



Circular of Information for the Use of Cellular Therapy Products (Circular) Resource Overview of Changes from October 2018 Circular to June 2021 Circular

NOTE: This update includes additional edits, not mentioned below, such as grammatical, organizational updates, and other edits to content.

Not all edits are listed below, the *Circular* should be reviewed in its entirety.

- In the “Note to All Users” section, page 4, paragraph 1, the sentence, “**When the product is licensed by a Competent Authority the distributing accompanying labeling information supersedes this Circular.**” has been added.
The addition was made to ensure that it is understood that national, federal or local regulations can supersede the requirements in the Circular and should be followed.
- In the “Donors” section, page 6, the sentence, “A donor questionnaire and accompanying donor screening materials* have been developed for cellular therapy ~~donors~~ **products** and cord blood **products** ~~donors~~ **(for cord blood products, although the neonate is the donor, the health history questionnaire is administered to the birth mother).**” has been edited.
The clarification was made to clarify that the questionnaire while administered to an individual, the information gathered is related to the product to be procured.
- In the “Cellular Therapy Product Sources” section, page 7, paragraph 1, the sentence, “Some of these cells are capable of reconstituting the hematologic ~~and lymphoid~~ systems of an autologous or allogeneic recipient.” has been edited.
The removal of the clause “and lymphoid” was done recognizing that this level of specificity is not necessary.
- In the “Cellular Therapy Product Sources” section, page 7, under the “Nucleated Cell Preparations” paragraph 1, the sentence, “MNC, Apheresis [MNC(A)] preparations contain ~~nucleated~~ **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.” has been edited.
The term “nucleated” was replaced with “mononuclear” to be consistent with ISBT 128 nomenclature and AABB and FACT definitions.
- In the “Cellular Therapy Product Descriptions” section, page 8, a new paragraph has been added that reads: “**MNC products contain mononuclear cells such as lymphocytes and monocytes that can be infused as a form of adaptive immune therapy post allogeneic hematopoietic stem cell transplant 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.**”
The paragraph was added to create parallel construction with HPC products listed in the paragraph above. An explanation was needed for MNC and NC products for completeness.
- In the “Cellular Therapy Product Descriptions” section, page 8, under the “Indications” paragraph, the sentence “Additional applications may be used as indicated in clinical trials and research protocols.” has been deleted “~~Additional applications may be used as indicated in clinical trials and research.~~” and replaced with “**Description of novel or additional indications for cellular therapies used in clinical trials and research can be found in their respective protocols.**”

The sentence was edited for clarity and made to focus on the use of novel or additional indications for cellular therapies. The previous sentence was viewed as commonly understood while requirements for novel clinical therapies would require an explanation.

- In the “Cellular Therapy Product Descriptions” section, page 9, paragraph 1, the sentence, “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.)” has been edited.

The clause “using apheresis” was included for completeness as it related to HPC(A) products. The clause “or without” was included for accuracy.

- On page 10 under “Other Cellular Products”, the first sentence, “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.” has been edited.

The clause “using apheresis” was added to ensure that there was clarity that peripheral blood in this instance was not meant to be interpreted as from whole blood.

- On page 10, the title “MNC, APHERESIS; **MNC**, WHOLE BLOOD; **MNC CORD BLOOD**; NC, MARROW” has been expanded.

The addition of new terminology in the title was done to match the new terms implemented by ICCBBA for ISBT 128 labeling. This addition was made for completeness.

- On page 10, under the title MNC, APHERESIS; MNC, WHOLE BLOOD; MNC CORD BLOOD; NC, MARROW, the first sentence, “These products are most frequently used for DLIs **or further processed into immune effector cell therapies.**” has been expanded.

The phrase in bold was included to ensure that the Circular matches current requirements in the AABB CT Standards and FACT standards that now include these requirements.

- On page 10, under the “Instructions for Storage and Administration of Cellular Therapy Products”, in bullet point 7, “Products may be filtered through a 170- to 260-micron filter designed to remove clots **and aggregates.**” has been edited.

The clause “and aggregates” was added to the bullet point for completeness. Clots as a stand alone is not representative of any matter that can be removed through the use of a 170- to 260-micron filter.

- On page 11, under “Dosage and Administration”, in sentence number 7, “Manufacturers may recommend that products be filtered using a 170- to 260-micron filter to remove **clots clumps** or aggregates.” has been edited.

To maintain parallel terminology, the term “clumps” has been replaced with “clots” for consistency.

- On page 11, under “Storage”, in sentence two, “It is the responsibility of the facility providing storage to institute measures to maintain conditions that will prevent **errors**, mix-ups, contamination, and cross-contamination of cellular therapy products, supplies, and reagents (CFR 1271.260).” has been edited.

