

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, College of American Pathologists, Foundation for the Accreditation of Cellular Therapy, ICCBBA International Society for Cellular Therapy, Joint Accreditation Committee, National Marrow Donor Program, and Netcord. Federal law prohibits dispensing the cellular therapy products described in this circular without a prescription.

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.¹ The focus of this *Circular* is restricted to unlicensed cellular therapy products that are minimally manipulated. These unlicensed products can be: hematopoietic progenitor cells (HPCs), leukocytes and other cells derived from bone marrow, umbilical cord blood, or cellular products collected by apheresis. This *Circular* does not apply to products that have already received a license as a cellular therapy product in the United States. Per requirements of other national competent authorities, cellular therapy products may be designated as licensed biological products, medical devices, or advanced therapy medicinal product. Principles expressed here may also be applied to other cellular therapy products. 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 including bacteria, viruses, fungi, protozoa, and prions. Donor screening and testing procedures are in place to minimize the risk of transmitting such infections but cannot eliminate this risk. Transmission of malignant disease has been reported. 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, platelets, and plasma proteins. Therefore, this *Circular*, in 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 they are used for their intended purpose. Attention to the specific indications for cellular therapy products is needed to prevent inappropriate administration.

This *Circular* addresses some of the applicable regulations established by regulatory/competent authorities such as the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and Directive 2004/23/EC (and other European Commission directives) of the European Parliament and the Council of the European Union (EU).²⁻⁶ This *Circular* is not a comprehensive reference for applicable regulations.

The nomenclature used throughout this *Circular* is consistent with *ISBT 128* terminology and was current at the time of publication.⁸⁻¹¹ However, acronyms such as HPC(CB), MNC(A), and HPC(M) are used only as abbreviations and are not intended to be used on the full product labels. (Check reference 8 for appropriate usage of acronyms.) Users of this *Circular* should confirm that the terminology is still in effect before labeling and distributing a cellular therapy product for patient use.

General Information

This *Circular* is prepared by the Circular of Information for Cellular Therapy Products Task Force consisting of representatives from AABB, American Association of Tissue Banks (AATB), American Red Cross (ARC), American Society for Blood and Marrow Transplantation (ASBMT), American Society for Apheresis (ASFA), America's Blood Centers (ABC), College of American Pathologists (CAP), Foundation for the Accreditation of Cellular Therapy (FACT), ICCBBA, International Society for Cellular Therapy (ISCT), National Marrow Donor Program (NMDP), Joint Accreditation Committee of ISCT and EBMT (JACIE), and NetCord. The text of this document has been approved by the Board of Directors of each of these organizations. Representatives from the FDA and HRSA participated in deliberations of this Task Force.

This *Circular* is intended to provide general information to those who administer cellular therapy products and serves as an extension and enhancement of the label found on the cellular therapy product. The Task Force has chosen to describe only those cellular therapy products that are most frequently used in clinical practice. **Not all cellular therapy products are described in this *Circular*.**

In order to address other cellular therapy products that are not listed in the *Circular*, this document is designed with a section of blank pages at the end to allow for inclusion of facility-specific information. It is important for users of this document to examine this section of the *Circular* for any additional information provided by the distributing facility and/or the manufacturer of the cellular therapy product. The portion preceding this section of the document cannot be changed.

This *Circular* is intended to be used by facilities based in different countries. The Task Force has made a concerted effort to accommodate both US and EU requirements in the document text. However, the regulatory approaches to cellular therapy products in the United States and the EU, as well as in other countries, differ in some aspects. Users should consult the appropriate regulatory authority for specific requirements related to their facility.

For investigational products manufactured and administered in the United States, an FDA-approved investigational new drug (IND) application or an Investigational Device Exemption (IDE) is required. For investigational products manufactured and administered outside the United States, other local regulations apply. The relevant clinical protocol should be consulted for 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.

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's stem and progenitor cells with growth factors, chemotherapy, or both. Donors of other cellular therapy products may or may not require stimulation by growth factors, depending on the protocol employed. Allogeneic HPC collection usually occurs after mobilization with growth factors alone. Certain products such as HPC, Marrow [HPC(M)] and MNC, Apheresis [MNC(A)] are usually collected from donors who are not mobilized.

Allogeneic donors are screened through the use of questions designed to detect risk factors for infectious diseases transmissible by the cellular therapy product and are tested for transmissible infectious diseases. (See Tables 1A and 1B.) The questions are based on donor screening requirements promulgated by regulatory agencies and criteria set forth by standard-setting organizations. A donor questionnaire and accompanying donor screening materials* have been developed for cell therapy products and cord blood donors. 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.

