CIRCULAR OF INFORMATION

FOR THE USE OF CELLULAR THERAPY PRODUCTS

This *circular* was prepared jointly by the AABB, America's Blood Centers, the American Red Cross, the American Society for Apheresis, the American Society for Transplantation and Cellular Therapy, the College of American Pathologists, the Cord Blood Association, the Foundation for the Accreditation of Cellular Therapy, ICCBBA, the International Society for Cell & Gene Therapy, the Joint Accreditation Committee of ISCT and EBMT, the NMDP[SM], and the World Marrow Donor Association. Federal law prohibits dispensing the cellular therapy products described in this *circular* without a prescription.

Contact Information

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

AABB
www.aabb.org

American Red Cross (ARC)
www.redcross.org

American Society for Apheresis
www.apheresis.org

American Society for Transplantation and Cellular Therapy (ASTCT)
www.astct.org

America's Blood Centers (ABC)
www.americasblood.org

College of American Pathologists (CAP)
www.cap.org

Cord Blood Association (CBA)
www.cb-association.org

Foundation for the Accreditation of Cellular Therapy (FACT)
www.factglobal.org

ICCBBA
www.isbt128.org

International Society for Cell & Gene Therapy (ISCT)
www.isctglobal.org

JACIE Accreditation Office
www.jacie.org

NMDP
www.bethematch.org

World Marrow Donor Association (WMDA)
www.wmda.info

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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] When the product is licensed by a competent authority, the distributor's accompanying labeling information supersedes this *Circular*.

The focus of this *Circular* is restricted to cellular therapy products that are minimally manipulated and not subject to licensure or other approval mechanisms by competent authority. These products can include: hematopoietic progenitor cells (HPCs), leukocytes and other cells derived from bone marrow, umbilical cord blood, whole blood, or cellular products collected by apheresis.

Note that in the United States of America, this *Circular* does not solely apply to products that have received a license or approval for distribution as an investigational cellular therapy drug product.

When this *Circular* is used for investigational products or unlicensed products subject to licensure, it should complement, but not supersede, any written specific instructions from the investigator, sponsor, or other accompanying materials.

Per requirements of other competent authorities, cellular therapy products may be designated as licensed or approved biological products, medical devices, or advanced therapy medicinal products. Principles expressed here may also be applied to other cellular therapy products. Cellular therapy products are biological 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: Cellular therapy products derived from human blood or tissues 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 the risk.

Transmission of malignant disease has been reported. Also, serious life-threatening septic and toxic reactions can result from administration of products containing bacteria, fungi, or 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).[2-7] This *Circular* is not a comprehensive reference for applicable regulations.

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.[8-10] The nomenclature used throughout this *Circular* is consistent with ISBT 128 terminology and was current at the time of publication.[8-10] 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. 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* was prepared by the Circular of Information for Cellular Therapy Products Task Force, consisting of representatives from the AABB, the American Red Cross (ARC), the American Society for Apheresis (ASFA), the American Society for Transplantation and Cellular Therapy (ASTCT), America's Blood Centers (ABC), the College of American Pathologists (CAP), the Cord Blood Association (CBA), the Foundation for the Accreditation of Cellular Therapy (FACT), ICCBBA, the International Society for Cell & Gene Therapy (ISCT), NMDP, the Joint Accreditation Committee of

ISCT and EBMT (JACIE), and the World Marrow Donor Association (WMDA). 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 the 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 European Union, 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, and any expected toxicities. For corporate-sponsored or multicenter clinical trials, the indications and 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, other agents such as plerixafor, or a combination of agents. 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 HPCs from marrow [HPC, Marrow; or HPC(M)] and mononuclear cells from apheresis [MNC, Apheresis; or MNC(A)] are usually collected from donors who are not mobilized.

If required by local regulation(s), autologous blood donors must be tested for transmissible agents. Accrediting organizations (eg, AABB, FACT-JACIE, WMDA) and some countries, states, or regions may require additional testing of autologous donors. Abnormal results should be communicated to the appropriate entity as per local regulations. Allogeneic donors are screened through the use of questions designed to detect risk factors for infectious diseases transmissible by the cellular therapy product. Allogeneic donors are also 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 cellular therapy products and cord blood products (for cord blood products, although the neonate is the donor, the health history questionnaire is administered to the birth mother). The provision of truthful and accurate information by donors during health/risk assessment is essential for the exclusion of donors whose products may transmit diseases to recipients.

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*An example of such a questionnaire, called the uniform donor questionnaire, has been prepared and can be accessed on the AABB website (www.aabb.org) under "News & Resources" > "Resources" > "Donor History Questionnaires."

