CIRCULAR OF INFORMATION

FOR THE USE OF CELLULAR THERAPY PRODUCTS

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CIRCULAR OF INFORMATION

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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.

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Table of Contents

Contact Information iii

Notice to All Users 1

General Information 2

Donors 2

Cellular Therapy Product Sources 3
- HPC, Marrow 3
- HPC, Apheresis 8
- HPC, Cord Blood 8
- TC, Apheresis 8
- TC, Whole Blood 8
- TC, Marrow 9

Cellular Therapy Products 9
- Description 9
- Actions 9
- Indications 9
- Contraindications 11

Dosage and Administration 11

Instructions for Storage and Administration of Cellular Therapy Products 12

Cellular Therapy Product Descriptions 13
- HPC, (Plasma reduced) 13
- HPC, (RBC reduced) 13
- HPC, (Buffy coat enriched) 13
- HPC, (Mononuclear cell enriched) 13
- Cryopreserved HPC 13
- HPC, (CD34 enriched) 14
- Therapeutic Cells (TC) 14

Storage 14

Cellular Therapy Product Labeling and Supporting Documents 14

Biohazard and Warning Labels 15

Pregnancy Category 15

Reporting of Adverse Reactions 16

Side Effects and Hazards 16
- Immunologic Complications, Immediate 16
- Immunologic Complications, Delayed 18
- Nonimmunologic Complications 19

References 21

Facility-Specific Section 23

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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.[1,2] The focus of this *Circular* is restricted to cellular therapy products, such as hematopoietic progenitor cells (HPCs) and other leukocytes that are minimally manipulated. 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 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).[3-7] This *Circular* is not a comprehensive reference for applicable regulations.*

The nomenclature used throughout this *Circular* is consistent with ISBT 128 terminology.[8,9] However, acronyms such as HPC(CB), HPC(A), and HPC(M) are used only as abbreviations and are not intended to be used in the labeling process or on the product labels.

*The manufacturers of cellular therapy products regulated as biologic drugs, in particular, should consult applicable regulations regarding labeling requirements in the 21 CFR Part 201 and 21 CFR Part 610 Subpart G. Furthermore, some of the information in this *Circular* goes beyond the labeling requirements for cellular therapy products regulated solely under section 361 of the Public Health Service Act, and manufacturers of such products should refer to the applicable labeling regulations in 21 CFR Part 1271.

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 the clinical practice. **Not all investigational or licensed cellular therapy products are listed in this *Circular.***

In order to address other cellular therapy products that are not listed in the *Circular*, the design of this document allows for inclusion of facility-specific information at the end of this *Circular.* It is important for the 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 preceding portion 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 United States (US) and EU requirements in the text of this document. However, the regulatory approaches to cellular therapy products in the US and EU differ in some aspects. Consult the appropriate regulatory authority for specific requirements.

For investigational products manufactured and administered in the US, an FDA-approved investigational new drug (IND) application or an Investigational Device Exemption (IDE) is required. For investigational products manufactured and administered outside of the US, 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 Therapeutic Cells [eg, TC, Apheresis, or TC(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 that have not been met by the donor is included in the summary of records. The cellular therapy products from such donors are also labeled accordingly (see Table 2).

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 Sources

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 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) prod-

*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."

Table 1A. Testing for Transmissible Agents in Cellular Therapy Products that are Collected, Processed, and/or Administered in the United States*†

	Donors of HPC(M) and HPC(A)	Donors of HPC(CB)	Donors of Other Products (Allogeneic)
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
Treponema pallidum (syphilis)	X	X (MS)	X
West Nile virus (WNV)‡	X	X (MS)	X
Trypanosoma cruzi (Chagas' disease)‡	X	X (MS)	X

*Testing is performed using FDA-licensed, -cleared, or -approved donor screening tests for transmissible agents. Additional tests for infectious transmissible agents may be required or performed.

†The governmental regulations do not require testing of autologous donors for transmissible agents. However, the voluntary accrediting organizations (eg, AABB, FACT/JACIE) require testing of autologous donors.

‡West Nile virus and *T. cruzi* are considered relevant communicable disease agents as defined under 21 CFR 1271.3(r)(2) by the FDA.[10] However, at this time (12/2009), testing for WNV is not required but, if performed, it is generally done on the day of collection of the cellular therapy product. Similarly, donor testing requirements for *T. cruzi* have not been finalized.

MS = maternal sample.