Some allogeneic donors may not meet all the requirements; however, because of the patient's clinical circumstances, they may be approved for donation. In such situations, information regarding requirements

* An example of such a questionnaire, called the uniform donor questionnaire, has been prepared with input from AABB, AATB, ASFA, and FACT and can be accessed on the AABB Web site (www.aabb.org) under "Donate Blood > Donor History Questionnaires."

that the donor has not met is included in the summary of records/information provided to the transplant center. The cellular therapy products from such donors are also labeled accordingly. (See Table 2.) Cellular therapy products from a donor with abnormal screening and/or 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 Sources

HPC, Marrow

HPC, Marrow [HPC(M)] preparations are collected as a source of HPCs. They are obtained by multiple needle aspirations from the posterior iliac crests 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 of HPC(M) products varies and may range from 100 mL to 2000 mL. 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) products are reduction of the volume of ABO-incompatible red cells, removal of ABO-incompatible plasma, selection of CD34+ progenitor cells, or removal of donor T lymphocytes. The most common modification of autologous HPC(M) products is to reduce the volume by removing plasma and red cells before cryopreservation.

HPC, Apheresis

HPC, Apheresis [HPC(A)] preparations are collected as a source of HPCs obtained from the peripheral blood during an apheresis procedure, usually after recombinant hematopoietic growth factor administration or other agents. Autologous donors may also have undergone chemotherapy mobilization. Allogeneic HPC(A) collections are frequently infused without further processing. The most common additional processing of allogeneic HPC(A) products are reduction or removal of ABO-incompatible red cells, removal of ABO-incompatible plasma, selection of CD34+ progenitor cells, or removal of donor T lymphocytes. The most common types of additional processing of autologous HPC(A) products are reduction of volume by removing plasma before cryopreservation, selection of CD34+ progenitor cells, and washing the cells to remove dimethyl sulfoxide (DMSO) after thawing.

HPC, Cord Blood

HPC, Cord Blood [HPC(CB)] preparations are collected as a source of HPCs obtained from the umbilical cord during the third stage of labor or after delivery of the placenta. After thorough cleansing of the cord, the blood is collected by gravity drainage into standard blood collection bags containing citrate-phosphate-dextrose (CPD) anticoagulant. Before cryopreservation, cord blood collections are usually processed by red cell and plasma reduction. HPC(CB) products are typically stored with final 10% DMSO cryoprotectant in bags with integral segments designed to be a source of material for identity and potency testing. Frozen cord blood products are transported to the transplant center before patient conditioning begins and are typically thawed using a wash or reconstitution method before infusion.

Nucleated Cell Preparations

MNC, Apheresis

MNC, Apheresis [MNC(A)] preparations contain nucleated cells collected from the peripheral blood by an apheresis procedure intended for clinical use other than HPCs. Autologous MNC(A) collections are generally further processed. Allogeneic MNC(A) collections are most commonly used as donor lymphocyte infusions (DLIs). The dose for MNC(A) will be determined by institutional policies and is usually based on the number of T cells (eg, CD3+ cells), nucleated cells, or mononuclear cells.

NC, Cord Blood

NC, Cord Blood [NC(CB)] preparations are collected as a source of nucleated cells obtained from the umbilical cord during the third stage of labor or after delivery of the placenta and are intended for clinical use other than as HPCs.

NC, Whole Blood

NC, Whole Blood [NC(WB)] preparations contain nucleated cells collected as peripheral whole blood intended for clinical use other than as HPCs.

NC, Marrow

NC, Marrow [NC(M)] preparations contain nucleated cells collected from bone marrow intended for clinical use other than as HPCs.

Cellular Therapy Product Descriptions

Cellular therapy products consist of somatic-cell-based products (eg, HPC, Apheresis; HPC, Marrow; HPC, Cord Blood; MNC, Apheresis; NC, Whole Blood) that are collected or procured from the donor and intended for manipulation and/or administration to the patient.

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 as well as lymphocytes.

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.

Allogeneic cellular therapy products may also be used to provide additional donor lymphocytes to enhance a graft-vs-leukemia effect. Other applications of cellular therapy products may have different potential mechanisms of action depending on the cell type and clinical setting.