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) and NC(CB)	Donors of NC(WB), MNC(A), and NC(M)
Timing of specimen collection	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
Human immunodeficiency virus, types 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, types I and II (HTLV-I, HTLV-II)	X	X (MS)	X
Cytomegalovirus (CMV)[§] (if allogeneic)	X	X (MS)	X
Treponema pallidum (syphilis)	X	X (MS)	X
West Nile virus (WNV) (in living donors)	X	X (MS)	X

(Continued)

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

*Testing is performed according to manufacturers' instructions using donor screening tests that have been licensed, approved, or cleared by the US Food and Drug Administration (FDA) for transmissible agents as defined by the FDA. More than one test may need to be conducted to adequately and appropriately test for a single communicable disease agent or disease. Refer to the FDA Center for Biologics Evaluation and Research website for a list of guidance documents and approved tests.[11] Additional testing must be performed for relevant communicable diseases and emerging infections and may be implemented per facility-specific guidance prior to an FDA testing requirement (eg, *Trypanosoma cruzi*).

†US federal regulations do not require testing of autologous donors for transmissible agents. However, the voluntary accrediting organizations (eg, AABB, FACT-JACIE, WMDA) and some states or regions may require additional testing for allogeneic or 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 FDA-licensed screening tests for HIV-1 group O antibodies must evaluate donors for risk associated with HIV-1 group O infection.

§FDA Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (August 2007).

HPC(A) = HPCs from apheresis; HPC(CB) = HPCs from cord blood; HPC(M) = hematopoietic progenitor cells from marrow; MNC(A) = mononuclear cells from apheresis; MS = maternal sample; NC(CB) = NCs from cord blood; NC(M) = nucleated cells from marrow; NC(WB) = NCs from whole blood.

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

	Donors of HPC(M) and HPC(A)	Donors§ of HPC(CB), MNC(A), NC(M), and NC(CB)
Timing of specimen collection	Within 30 days before donation	Day of or up to 7 days after delivery
Human immunodeficiency virus, types 1 and 2 (HIV-1, HIV-2)	X	X
Hepatitis B virus (HBV)	X	X
Hepatitis C virus (HCV)	X	X
Treponema pallidum (syphilis)	X	X
Human T-cell lymphotropic virus, type I (HTLV-I)	X◊	X

*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, RhD, HLA, malaria, toxoplasma, cytomegalovirus, Epstein-Barr virus, *Trypanosoma cruzi*).

(Continued)

Table 1B. EU Minimal Requirements for Testing for Transmissible Agents in Cellular Therapy Products*[†‡] (Continued)

[†]Member countries of the European Union may amend and/or introduce additional requirements. 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. (In 2015, the European Commission published a report mapping more stringent testing requirements for donors of tissues and cells; see https://health.ec.europa.eu/index_en.)

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

[§]Refer to applicable local and national regulations to determine appropriate testing methods for the transmissible agents listed.

[◊]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.

HPC(A) = HPCs from apheresis; HPC(CB) = HPCs from cord blood; HPC(M) = hematopoietic progenitor cells from marrow; MNC(A) = mononuclear cells from apheresis; NC(CB) = NCs from cord blood; NC(M) = nucleated cells from marrow.

See references for a list of selected publications containing testing requirements and standards.

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 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 as per the local regulations 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 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, and 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.

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 Performed per FDA Criteria	**Abnormal Results of Donor Screening†**	**Abnormal Results of Donor Testing†**	**Urgent Medical Need‡**	**Biohazard Legend [21 CFR 1271.3(h)]**	**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	Yes	R	NA	R	R
A first-degree or second-degree blood relative	Yes	Yes	No	Yes	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[◊]								

(Continued)

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

*Application of biohazard and warning labels extends outside the HCT/Ps described in 21 CFR 1271 based on voluntary adherence to professional standards and applies to all products defined in this *Circular*, 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 May 25, 2005, and may or may not be implemented for units collected before this date per facility-specific policy.

†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 transplantation from a related or unrelated donor with an "incomplete" eligibility status, or when a donation is used for transplantation from an unrelated donor with an "ineligible" eligibility status.

When an HCT/P is made available for use before the donor eligibility determination is completed under the urgent medical need provision, the physician using the HCT/P must be notified that the testing and screening were not complete, and the notification must be documented [21 CFR 1271.60(d)(3)].