Table 1B. Minimal Requirements for Testing for Transmissible Agents in Cellular Therapy Products that Are Collected, Processed, and/or Administered in the European Union*[†‡]

	Donors of HPC(M), HPC(A), and TC(A)	Donors of HPC(CB)[¶]
Timing of specimen collection	Up to 30 days before collection	Day of or up to 7 days after delivery
Human immunodeficiency virus, type 1 and 2 (anti-HIV-1, HIV-2)	X	X (MS/CBU)
Hepatitis B virus (HBsAg and anti-HBc)	X	X (MS/CBU)
Hepatitis C virus (anti-HCV)	X	X (MS/CBU)
Treponema pallidum (syphilis)	X[§]	X (MS/CBU)
Human T-cell lymphotropic virus, type I (anti-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. This table is not intended to reflect all national variations but rather present general requirements within the EU.
[‡]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) require testing of autologous donors.
[§]A validated test algorithm needs to be applied to exclude the presence of infection (for additional information see Directive 2006/17/EC).
[‖]Performed only on a selected donor population with increased risk of infection.
[¶]The testing is repeated on the CBU if they are stored for a long period of time, or alternatively NAT technology is used.
MS = maternal sample; CBU = cord blood unit.

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

		Status					Product Labels				
		All Donor Screening and Testing Completed	Abnormal Results of Donor Screening	Abnormal Results of Donor Testing	Other Condition*	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†	No	No	No		Yes			X	X	
2.	Allogeneic donors found ineligible										
	A first-degree or second-degree blood relative‡	Yes	No/ Yes	Yes		NA	X			X	X
	A first-degree or second-degree blood relative‡	Yes	Yes	No		NA	X			X	
	Unrelated donor§	Yes	No/ Yes	Yes		Yes	X			X	X
	Unrelated donor§	Yes	Yes	No		Yes	X			X	
	Unrelated donor	Yes	No	No	Yes	Yes			X	X	
Donor Eligibility Determination Not Required [21 CFR 1271.90(a)]											
3.	Autologous donors‖										
	Autologous donor¶	No	No	No		NA		X	X		
	Autologous donor#	Yes	No/ Yes	Yes		NA	X	X			X
	Autologous donor#	Yes	Yes	No		NA	X	X			

NOTE: Application of biohazard and warning labels extends outside the product described in 21 CFR 1271 based on adherence to professional standards and applies to unmanipulated HPC(M). Alternatively, unmanipulated HPC(M) is not regulated under 21 CFR 1271 but is included based on voluntary adherence to professional standards. Other cellular products which are not described in the 21 CFR 1271 [eg, HPC(A) from unrelated donors; HCP(CB)] are included in this table.

*Testing for infectious disease markers performed in non-CLIA-certified laboratory and/or using non-FDA cleared, approved,or licensed tests.

†The donor eligibility determination 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)]. Abnormal results of any screening or testing requires labeling as in item 2 in this table (21 CFR 1271.65 applies).

‡Notification of the recipient's and donor's physicians of abnormal screening and/or testing results is required. 21 CFR1271.65 (b)(1)(i).

§21 CFR 1271.65 (b)(1)(iii).

‖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)]. 21 CFR 1271.90(a)(b).

¶21 CFR 1271.90(a)(1)(2).

#21 CFR 1271.90(b)(1)(3).

CFR = Code of Federal Regulations; CLIA = Clinical Laboratory Improvement Ammendments of 1988; FDA = Food and Drug Administration.

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ucts 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 contain HPCs collected from the peripheral blood during 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) 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 modifications 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 DMSO after thawing.

HPC, Cord Blood

HPC, Cord Blood [HPC(CB)] preparations contain HPCs obtained from the umbilical cord by the delivery team during the third stage of labor or by cord blood bank staff after full 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. Less often, the blood is collected by aspiration into syringes. Before cryopreservation, cord blood collections are modified by red cell and plasma reduction, although simple plasma reduction is practiced in some programs. HPC(CB) products are typically stored with final 10% dimethyl sulfoxide (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.

TC, Apheresis

TC(A) preparations contain leukocytes collected from the peripheral blood by an apheresis procedure. Autologous TC(A) collections are generally used for further processing, which may include expansion of a specific cell type. Allogeneic TC(A) collections are most commonly used as donor lymphocyte infusions (DLIs). The dose for TC(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.

TC, Whole Blood

TC, Whole Blood [TC(WB)] preparations contain nucleated cells collected as peripheral whole blood intended for therapeutic use.

TC, Marrow

TC, Marrow [TC(M)] preparations contain nucleated cells collected from bone marrow intended for therapeutic use.