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 and immune-mediated therapy. Autologous HPCs are collected and used following myeloablative or myelotoxic therapy to enhance hematopoietic reconstitution. The therapy is intended to treat the patient's underlying malignancy, and autologous HPC products are administered to minimize morbidity and mortality caused by the

myelotoxic effects of the therapy. Additional applications may be used as indicated in clinical trials and research protocols.

Contraindications

MNC, Apheresis and NC, Whole Blood are generally contraindicated for patients experiencing severe graft-vs-host disease (GVHD). Institutional policies and protocols and federal regulations dictate specific contraindications for cellular therapy product administration. Additional information regarding contraindications may be included at the end of this document, if provided by the distributing facility.

The following section provides common cellular therapy product descriptions in the product description format consistent with *ISBT 128* information and labeling standards.

HPCs contain self-renewing or multipotential stem cells capable of maturing into any hematopoietic lineage, lineage-restricted pluripotential progenitor cells, and committed progenitor cells. They may be collected from bone marrow (HPC, Marrow), peripheral blood with or without prior mobilization (HPC, Apheresis), whole blood with mobilization (HPC, Whole Blood), or placental/umbilical cord blood (HPC, Cord Blood). They may then be subjected to volume reduction or further manipulations. (See below.)

HPC, (PLASMA REDUCED) PRODUCTS

HPC, APHERESIS	HPC, CORD BLOOD
Plasma Reduced	Plasma Reduced

HPC, MARROW
Plasma Reduced

These products contain the cellular elements of the starting HPC collection(s) that remain after the bulk of the plasma is removed by centrifugation.

HPC, (RBC REDUCED) PRODUCTS

HPC, APHERESIS	HPC, CORD BLOOD
Red Cells Reduced	Red Cells Reduced

HPC, MARROW
Red Cells Reduced

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

HPC, (BUFFY COAT ENRICHED) PRODUCTS

HPC, APHERESIS	HPC, CORD BLOOD
Buffy Coat Enriched	Buffy Coat Enriched

HPC, MARROW
Buffy Coat Enriched

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

HPC, (MONONUCLEAR CELL ENRICHED) PRODUCTS

HPC, APHERESIS	HPC, CORD BLOOD
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Mononuclear Cell Enriched

Mononuclear Cell Enriched

HPC, MARROW

Mononuclear Cell Enriched

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.

HPC, CRYOPRESERVED PRODUCTS

HPC, APHERESIS

CRYOPRESERVED

HPC, CORD BLOOD

CRYOPRESERVED

HPC, MARROW

CRYOPRESERVED

These are HPCs that have been frozen using cryoprotectant solutions and containers suitable for the purpose.

HPC, (CD34 ENRICHED) PRODUCTS

HPC, APHERESIS

CD34 Enriched

HPC, CORD BLOOD

CD34 Enriched

HPC, MARROW

CD34 Enriched

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

Other Cellular Products

These are nucleated cells and from any source (marrow, peripheral blood, whole blood, or umbilical cord/placental blood) intended for clinical use other than as HPCs. They may be further categorized according to the specific subpopulations.

MNC, APHERESIS; NC, WHOLE BLOOD; NC, MARROW

These products are most frequently used for DLIs. 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.

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-JACIE, NetCord-FACT, or NMDP standards.¹³⁻¹⁷

NOTE: If the administration of a cellular therapy product is delayed, the distributing/issuing facility should be contacted for instructions on proper storage of the product during the delay.

- Prior to the administration of the product, it is critical to coordinate patient and product preparation to support timely product infusion according to the facility standard operating procedure. Infusion coordination may include confirmation of the number of containers and type of product (fresh or

cryopreserved), verification of product infusion order, verification of consent for infusion, and verification of patency of intravenous access for infusion of the product.

- The intended recipient and the product container must be properly identified according to facility standard operating procedure before the product is administered.
- The product must be inspected for changes in the integrity of the container and product condition before administration. Any questions about the product should be directed to the facility distributing or issuing the product.
- Aseptic technique must be employed when handling and administering the product.
- 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 as products, with the exception of 0.9% Sodium Chloride, Injection (USP) or facility-approved solutions, as directed by the distributing facility. 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.
- Sequence and timing of multiple product infusions should be performed according to the administering facility's standard operating procedures. Adequate time between product infusions should be allowed to permit assessment for adverse reactions.