The release of products with incomplete requisite testing for the country in which the product is infused should be addressed by the releasing facility and acknowledged/authorized by the administering/ordering clinician. When not feasible to complete screening and/or testing per FDA criteria before issuing products, documentation should be on file to justify their use. The biohazard label may be applied per facility-specific guidance for "incomplete" eligibility status.

§Donor eligibility status of "incomplete" means donor eligibility determination was not completed 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 use. The biohazard label may be applied per facility-specific guidance for "incomplete" 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; HCT/Ps = human cells, tissues, and cellular and tissue-based products; HPC(M) = hematopoietic progenitor cells from marrow; NA = not applicable; NR = not required; R = required.

HPC, Apheresis

HPC, Apheresis [HPC(A)] preparations are collected as a source of HPCs obtained from the peripheral blood using an apheresis technology, 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.

Additional processing of allogeneic HPC(A) products includes reduction or removal of ABO-incompatible red cells, removal of ABO-incompatible plasma, selection of CD34+ progenitor cells, or removal of donor T lymphocytes. Common types of additional processing of autologous HPC(A) products are reduction of volume by removing plasma before cryopreservation and selection of CD34+ progenitor cells. Cryopreserved HPC(A) products may be washed to remove dimethyl sulfoxide (DMSO) after thawing prior to infusion.

HPC, Cord Blood

HPC, Cord Blood [HPC(CB)] preparations are collected as a source of HPCs. They are obtained from the placenta through the umbilical cord when the placenta is still in utero or ex utero. After thorough cleansing of the cord, the blood is collected by gravity drainage into standard collection bags containing 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. Cryopreserved 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. HPC(CB) products that are not red cell reduced should be washed or diluted to lessen the potential effects of hemolysate.

HPC(CB) products that are not red cell reduced and are ABO incompatible should be cautiously evaluated for further processing to reduce the amount of incompatible red cells in the final product before infusion.

Nucleated Cell Preparations

MNC, Apheresis

MNC, Apheresis [MNC(A)] preparations contain mononuclear cells collected from the peripheral blood by an apheresis procedure and are intended for clinical use other than as 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) is determined by institutional policies and is usually based on the number of T cells (eg, CD3+ cells) or mononuclear cells.

NC, Cord Blood

NC, Cord Blood [NC(CB)] preparations are collected as a source of nucleated cells. They are obtained from the placenta through the umbilical cord when the placenta is still in utero or ex utero 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 and are intended for clinical use other than as HPCs.

NC, Marrow

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

Cellular Therapy Product Descriptions

Cellular therapy products consist of somatic-cell-based products [eg, HPC(A), HPC(M), HPC(CB), MNC(A), NC(WB)] 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 prod-

ucts contain pluripotent and lineage-committed hematopoietic progenitors as well as lymphocytes.

MNC products contain mononuclear cells such as lymphocytes and monocytes that can be infused as a form of adoptive immune therapy after allogeneic hematopoietic stem cell transplantation or further processed into immune effector cell therapy.

NC products contain nucleated cells representative of the source and clinically may be used for indications other than for hematopoietic and immune reconstitution.

Actions

HPCs administered intravenously migrate to the marrow, where they divide and mature. The mature cells are released into the bloodstream, restoring hematopoiesis. 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.

Descriptions of novel or additional indications for cell therapies used in clinical trials and research can be found in their respective protocols.

Contraindications

MNC(A) and NC(WB) 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 pluripotent progenitor cells, and committed progenitor cells. They may be collected from bone marrow [HPC(M)], peripheral blood with or without prior mobilization using apheresis [HPC(A)], whole blood with or without mobilization (HPC, Whole Blood), or placental/umbilical cord blood [HPC(CB)]. They may then be subjected to volume reduction or further manipulations. (See below.)

HPC (PLASMA REDUCED) PRODUCTS

HPC, APHERESIS
Plasma Reduced

HPC, CORD BLOOD
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, CORD BLOOD
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, CORD BLOOD
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, CORD BLOOD
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 from any source (eg, marrow, peripheral blood using apheresis, whole blood, or umbilical cord/placental blood) and intended for clinical use other than as HPCs. They may be further categorized according to the specific subpopulations.

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

These products are most frequently used for DLIs or further processed into immune effector cell therapies. They are usually collected from the HPC donor and contain a mixture of mature nucleated cells (eg, T and B lymphocytes, granulocytes, and others), 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 regulations required by local and national authorities as well as relevant standard-setting and/or accreditation organizations (eg, AABB, FACT-JACIE, NMDP, or WMDA[12-16]).

  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.