The term “errors” has been included for consistency in language.

- On page 12, under “Cellular Therapy Product Labeling and Supporting Documents” in bullet point 2, “Unique identifier **in both human readable and machine readable formats.**” has been edited.

The addition in bold ensures that the requirement matches the AABB CT Standards and provides clarity.

- On page 13, under “Side Effects and Hazards” and “Immunologic Complications, Immediate” the first sentence in the first bullet, “**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 ABO or other blood groups** incompatibility.” has been edited.

The entry has been edited for clarity. The inclusion of “bidirectional incompatibility” in place of “incompatibility” as it better reflects what patients can experience in terms of ABO incompatibility.

- On page 13, under “Side Effects and Hazards” and under “Immunologic Complications, Immediate”, under “Signs and symptoms of acute hemolytic reactions may include one or more of the following:” has been edited.

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.**
- **Disseminate Intravascular Coagulation (DIC),** abnormal bleeding.
- Facial flushing.
- **Fever, chills.**
- **Hypotensive** shock, tachycardia.
- Rapid, labored respiration.
- ~~Hemoglobinuria~~ Development of a positive direct antiglobulin test (DAT).
- Elevation of lactate dehydrogenase (LDH) or bilirubin; **decreased haptoglobin, decrease hematocrit, hemoglobinuria.**

The list has been put into alphabetical order. Bullet point 1 now contains elements that existed in bullet points 5, 6, and 8 to put all of the elements related to “pain” in one list.

The clause “of infusion” was included in bullet point 2 for completeness.

Bullet point 3 now includes “Disseminate Intravascular Coagulation” for completeness and clarity.

Bullet point 5 has combined former bullet points 1 and 2.

Bullet point 6 has combined former bullet points 9 and 10 while adding the term “Hypotensive” for completeness.

Previously, former bullet point 11 stood as a stand alone entry with current bullet points 8 and 9 falling underneath.

Bullet point 9 has added the requirements that “decreased haptoglobin” and “decrease hematocrit, hemoglobinuria” for completeness.

- On page 13, under “Side Effects and Hazards” and under “Immunologic Complications, Immediate”, under “Treatment.”

Treatment:

- Measures to maintain or correct arterial blood pressure, ~~correct coagulopathy~~ **promote and maintain urine output flow and venous access.**
- **Respiratory support, if needed.**
- **Correct coagulopathy as needed.**

Bullet point 1 has been edited to remove the term “blood” as it relates to arterial pressure, the term was deemed unnecessary.

The clause “promote and” was removed from bullet point 1, as it was deemed unnecessary.

“Correct coagulopathy” has been removed from bullet point 1 and has been made to become new bullet point 3.

Bullet point 2, “Respiratory support, if needed” is new and was added for clarity and completeness.

- On page 13, under “Side Effects and Hazards” and under “Immunologic Complications, Immediate”, under “Prevention.”

Prevention:

- Red cell reduction.
- Plasma reduction.
- **Washing product prior to administration.**

Bullet point 3 was added for completeness.

- On page 13, under “Febrile Nonhemolytic Reactions”, and “Signs and symptoms of febrile nonhemolytic reactions include:”, the bulleted list was put in alphabetical order, and
 - 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).

Bullet points 2 and 3 were added for completeness.

- On page 14, under “Allergic/Anaphylactoid/Anaphylactic Reactions” and “Signs and symptoms of allergic reactions include.”, the bulleted list was put in alphabetical order and
 - Bronchospasm and/or laryngospasm **with wheezing/stridor.**
 - Dyspnea.
 - Facial, glottal, and/or laryngeal edema.
 - Hypotension.
 - Pruritus (itching).
 - Urticaria (hives).
 - Other symptoms such as facial burning and flushing, abdominal pain, nausea, vomiting, diaphoresis, diarrhea, and dizziness.

Bullet point 1 added the clause “with wheezing/stridor” for completeness.

- On page 14, under “Allergic/Anaphylactoid/Anaphylactic Reactions” and “Treatment.”
 - Antihistamines.
 - In severe cases, fluids, epinephrine, and/or steroids.
 - **Respiratory support.**

Bullet point 3 was added for completeness.

- On page 14, under “Allergic/Anaphylactoid/Anaphylactic Reactions” and “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.

Bullet point 2 was added for completeness.

- On page 14, under “Transfusion Related Acute Lung Injury (TRALI)”, under “In the absence of evidence for another cause of pulmonary compromise, signs and symptoms of TRALI” include:
 - Acute respiratory distress within 6 hours of administration.
 - Bilateral pulmonary infiltrates (**non-cardiogenic pulmonary edema**) on frontal chest x-ray.
 - **Fever.**
 - **Hypotension mostly, but hypertension can occur.**
 - **Hypoxemia.**
 - **No evidence of circulatory overload.**

Bullet points 3, 4, 5, 6 and 7 have been added for completeness. Bullet point 2 added the clause “non-cardiogenic pulmonary edema” to clarify what is intended by “bilateral pulmonary infiltrates.”

