Description

These products contain the cellular elements of HPCs that have been enriched by CD34 selection.

Indications

A CD34-enriched HPC product may be indicated 1) when circulating tumor cells are present in the peripheral blood and/or marrow and, therefore, will likely be present in the HPC product, 2) as a means to reduce the number of T lymphocytes contained in the allogeneic HPC product, and 3) as a means of volume reduction for recipients who may have reactions to DMSO.

Administration

The product should be administered or cryopreserved immediately after processing. Filtration of a fresh or previously frozen product at the bedside is not required. In the presence of aggregates the product should be filtered using a 170- to 260-micron filter. The infusion should be started slowly to observe for reactions and completed as quickly

as tolerated. However, the administration time will be determined by the total volume to be infused and whether the cells are fresh or previously frozen.

Lymphocytes

- **Lymphocytes, Apheresis**
- **Lymphocytes, Whole Blood**

Description

These products are most frequently used for donor lymphocyte infusion (DLI). They are usually collected from the HPC donor and contain a mixture of mature nucleated cells (eg, T and B lymphocytes, granulocytes), red cells, and plasma. Lymphocytes may be collected from peripheral blood via a whole blood collection or via an apheresis procedure. The donor may be mobilized with growth factors, in which case the product would also contain HPCs.

Indications

Lymphocytes are primarily used to prevent or treat tumor relapse following allogeneic HPC transplantation. However, absolute indications for lymphocytes have not been defined. If the recipient has not sufficiently engrafted with donor hematopoietic cells, a growth-factor-mobilized donor cell product may be used to provide both lymphocytes and HPCs. Lymphocytes have also been used to treat posttransplant infectious complications, particularly those caused by CMV and Epstein-Barr virus.

Contraindications

Lymphocytes are contraindicated for patients experiencing severe GVHD.

Dosage and Administration

The dosage of T cells will be specified by institutional policies. The product should be administered or cryopreserved immediately after processing. Filtration of a fresh or previously frozen product at the bedside is not required. In the presence of aggregates the product should be filtered using a 170- to 260-micron filter.

The infusion should be started slowly to observe for reactions and completed as quickly as tolerated. However, the administration time will be determined by the total volume to be infused and whether the cells are fresh or previously frozen.

More than Minimally Manipulated Cellular Therapy Products

Cellular therapy products that are more than minimally manipulated must be prepared and administered using an FDA-approved Investigational New Drug (IND) protocol. The

clinical protocol is part of the overall IND protocol. The clinical protocol contains information regarding the indications for use, specific details for the administration of the product, as well as any expected toxicities. For corporate-sponsored or multi-center clinical trials, the indications, administration, and toxicity information can also be found in the investigator's brochure.

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Contact Information

If you have any questions regarding the cellular product contact:

If you want to learn more about cellular therapy, contact any of the following co-sponsors of this publication.

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<p>American Red Cross (ARC) Medical Office 2025 E Street, NW Washington, DC 20036, USA Phone: (202) 303-5610 Fax: (202) 303-0087 www.redcross.org</p>	<p>American Society for Blood and Marrow Transplantation (ASBMT) 85 W. Algonquin Road, Suite 550 Arlington Heights, IL 60005, USA Phone: (847) 427-0224 Fax: (847) 427-9656 www.asbmt.org</p>
<p>American Society for Apheresis (ASFA) 570 West 7th Avenue, Suite 402 Vancouver, BC Canada V5Z 1B3 Phone: (604) 484-2851 Fax: (604) 874-4378 www.apheresis.org</p>	<p>America's Blood Centers (ABC) 725 15th Street, NW, Suite 700 Washington, DC 20005, USA Phone: (202) 393-5725 Fax: (202) 393-1282 www.americasblood.org</p>
<p>Foundation for the Accreditation of Cellular Therapy (FACT) FACT Accreditation Office University of Nebraska Medical Center 986065 University Medical Center Omaha, NE 68198-6065, USA Phone: (402) 559-1950 Fax: (402) 559-1951 www.factwebsite.org</p>	<p>ICCBBA, Inc 204 St. Charles Way, Unit 179E York, PA 17402 Phone: (717) 845-4790 Fax: (717) 845-9727 www.iccbba.org</p>
<p>International Society for Cellular Therapy (ISCT) 570 West 7th Avenue, Suite 402 Vancouver, BC, Canada, V5Z 1B3 Phone: (604) 874-4366 Fax: (604) 874-4378 www.celltherapy.org</p>	<p>National Marrow Donor Program (NMDP) 3001 Broadway St. NE, Suite 500 Minneapolis, MN 55413-1753, USA Phone: (800) 526-7809 Fax: (612) 627-8125 www.nmdp.org</p>