Dosage and Administration

The minimum number of HPCs necessary for engraftment in a myeloablated recipient has not been established for all HPC sources. However, eligibility criteria for some protocols may dictate a minimum number of cells to be collected and/or infused. Some examples of cell types measured to determine HPC dosage are CD34+ cells, nucleated or mononuclear cells, and colony-forming units–granulocyte-macrophage (CFU-GM). The dose for MNC, Apheresis or NC, Whole Blood is determined by institutional policies and is usually based on the number of T cells, nucleated cells, or mononuclear cells. For specific dosage and administration of other cellular therapy products, the investigator's brochure or special instructions should be followed. Such information may be found at the end of this document, if provided by the distributing facility.

Administration of any cellular therapy product should begin only after identification of the product(s) and the intended recipient according to institutional policies. Manufacturers may recommend that products be filtered using a 170- to 260-micron filter to remove clumps or aggregates. Some institutions may have specific policies regarding the use of these filters for cellular therapy products. (See facility-specific section at the end of this document.) Cellular therapy product 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. The administration time will be determined by the total volume to be infused and by whether the cells are fresh or previously cryopreserved. 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 a 10% solution contains 10 mL of DMSO).

Storage

Cellular therapy products may be transported for administration in fresh or cryopreserved state. They may require either long-term or short-term storage prior to administration. Institutional policies and protocols dictate specific storage requirements for cellular therapy products. The recommended storage duration and temperature may be included in the product labeling and should indicate the cell dose, storage

temperature, and duration of storage to ensure acceptable cell viability and function. If an expiration date has been defined, it should be included on the product label. Prior to infusion, products received for the treatment of a patient should be stored according to the instructions on the label or those supplied in accompanying documentation. If there is an unexpected delay in administration and the product must be held for infusion after the expiration period indicated on the label, if applicable, the distributing/issuing and/or local cell processing facility should be contacted for further handling and storage instructions.

Noncryopreserved Cellular Therapy Products

Fresh products may be transported from distant collection facilities or undergo short-term local storage prior to administration.

Cryopreserved Cellular Therapy Products

Cryopreserved products may be received and stored long-term according to manufacturer's direction or by a validated method. These products may be thawed at the local cell processing laboratory, with or without additional processing, or thawed at the bedside immediately prior to administration. These products should be infused as soon as possible after thawing occurs.

Cellular Therapy Product Labeling and Supporting Documents

At the time of issue, cellular therapy products will have the following information either on the affixed product label, on an attached label, or in accompanying documentation:

- Proper name of the product, including an indication of any qualification or modification
- Unique identifier
- Approximate volume
- Name and volume of anticoagulant or other additives
- Date and time of collection
- Expiration date and time (if applicable)
- Recommended storage temperature
- Identity and address of collection facility or donor registry
- Identity and address of processing/distributing 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 the ABO group and Rh (D) type of a cord blood product
- Red cell compatibility testing results (if applicable)

Many products will be accompanied by additional records that are included to meet regulatory requirements. These accompanying records will include:

- A statement indicating whether the donor has been determined to be eligible or ineligible, or that the donor eligibility determination is incomplete
- A summary of the records used to make the donor eligibility determination
- Infectious disease testing results and supporting documents

International standards for nomenclature and labeling of cellular therapy products using *ISBT 128* have been determined by the International Cellular Therapy Coding and Labeling Advisory Group.^{8,9,10,11}

Biohazard and Warning Labels

The application of biohazard and warning labels on the cellular therapy products summarized in Table 2 is defined by facility-specific policies and procedures. The FDA defines requirements for the use of biohazard and specific warning labels for products subject to the regulations as defined in 21 CFR 1271, implemented on 05/25/05. As such, cellular therapy products subject to these FDA regulations require the use of these labels as specified by FDA for an “incomplete” or “ineligible” donor eligibility determination. Refer to 21 CFR 1271 for specific labeling guidance. Application of these labels extends outside the FDA-defined requirements, such as to HPC(M), based on voluntary adherence to professional industry standards and facility-specific guidance or other applicable laws. Questions about the interpretation of any label on a specific product should be directed to the facility distributing the product.

Side Effects and Hazards

Some of the side effects and complications may require reporting to a relevant national competent authority. See “Reporting of Adverse Reactions” section later in this *Circular* for additional details.

The following most common 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 can be caused by donor-recipient major or minor ABO or other blood group incompatibility. Acute hemolytic reactions may be immediate and occur up to 24 hours following infusion. In some instances acute hemolytic reactions may not be overtly apparent.