- Before 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, per the facility standard operating procedure. 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 and aggregates.
- 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(A) or NC(WB) 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 clots 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 rapidly 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 stored in a fresh or cryopreserved state. It is the responsibility of the facility providing storage to institute measures to maintain conditions that will prevent errors, mix-

ups, contamination, loss of potency, and cross-contamination of cellular therapy products, supplies, and reagents (CFR 1271.260). Institutional policies and protocols dictate specific storage requirements, which include storage duration and temperature. This information may be included in the product labeling, which should also indicate the cell dose and expiration date (if defined).

If a product is transported from another facility, it is to 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, 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 before administration.

Cryopreserved Cellular Therapy Products

Cryopreserved products may be received and stored long term according to the manufacturer's directions 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 before 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 in both human-readable and machine-readable formats.
- Approximate volume.
- Name and volume of anticoagulant or other additives.

- Date and end 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.
- 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.
- For ineligible donors, a statement noting the reasons for ineligibility [21 CFR 1271.55(b)(4)].
- For products that are made available before the donor eligibility has been completed:
  - The results of any donor screening and testing that has been completed [21 CFR 1271.60(d)(2)(i) and (ii)].
  - A list of any screening and testing that has not yet been completed [21 CFR 1271.60(d)(2)(iii)].

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.[8-10]

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 May 25, 2005. 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

Infusion of cellular therapy products can result in mild, moderate, or serious infusion reactions. The following side effects and hazards pertain to administration of cellular therapy products.

Immunologic Complications, Immediate

1. ***Acute Hemolytic Reactions*** can be a complication of cellular therapy product administration and can be caused by donor-recipient major, minor, or bidirectional incompatibility or incompatibility due to other blood groups. Acute hemolytic reactions may be immediate or occur up to 24 hours following infusion.

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

- Abdominal, chest, flank, and/or back pain; headache.
- Burning sensation along the vein of infusion.
- Disseminated intravascular coagulation (DIC), abnormal bleeding.
- Facial flushing.
- Fever, chills.

- Hypotensive shock.
- Rapid, labored respiration.
- Tachycardia.
- Development of a positive direct antiglobulin test (DAT).
- Elevation of lactate dehydrogenase (LDH) or bilirubin; decreased haptoglobin, decreased hemoglobin/hematocrit, hemoglobinuria.
- Other symptoms may be present.

Treatment:
- Measures to maintain or correct arterial pressure, maintain urine output, and maintain venous access.
- Respiratory support, if needed.
- Correct coagulopathy as needed.

Prevention:
- Red cell reduction.
- Plasma reduction.
- Washing product prior to administration.

2. ***Febrile Nonhemolytic Reactions*** may reflect the action of cytokines, either present in the product or generated by recipient antibodies against infused white cells. These reactions occur more frequently in patients previously alloimmunized by transfusion or pregnancy.

Signs and symptoms of febrile nonhemolytic reactions include:
- Chills/rigors.
- Headache.
- Nausea/vomiting.
- Temperature elevation of 1 C (2 F) or more (shortly after or up to 4 hours following product administration and in the absence of another pyretic stimulus).

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 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:

- Bronchospasm and/or laryngospasm with wheezing/stridor.
- Dyspnea.
- Facial, glottal, and/or laryngeal edema.
- Hypotension.
- Pruritus (itching).
- Tachycardia.
- Urticaria (hives).
- 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.
- Respiratory support.

Prevention:

- Premedication with antihistamines is sometimes used to mitigate mild reactions.
- Washing of cryopreserved products after thawing.
- 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 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 (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 may include:

- Acute respiratory distress within 6 hours of administration.
- Bilateral pulmonary infiltrates (noncardiogenic pulmonary edema) on frontal chest x-ray.
- Fever.
- Hypotension mostly, but hypertension can occur.
- Hypoxemia.
- No evidence of circulatory overload.
- Tachycardia.

Treatment:

- Avoid diuretics.
- 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 antibody to human neutrophil antigen (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 after infusion of cellular products. Primary immunization does not become apparent until days or weeks after the immunizing event and does not usually cause symptoms or physiologic changes. However, in patients who have developed alloantibodies, 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.

Treatment:
- Selective use of blood components for transfusion support that are negative for the antigen recognized by the alloantibody.