Cellular Therapy Products

Description

Cellular therapy products consist of somatic-cell-based products (eg, HPC, Apheresis; HPC, Marrow; HPC, Cord Blood; pancreatic islet cells; TC, Apheresis; TC, Whole Blood) that are collected or procured from the donor and are intended for administration to the patient for clinical use with or without manipulation.

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. Other uses for cell populations derived/obtained from HPCs, such as dendritic cells, mesenchymal stem cells, and other cell types, are currently under investigation. Procedures have been developed for reduction of plasma and either the selection or removal of various cell populations from these 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.

Allogeneic cellular therapy products may also be used to provide additional donor lymphocytes to enhance a graft-vs-leukemia effect. Autologous dendritic cells may be used as a source of antigen-presenting cells for preparation of tumor vaccine. 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 immunotherapy, 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 caused by the myelotoxic effects of the therapy.

Additional applications that may be used in clinical trials and research protocols include adoptive immunotherapy, collection of dendritic cells (ie, circulating antigen-presenting cells) to develop tumor vaccines, and for harvest of other potential progenitor cells capable of differentiation into other cell lines (eg, to differentiate into blood vessels, osteoblasts, etc).

HPC, (Plasma reduced)

[HPC, MARROW (PLASMA REDUCED); HPC, APHERESIS (PLASMA REDUCED); HPC, CORD BLOOD (PLASMA REDUCED)]

A plasma-reduced HPC product may be 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 before cryopreservation.

HPC, (RBC reduced)

[HPC, MARROW (RBC REDUCED); HPC, APHERESIS (RBC REDUCED); HPC, CORD BLOOD (RBC REDUCED)]

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.

HPC, (Buffy coat enriched)

[HPC, MARROW (BUFFY COAT ENRICHED); HPC, APHERESIS (BUFFY COAT ENRICHED); HPC, CORD BLOOD (BUFFY COAT ENRICHED)]

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.

HPC, (Mononuclear cell enriched)

[HPC, MARROW (MONONUCLEAR CELL ENRICHED); HPC, APHERESIS (MONONUCLEAR CELL ENRICHED); HPC, CORD BLOOD (MONONUCLEAR CELL ENRICHED)]

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.

Cryopreserved HPC

[CRYOPRESERVED HPC, MARROW; CRYOPRESERVED HPC, APHERESIS; CRYOPRESERVED HPC, CORD BLOOD]

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

HPC, (CD34 enriched)

[HPC, Marrow (CD34 enriched); HPC, Apheresis (CD34 enriched); HPC, Cord Blood (CD34 enriched)]

A CD34-enriched HPC product is indicated 1) when CD34-negative 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.

TC, Apheresis and TC, Whole Blood

Therapeutic cells are indicated for prevention or treatment of tumor relapse following allogeneic HPC transplantation. 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 post-transplant infectious complications, particularly those caused by cytomegalovirus (CMV) and Epstein-Barr virus.

Contraindications

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.

TC, Apheresis and TC, Whole Blood are generally contraindicated for patients experiencing severe graft-vs-host disease (GVHD).

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-positive cells, nucleated or mononuclear cells, and colony-forming units–granulocyte-macrophage (CFU-GM). The dose for TC, Apheresis or TC, 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). 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. The administration time will be determined by the total volume to be infused and 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).

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.[11-15]

  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.
- 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 for container integrity and unusual appearance immediately before administration. Any questions about 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) 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.

Cellular Therapy Product Descriptions

HPC, (Plasma reduced)

[HPC, Marrow (Plasma reduced); HPC, Apheresis (Plasma reduced); HPC, Cord Blood (Plasma reduced)]
These products contain the cellular elements of the HPCs that remain after the bulk of the plasma is removed by centrifugation.

HPC, (RBC reduced)

[HPC, Marrow (RBC reduced); HPC, Apheresis (RBC reduced); HPC, Cord Blood (RBC reduced)]
These are the HPCs remaining after the mature red cells have been depleted by sedimentation, centrifugation, or lysis.

HPC, (Buffy coat enriched)

[HPC, Marrow (Buffy coat enriched); HPC, Apheresis (Buffy coat enriched); HPC, Cord Blood (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 have been removed by sedimentation or centrifugation techniques.

HPC, (Mononuclear cell enriched)

[HPC, Marrow (Mononuclear cell enriched); HPC, Apheresis (Mononuclear cell enriched); HPC, Cord Blood (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.