Signs and symptoms of acute hemolytic reactions may include one or more of the following:

- Chills
- Fever
- Headache
- Burning sensation along the vein
- Abnormal bleeding
- Low back pain
- Facial flushing
- Chest pain; rapid, labored respirations
- Tachycardia
- Shock
- Hemoglobinuria

Treatment:

- Measures to maintain or correct arterial blood pressure; correct coagulopathy, if present; and promote and maintain urine flow.

Prevention:

- Red cell reduction
- Plasma reduction
- Washing to remove free hemoglobin

2. **Febrile, Nonhemolytic Reactions** 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. They occur more frequently in patients previously alloimmunized by transfusion or pregnancy. No routinely available tests are helpful in predicting these reactions.

Signs and symptoms of febrile, nonhemolytic reactions include:

- Temperature elevation of 1 C (2 F) or more (shortly after or up to 2 hours following product administration and in the absence of another pyretic stimulus)
- Chills

Treatment:

- Antipyretics

Prevention:

- Antipyretics

3. **Allergic/Anaphylactoid/Anaphylactic 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. These reactions have typically been reported in IgA-deficient patients who have IgA-specific antibodies of the IgG and/or IgE class and who receive even small amounts of IgA-containing plasma. Allergic reactions to hydroxyethyl starch (HES) or DMSO used in cellular therapy product processing or cryopreservation may occur in sensitized patients.

Signs and symptoms of allergic reactions include:

- Urticaria (hives)
- Pruritus (itching)
- Bronchospasm and/or laryngospasm
- Hypotension
- Severe dyspnea
- Facial, glottal and/or laryngeal edema
- Other symptoms such as facial burning and flushing, abdominal pain, nausea, vomiting, diaphoresis, diarrhea, and dizziness

Treatment:

- Antihistamines
- In severe cases, fluids, epinephrine, and/or steroids

Prevention:

- Premedication with antihistamines or steroids may help prevent mild reactions.
- Washing of products can help prevent symptoms, but this procedure is usually reserved for patients with a history of severe/anaphylactic reactions.

4. **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 anti-leukocyte antibodies (eg, anti-HLA) in the donor or recipient. As such, these reactions are rare in recipients of HLA-matched products.

In the absence of evidence for another cause of pulmonary compromise, signs and symptoms of TRALI include:

- Acute respiratory distress within 6 hours of administration
- Hypoxemia
- Bilateral pulmonary infiltrates on frontal chest x-ray

Treatment:

- Respiratory support

Prevention:

- Plasma-reduction or washing can help reduce the risk of TRALI in the setting of a graft with known anti-HLA or anti-human neutrophil antibody (HNA), but these procedures are rarely performed for this indication.

Immunologic Complications, Delayed

1. ***Alloimmunization to Antigens*** of red cells, white cells, platelets, or plasma proteins may occur prior to infusion of cellular products or 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 blood or 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 that may contribute to graft failure, red cell aplasia, and transfusion refractoriness.

Prevention:

- Selective use of antigen-compatible blood components for transfusion support
- In some cases, prophylactic antihistamine medications prior to infusion of the cellular therapy product

2. ***Delayed Hemolytic Reactions*** may occur in two different allogeneic settings. Clinically significant antibodies to red cell antigens in previously alloimmunized patients are usually detected by preadministration testing. Occasionally, however, levels may diminish to below the limits of detection. In these cases, 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 red cells are still present in the circulation. The usual time frame for reappearance of antibody is 2 to 14 days after product administration. Delayed hemolytic reaction may also occur in recipients who receive minor incompatible transplants, whether in regard to ABO or to other red cell antigens. In this setting, the infused donor's B lymphocytes may produce antibodies to red cell antigen, 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.

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 lactate dehydrogenase (LDH) or bilirubin
- Hemoglobinemia and hemoglobinuria (rare)
- Symptoms of acute intravascular hemolysis (rare)

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 severe cases may require more rapid antigen-negative red cell replacement, fluid administration, and perhaps red cell exchange

Prevention:

- Providing red cells posttransplant that are compatible with the donor and recipient

3. **Graft-vs-Host Disease** (GVHD) is an extremely serious condition that occurs frequently in recipients of allogeneic cellular therapy products.¹⁸ GVHD occurs when viable T lymphocytes in the infused product engraft and react against tissue antigens in the recipient. GVHD may also follow the administration of nonirradiated blood components or any product that contains even a small number of viable T lymphocytes. Therefore, blood components are irradiated in the transplant setting. Severely immunocompromised recipients receiving allogeneic cellular therapy products are at greatest risk.