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 pretransfusion testing. Occasionally, however, levels may diminish to below the limits of detection. In these cases, antigens on transfused red cells can stimulate anamnestic production of antibody. The antibody levels may reach a significant circulating level while the transfused red cells are still present in the circulation, leading to hemolysis. The usual time frame for reappearance of antibody is 2 to 14 days after product administration. Delayed hemolysis may also occur in recipients who receive plasma-incompatible transplants, whether in regard to ABO antigens or to other red cell antigens. In this setting, the infused donor's B lymphocytes may produce antibodies to red cell antigens, 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:
- Development of a positive DAT.
- Elevation of LDH or bilirubin; decreased haptoglobin.
- Hemoglobinemia and hemoglobinuria (rare).
- Mild jaundice.
- Symptoms of acute intravascular hemolysis (rare).
- Unexplained decrease in hemoglobin/hematocrit.
- Unexplained fever.

Treatment:
- More severe cases may require treatment similar to an acute hemolytic reaction and more rapid antigen-negative red cell replacement.
- Use of antigen-negative red cells if transfusion is needed.

Prevention:
- Providing red cells after transplantation that are ABO compatible with the donor and recipient.
- Avoiding antigens to which the donors or patients may have been previously alloimmunized.

3. *Graft-vs-Host Disease (GVHD)* can be acute or chronic and occurs frequently in recipients of allogeneic cellular therapy products.[17] GVHD occurs when viable T lymphocytes in the infused product engraft and react against tissue antigens in the recipient.

Signs and symptoms:
- Wide variety of immune-mediated tissue and organ damage.

Treatment:
- Posttransplant immunosuppression, according to institutional guidelines and policies.

Prevention:
- Incorporation of immune suppression into the transplant regimen.
- Use of optimally matched HLA-compatible donor grafts.

Nonimmunologic Complications

1. *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:
- Burning sensation, flushing, and/or rash.
- Cardiovascular instability and/or chest tightness.
- Dyspnea, wheezing, and/or coughing.
- Headache, seizure activity.
- Nausea, vomiting, and/or halitosis.

Treatment:
- Medicating with antihistamines and steroids.

- Slowing the rate of infusion.
- Supportive care.

Prevention:
- Decreased rate of administration.
- Prophylactic antihistamine therapy.
- Providing hard candy to prevent nausea caused by the odor and/or taste.
- Removing DMSO from the product by washing the cells before administration to recipients with significant renal and cardiac disease may reduce the risk of symptoms. It is not generally required to wash every thawed cellular product because doing so may result in unintended cell loss. Cord blood units that were not red cell depleted prior to cryopreservation should be washed before administration to the recipient.

2. ***Septic Infusion Reactions*** may result from bacterial contamination of cellular therapy products, but they rarely cause acute, severe, or life-threatening effects. Prompt recognition of a possible septic reaction is essential. The onset of fever (>1 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:
- Acute renal failure.
- DIC.
- Fever and/or chills, rigors.
- Hypotension.
- Pain in abdomen, back, and extremities.
- Respiratory distress with hypoxemia.
- Tachycardia.
- Other symptoms: nausea, vomiting, diarrhea, dry and/or flushed skin.

Treatment:
- Correct coagulopathy, as needed.
- Measures to maintain or correct arterial pressure and venous access.

- 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.
- Appropriate antibiotic prophylaxis should be considered when using nonconforming products with positive culture results according to institutional protocol and relevant national competent authorities.

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

Signs and symptoms:
- Confusion, irritability, restlessness (mental status change).
- Dyspnea and coughing.
- Hypoxia.
- Petechiae.
- Tachycardia.
- Tightness of the chest.

Treatment:
- Corticosteroids, including methylprednisolone, which have reduced posttraumatic hypoxemia believed to be due to fat emboli syndrome.
- Respiratory support.

Prevention:
- Routine filtering of bone marrow products with 170- to 260-micron filters before 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 proce-

dures 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 "Donors" section.) 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:
- Infusion rates may be adjusted depending on the clinical conditions; products may be washed when cell loss is not a concern.
- Product/anticoagulant specific.

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.

Signs and symptoms:
- Dyspnea.
- Peripheral edema.
- Rapid increase of blood pressure.

Treatment:
- Diuresis.

Prevention:
- Minimize the volume of colloidal preparations and, if appropriate, split or volume-reduce the product for infusion.
- Reduce the rate of administration.

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. A blood warming device should not be used unless approved by the manufacturer of the cellular therapy product.

Signs and symptoms:
- Cardiac arrhythmia or arrest.
- Chills.

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, co-administration

with incompatible fluids, or 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 does 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.
- Prevention relates 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. There are centralized databases where adverse reactions are collected (eg, CIBMTR, WMDA).

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

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

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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 IND application or an IDE in the United States. Products manufactured and administered outside the United States must comply with local regulations.

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