Cryopreserved HPC

[Cryopreserved HPC, Marrow; Cryopreserved HPC, Apheresis; Cryopreserved HPC, Cord Blood]
These are HPCs that have been frozen using cryoprotectant solutions and containers.

HPC, (CD34 ENRICHED)

[HPC, MARROW (CD34 ENRICHED); HPC, APHERESIS (CD34 ENRICHED); HPC, CORD BLOOD (CD34 ENRICHED)]
These products contain the cellular elements of HPCs that have been enriched by CD34 selection.

Therapeutic Cells (TC)

[TC, APHERESIS; TC, WHOLE BLOOD; TC, MARROW]
These products are most frequently used for 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.

Storage

Cellular therapy products are stored using various methods and temperatures depending on the required duration of storage. Institutional policies and protocols dictate specific storage requirements for cellular therapy products. Products received for the treatment of a patient should be stored according to the instructions on the label until time for infusion.

If the cryopreserved product is to be thawed and administered at the bedside, the products are brought to the bedside frozen. An overwrap or equivalent method may be used to minimize contamination of the external surface of the bag(s) during thawing. The product should be infused immediately after thawing occurs.

If there is an unexpected delay in administration and the product must be held for later infusion, the distributing/issuing facility should be contacted for instructions on proper handling and storage of the product.

Any additional special instructions are listed at the end of this document.

Cellular Therapy Product Labeling and Supporting Documents

At the time of issue, cellular therapy products will be labeled with the following information:

- 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 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]
- 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
- 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 published by the International Cellular Therapy Coding and Labeling Advisory Group.[8,9]

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 facility distributing the product.

Pregnancy Category

The use of cellular therapy products in pregnant women has not been evaluated. Additional information regarding the use of this product in pregnant women may be addressed in the investigator's brochure, which may be included at the end of this document, if provided by the distributing facility.

Reporting of Adverse Reactions

Any adverse reaction defined as a suspected or proven unfavorable response to administration of cellular therapy products 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 the medical director of the facility that issued the product.

The reporting requirements vary based on the extent of the regulatory oversight required by the type of product and manufacturing process. The user must contact the manufacturing/issuing facility for specific requirements.

All entities involved in the manufacture of the product must be contacted in the investigation/reporting of an adverse reaction.

Side Effects and Hazards

Some of the side effects and complications may require reporting to a relevant authority. See Reporting of Adverse Reactions above.

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:
   - Chills, fever [temperature may be 40.5 C (105 F) or higher]
   - Headache
   - Burning sensation along the vein
   - Abnormal bleeding

- Low back pain
- Facial flushing
- Chest pain; rapid, labored respirations
- 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 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 IgG and/or 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 cardiorespiratory support.

   Signs and symptoms of anaphylactoid reactions include:
   - Bronchospasm and/or laryngospasm
   - Hypotension
   - Severe dyspnea
   - Pulmonary and/or laryngeal edema

- Other symptoms such as facial burning and flushing, abdominal pain, diaphoresis, diarrhea, and dizziness

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 preexisting lung injury, cardiac failure, or transfusion-associated circulatory overload (TACO)*, 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. Clinically significant antibodies to red cell antigens in previously alloimmunized patients are usually detected by preadministration testing. 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 that are incompatible with ABO or other red cell antigens on 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, 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

*TACO is hydrostatic pulmonary edema caused by circulatory overload. Both TRALI and TACO lead to pulmonary edema and lung injury through different mechanisms. Although the differential diagnosis between TRALI and TACO is difficult, distinction of the two is feasible. Knowledge of strengths and limitations of different diagnostic techniques is necessary.

- 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)

2. ***Alloimmunization to Antigens*** of 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. Alloimmunization to antigens of white cells, platelets, or plasma proteins can be detected only by specialized testing.
3. ***Graft-vs-Host Disease*** is an extremely serious condition that occurs frequently in recipients of allogeneic cellular therapy products.[16] 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 is 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 bacte-

rial 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 evaluation of blood cultures and aggressive therapy with broad-spectrum antimicrobials. The remaining product in the container should be evaluated promptly by Gram's staining 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. Disease may be caused by known agents, such as viruses, or unknown agents. Donor selection criteria are designed to screen out 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. 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 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) 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. ***Transfusion-Associated Circulatory Overload (TACO)*** 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. See also section on TRALI.
7. ***Hypothermia*** 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.
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.
9. ***Granulocyte-Related Complications****:* The increased total number of granulocytes in HPC, Apheresis before cryopreservation is associated with increased frequency and severity of adverse events during infusion of thawed products. Symptoms reported to be associated with increased granulocyte content are highly variable.

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