Signs and symptoms:

- Wide variety of immune-mediated tissue and organ damage

Treatment:

- Post-transplant immunosuppression, according to institutional guidelines and policies

Prevention:

- Use of optimally matched HLA-compatible donor graft
- Incorporation of immune suppression into the conditioning regimen

Nonimmunologic Complications

1. **Dimethyl sulfoxide (DMSO) Toxicity** is the most common complication of cryopreserved product administration. DMSO is a cryoprotectant used to cryopreserve cellular therapy products. Side effects and symptoms are generally associated with histamine release.

Signs and symptoms:

- Coughing
- Flushing
- Rash
- Chest tightness and wheezing
- Nausea and vomiting
- Cardiovascular instability

Treatment:

- Slowing the rate of infusion
- Medicating with antihistamines
- Treating symptoms

Prevention:

- Administer prophylactic antihistamine therapy
- Decrease rate of administration
- Provide hard candy to prevent nausea caused by the odor and/or taste
- Remove DMSO from the product by washing the cells before administration; while this may reduce the risk of symptoms, it is not generally required given typically mild reactions and it may result in unintended cell loss

2. **Septic Infusion Reaction** may occur due to bacterial contamination of cellular therapy products, but it rarely causes acute, severe, or life-threatening effects. Prompt recognition of a possible septic reaction is essential. The onset of high fever (>2 C rise in temperature) during or immediately after product administration should suggest the possibility of bacterial contamination and/or the presence of endotoxin in the product.

Signs and symptoms of septic infusion reactions include:

- Fever with chills
- Severe hypotension
- Dry, flushed skin
- Pain in abdomen and extremities
- Vomiting
- Bloody diarrhea

Treatment:

- Prompt and appropriate use of antimicrobial agents with modification based on evaluation of blood culture results from the patient and the product when available

Prevention:

- Appropriate aseptic technique during all aspects of product collection, manufacturing, and infusion
- Use of nonconforming products with positive culture results according to institutional protocol and relevant national competent authority

3. **Fat Emboli**, small fat droplets in marrow products, may block capillary perfusion and cause respiratory distress.

Signs and symptoms of Fat Emboli Syndrome (FES) include:

- Dyspnea
- Hypoxia
- Tightness of the chest
- Coughing
- Petechiae
- Confusion (mental status change)

Treatment:

- Supplemental oxygen therapy
- Ventilation as needed
- Corticosteroids, including methylprednisolone, which have reduced posttraumatic hypoxemia believed to be due to FES

Prevention:

- Routine filtering of bone marrow products with 170- to 260-micron filters prior to infusion

4. **Transmission of Infectious Disease and/or Disease Agents** may occur because cellular therapy products are collected from human blood and/or tissues. Disease may be caused by known or unknown agents. Donor selection criteria, screening, and testing are designed to minimize the potential risk of disease transmission. These procedures aim to identify potential donors with increased risk of infection with human immunodeficiency virus (HIV), human T-cell lymphotropic virus (HTLV), hepatitis B virus (HBV), hepatitis C virus (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 (CMV) 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 immunocompromised transplant recipients if they are CMV-seronegative. Administering CMV-seronegative cellular therapy products

reduces the risk of CMV transmission. For some infectious agents, there are no routine tests to predict or prevent disease transmission.

Treatment:

- Based on implicated infectious agent

Prevention:

- Minimize by robust screening procedures, identification of infectious donors, and proper labeling

5. **Bleeding Due to Excessive Anticoagulation** can occur if heparin or other anticoagulants were added to the product during collection and/or processing and remain in the cellular therapy product when administered.

Treatment:

- Anticoagulant specific
- A reversal agent can be considered

Prevention:

- Product/anticoagulant specific
- Infusion rates may be adjusted depending on the clinical conditions; products may be washed when cell loss is not a concern

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 at-risk patients, the infusion of colloid preparations (including plasma products and the suspending plasma in cellular therapy products) should be reduced to a minimum. See also section on TRALI.

Signs and symptoms of circulatory overload may include:

- Dyspnea
- Peripheral edema
- Rapid increase of blood pressure

Treatment:

- Aggressive diuresis

Prevention:

- Minimize the volume of colloidal preparations and, if appropriate, split or volume reduce the product for infusion

7. **Hypothermia** is related to the temperature of the cellular therapy product and the rate of infusion and can be caused by rapid infusion of large volumes of cold products. Hypothermia carries a risk of cardiac arrhythmia or cardiac arrest. A blood warming device should not be used unless approved by the manufacturer of the cellular therapy product.