- On page 14, under “Transfusion Related Acute Lung Injury (TRALI)”, under “In the absence of evidence for another cause of pulmonary compromise, signs and symptoms of TRALI” include under “Treatment”
 - **Avoid diuretics.**
 - Respiratory support.
Bullet point 1 was added for completeness.
- On page 15 under “Delayed Hemolytic Reactions”, under “Signs and symptoms of delayed hemolytic reactions may include” the bulleted list was put in alphabetical order and
 - Development of a positive DAT.
 - Elevation of lactate dehydrogenase (LDH) or bilirubin; **decreased haptoglobin.**
 - Hemoglobinemia and hemoglobinuria (rare).
 - Mild jaundice.
 - Symptoms of acute intravascular hemolysis (rare).
 - Unexplained decrease in hemoglobin/hematocrit.
 - Unexplained fever.
Bullet point 2 has added the clause “decreased haptoglobin” as a useful laboratory measurement indicating hemolysis, for completeness.
- On page 15 under “Delayed Hemolytic Reactions”, under “Treatment:”, the bulleted list was put in alphabetical order but no changes made.
- On page 15 under “Graft vs Host Disease”, under “Prevention:”, the bulleted list was put in alphabetical order but no changes made.
- On page 15 under “Nonimmunologic Complications”, under “DMSO Toxicity” and under “Signs and symptoms” the bulleted list has been alphabetized and
 - **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.**
Bullet point 1 has added “burning sensation” and moved “flushing” and “and/or rash” so all appear in one spot for accuracy.
Bullet point 3 has added “Dyspnea” and “wheezing” to “coughing” for completeness.
Bullet point 4 is new and was added for completeness.
Bullet point 5 has added the clause “and/or halitosis” in conjunction with nausea and vomiting for accuracy.
- On page 15 under “Nonimmunologic Complications”, under “DMSO Toxicity” and under “Treatment” the bulleted list has been alphabetized and
 - Medicating with antihistamines and steroids.
 - Slowing the rate of infusion.
 - **Supportive care** ~~Treatment of symptoms.~~
Bullet point 3 has replaced “treatment of symptoms” with “supportive care” as the term “treatment” was deemed redundant to the title of the section.
- On page 16 under “Nonimmunologic Complications”, under “DMSO Toxicity” and under “Prevention” the bulleted list has been alphabetized but not changed.
- On page 16 under “Septic Infusion Reactions”, under “Signs and symptoms” the list has been alphabetized and
 - **Acute renal failure.**

- **Disseminated intravascular coagulation.**
- Fever and/or chills, **rigors.**
- Hypotension.
- Pain in abdomen, back, and extremities.
- Respiratory distress with hypoxemia.
- Other symptoms: **nausea,** vomiting, diarrhea, dry and/or flushed skin.

Bullet point 1, 2 and 6 have been added for completeness.

Bullet point 3 has been edited to include “rigors” to accompany fever and chills.

Previously, the elements in “other symptoms” appeared as separate bullet points, but were consolidated into one category.

- On page 16 under “Septic Infusion Reactions”, under “Treatment”
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.
Bullet points 1 and 2 are new to this edition and were added for completeness.
- On page 16 under “Fat Emboli”, under “Signs and symptoms” the bulleted list was alphabetized and
 - Confusion, **irritability, restlessness** (mental status change).
 - Dyspnea and coughing.
 - Hypoxia.
 - Petechiae.
 - Tightness of the chest.
Bullet point 1 added “irritability” and “restlessness” for completeness to supplement “confusion.”
- On page 16 under “Fat Emboli”, under “Treatment” the bulleted list was alphabetized and
 - Corticosteroids, including methylprednisolone, which have reduced posttraumatic hypoxemia believed to be due to FES.
 - **Respiratory support.**
 - ~~Supplemental oxygen therapy.~~
 - ~~Ventilation as needed.~~
Bullet point 2 was added to replace former bullet points 3 and 4 to provide a broader term that encompassed the previous terms.

- On page 17 under “Bleeding Due to Excessive Anticoagulation”, under “Prevention” the bulleted list has been alphabetized but not changed.
- On page 17 under “Hypothermia” a category of “Signs and symptoms” was created and removed from the descriptor paragraph.

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

Signs and symptoms

- **Cardiac arrhythmia or arrest.**
- **Chills.**

The change was made to remain consistent and maintain parallel construction with the rest of the document.