Treatment:

- Warm the patient

Prevention:

- Decrease infusion rate when clinically appropriate

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 osmotic stress, mechanical injury, shear stress, coadministration with incompatible fluids, and intrinsic red cell abnormalities such as hemoglobinopathies or enzyme deficiencies. Some hemoglobinuria can be seen even with products containing only small amounts of free hemoglobin and do not necessarily indicate a reaction.

Signs and symptoms:

- May be the same as hemolytic reactions, either delayed or immediate

Treatment:

- Same as treatment of hemolytic reactions

Prevention:

- High levels of free hemoglobin can be removed by washing the product when clinically appropriate and using isotonic solutions during product preparation
- Related to proper product handling during all steps of product collection, manufacturing, and administration

Reporting of Adverse Reactions

Any adverse reaction that is defined as a suspected or proven unfavorable response to administration of cellular therapy products and is manifested by signs and symptoms (including 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 and/or applicable laws and regulations. At a minimum, any such event must be reported to the patient's physician and to the medical director of the facility that issued the product.

The reporting requirements vary based on the nature of the regulatory oversight required by the type of product and manufacturing process. The user must contact the manufacturing/distributing facility for specific requirements or report as defined by the IND/IDE holder, where applicable.

Entities involved in the manufacture of the product must be contacted in the investigation/reporting of an adverse reaction, as applicable.

Specific Product Information

This page is intended to be blank to provide space for the distributing institution to provide additional product information as applicable to its product.

As indicated in the General Information section, the distributing institution is responsible for providing specific information not already included in this *Circular* about the cellular therapy product, including but not limited to the following:

- Description
- Action
- Indications
- Contraindications
- Storage
- Dosage
- Administration

Note: Specific product labeling information is required if the product is manufactured under a US FDA-approved Investigational New Drug (IND) application or an Investigational Device Exemption (IDE) in the United States. Products manufactured and administered outside the United States must comply with local regulations.

Table 1A. US Minimal Requirements for Testing for Transmissible Agents in Cellular Therapy Products *

Testing for infectious agents	Donors of HPC(M) and HPC(A)		Donors of HPC(CB)		Donors of Other Hematopoietic Cell-Derived Products	
	Up to 30 days before or 7 days after collection	Up to 7 days before or after collection	Up to 7 days before or after collection	Up to 7 days before or after collection	Up to 7 days before or after collection	Up to 7 days before or after collection
Human immunodeficiency virus, type 1 and 2 (HIV-1, HIV-2)♦	X	X (MS)	X (MS)	X	X	X
Hepatitis B virus (HBV)	X	X (MS)	X (MS)	X	X	X
Hepatitis C virus (HCV)	X	X (MS)	X (MS)	X	X	X
Human T-cell lymphotropic virus, types I and II (HTLV-I, HTLV-II)	X	X (MS)	X (MS)	Xest	Xest	Xest
Cytomegalovirus (CMV) (if allogeneic)	X	X (MS)	X (MS)	X	X	X
<i>Treponema pallidum</i> (syphilis)	X	X (MS)	X (MS)	X	X	X

*You may need to conduct more than one test to adequately and appropriately test for a single communicable disease agent or disease. Refer to CBER Web site for a list of approved tests. Testing is performed following manufacturer's instructions using FDA-licensed, approved or cleared donor screening tests for relevant communicable disease agents and diseases (RCDADs) as defined by US FDA. FDA-licensed, approved or cleared donor screening tests are available for West Nile Virus (WNV) and HBV NAT and Trypanosoma Cruzi; testing may be implemented per facility-specific guidance prior to an FDA testing requirement. Additional tests for infectious transmissible agents may be required or performed.

†US federal regulations do not require testing of autologous donors for transmissible agents. However, the voluntary accrediting organizations (eg, AABB, FACT-JACIE) and some states or regions may require additional testing and/or testing of autologous donors. See References for a list of selected publications containing testing requirements and standards. Required testing must be performed by a laboratory that is either certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 USC §263a and 42 CFR 493) or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services.

♦ Establishments not using an FDA-licensed screening instrument that tests for HIV-1 group O antibodies must evaluate donors for risk associated with HIV-1 group O infection
MS = maternal sample

Table 1B. EU Minimal Requirements for Testing for Transmissible Agents in Cellular Therapy Products *†‡

Timing of specimen collection	Donors of	
	HPc(M), HPc(A), and TC(A)	HPc(CB) [§]
Human immunodeficiency virus, type 1 and type 2 (HIV-1, HIV-2)	Up to 30 days before collection	Day of or up to 7 days after delivery
Hepatitis B virus (HBV)	X	X (MS/CBU)
Hepatitis C virus (HCV)	X	X (MS/CBU)
<i>Treponema pallidum</i> (syphilis)	X	X (MS/CBU)
Human T-cell lymphotropic virus, type I (HTLV-I)	X	X (MS)

*The tests must be carried out by a qualified laboratory authorized as a testing center by the competent authority in the Member State, using CE-marked testing kits where appropriate. The type of test used must be validated for the purpose in accordance with current scientific knowledge. In certain circumstances, additional testing may be required depending on the donor's history and the characteristics of the tissue or cells donated (eg, malaria, toxoplasma, CMV, EBV, *Trypanosoma cruzi*).

†Member countries of the European Union may amend and/or introduce additional requirements within the EU directives. In some settings, testing by more than one method may be required for some infectious agents. This table is not intended to reflect all national variations but rather to present general requirements within the EU directives.

‡The governmental regulations require testing of autologous donors for transmissible agents only if removed cells are to be stored or cultured. However, the voluntary accrediting organizations (eg, AABB, FACT-JACIE) may require testing of autologous donors.

§ Performed on donors living in or originating from high-prevalence areas, or with sexual partners originating from those areas, or whose parents originate from those areas. The testing is repeated on the CBU if they are stored for a long period of time; alternatively, NAT technology is used.

MS = maternal sample; CBU = cord blood unit
See References for a list of selected publications containing testing requirements and standards.

Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States

	Status				Product Labels (See footnote)●				
	All Donor Screening and Testing Performed per FDA Criteria	Abnormal Results of Donor Screening♦	Abnormal Results of Donor Testing♦	Urgent Medical Need ▶	Biohazard Legend [21 CFR 1271.3(b)]	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*	No	No	No	Yes	NR See footnote*	R	R	NA	
Allogeneic donors with incomplete donor eligibility determination*	No	No/Yes	Yes	Yes	NR See footnote*	R	R	NR See footnote*	
Allogeneic donors with incomplete donor eligibility determination*	No	Yes	No	Yes	NR See footnote*	R	R	NA	
2. Allogeneic donors found ineligible									
A first-degree or second-degree blood relative	Yes	No/Yes	Yes	NA	R	NA	R	R	
A first-degree or second-degree blood relative	Yes	Yes	No	NA	R	NA	R	NA	
Unrelated donor	Yes	No/Yes	Yes	Yes	R	NA	R	R	
Unrelated donor	Yes	Yes	No	Yes	R	NA	R	NA	
Donor Eligibility Determination Not Required [21 CFR 1271.90(a)]									
3. Autologous donors									

NOTE: • Application of biohazard and warning labels extends outside the HCT/Pls described in 21 CFR 1271 based on voluntary adherence to professional standards and applies to all products defined in this COI, including HPC(M), which is not regulated under 21 CFR 1271. FDA eligibility processes and associated biohazard and warning labels were required on and after 05/25/05 and may or may not be implemented for units collected prior to 05/25/05 per facility-specific policy.

*Donor eligibility status of “incomplete” means donor screening and /or testing was not performed per US requirements. The donor eligibility determination must be completed for donor screening and testing per FDA requirements during or after the use of the cellular therapy product. When not feasible to complete screening and/or testing per FDA criteria, documentation should be on file to justify. The biohazard label may be applied per facility-specific guidance for incomplete eligibility status; however, abnormal results of any screening or testing should include appropriate biohazard and warning labeling per industry standard [21 CFR 1271.250 (c) applies].

◆ When abnormal results of any donor screening or testing are identified in the donor, the transplant physician is notified of those results.

◆ Urgent Medical Need must be documented when a donation is used for transplant from a related or an unrelated donor with an incomplete eligibility status, or when a donation is used for transplant from an unrelated donor with an “ineligible” eligibility status.

¶ FDA does not require donor testing or screening for autologous donors: FDA requires all autologous donations to be labeled “For Autologous Use Only.” When all donor screening and testing is not completed per FDA requirements, the label “Not Evaluated for Infectious Substances” is also required. 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(a)(b)].

CFR = Code of Federal Regulations; FDA = Food and Drug Administration; NR = not required; R = required; NA = not applicable

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