



Circular of Information for the Use of Cellular Therapy Products (*Circular*) Resource Overview of Changes from June 2021 *Circular* to June 2024 *Circular*

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

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

- In the “Notice to All Users” on page 1, the first sentence in paragraph 2 has been updated to read, “The focus of this *Circular* is restricted to ~~unlicensed~~ cellular therapy products that are minimally manipulated **and not subject to licensure or other approval mechanisms by competent authority.**”
This addition of the elements in bold and underline was made for clarity and specificity. The term “unlicensed” may not be applicable to facilities outside of the United States. This change ensures that the Circular remains relevant to all users.
- In the “Notice to All Users”, on page 1, the next sentence in paragraph 2 has been updated to read, “These ~~unlicensed~~ 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.”
The removal of the term “unlicensed” was done in concert with the change cited in the bullet above. The term “whole blood” was added to the sentence, reflecting that whole blood is included throughout the Circular.
- In the “Notice to All Users” on page 1, paragraph 3 has been updated to read, “**Note that in the United States of America,** this *Circular* does not **solely** apply to products that have ~~already received a license~~ **or approval for distribution** as an **investigational** cellular therapy **drug** product ~~in the United States~~.
The sentence was reordered for readability by moving the final phrase of the sentence to the beginning of the sentence. Also included were the elements of “approval for distribution” and “investigational,” which allow the Circular to reflect the parameters of products under investigational new drug (IND) application.
- In the “Notice to All Users” on page 1, new paragraph 4 has been added to read, “**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.**”
This addition was included to ensure that when individuals are using the Circular in conjunction with products under IND, they do not feel that the content would supersede any written instructions provided along with the products under IND.
- In the “Notice to All Users” on page 1, sentence 1 in paragraph 5 has been edited to read, “Per requirements of other ~~national~~ competent authorities, cellular therapy products may be designated as licensed **or approved** biological products, medical devices, or advanced therapy medicinal products.”
The addition in bold and underline was made for clarity and consistency of language.



- In the “Notice to All Users” on page 1, sentence 2 in the second “Warning” paragraph has been edited to read, “Also, serious life-threatening septic and toxic reactions can result from administration of products containing bacteria, **fungi**, or toxins.”
The addition of “fungi” was included for completeness.
- In the “Donors” section on page 4, in paragraph 1, sentence 2 has been edited to read, “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** both.”
The bold and underlined information has been included for clarity and to provide examples for users.
- In the “Donors” section on page 4, in paragraph 2, sentence 1 has been edited to read, “**If required by local regulation(s), autologous blood donors must be tested for transmissible agents.** ~~US federal regulations do not require testing of autologous donors for transmissible agents.~~”
The change has been made to reflect the expanding nature of the Circular to focus on countries outside the United States and regulations that are applicable to the country in which the user is located.
- In the “Donors” section on page 4, in paragraph 2, sentence 2 has been edited to read, “~~However, the voluntary~~ Accrediting organizations (eg, AABB, FACT-JACIE, **WMDA**) and some **countries**, states, or regions may require additional testing ~~and/or testing~~ of autologous donors.
The sentence was edited to include “WMDA” as an example of accrediting organizations for completeness. The term “countries” was added to the sentence to reflect other changes made to the Circular to recognize the global nature of this version.
- In the “Donors” section on page 4, in paragraph 2, a new sentence has been added to read, “**Abnormal results should be communicated to the appropriate entity as per local regulations.**”
The sentence was added to the Circular for completeness, recognizing that there are similar requirements for results related to allogeneic products and donors.
- On page 6 in Table 1A, “US Minimal Requirements for Testing for Transmissible Agents in Cellular Therapy Products,” in footnote “*”, sentence 4 has been edited to read, “**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 ~~Additional tests for infectious transmissible agents (eg, Trypanosoma cruzi) may be required or performed.~~”
The change to the entry was crafted recognizing that with diseases that are emerging, it is important to ensure that users are prepared to evaluate them and to test as needed.
- On page 6 in Table 1A, “US Minimal Requirements for Testing for Transmissible Agents in Cellular Therapy Products,” a new footnote (§) has been included to cite: **FDA Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (August 2007).**
The footnote has been applied to the entry for “Cytomegalovirus (CMV) (if allogeneic),” recognizing that that the FDA Guidance specifically discusses CMV.



- On page 8, in Table 1B, “EU Minimal Requirements for Testing for Transmissible Agents in Cellular Therapy Products,” the footnote symbol that previously was on “HPC(CB)” in the right column has been moved to appear with “Donors” in the same heading. The column title appears as follows: “Donors[§] of HPC(CB)-[§], MNC(A), NC(M), and NC(CB)”
The superscript applies to all donors, not just donors of cord blood products.
- On page 8, at Table 1B, “EU Minimal Requirements for Testing for Transmissible Agents in Cellular Therapy Products,” footnote “[§]” has been edited to read, “**Refer to applicable local, and national regulations to determine appropriate testing methods for the transmissible agents listed.** The testing is repeated on the CBU if the CBU is stored for a long period of time; alternatively, nucleic acid testing (NAT) technology is used. (“Where tissues and cells of allogeneic living donors can be stored for long periods, repeat sampling and testing is required after an interval of 180 days. In these circumstances of repeat testing, the donation sample can be taken up to 30 days prior to and 7 days post donation.”)
This change was made to allow users to determine the regulations that relate to donors following the requirements of their local competent authority, instead of using a one-size-fits-all approach that may not be relevant/appropriate in some circumstances.
- In the “Donors” section on page 9, in the first paragraph, last sentence, an addition was provided to read, “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.”
In line with other changes to the Circular to expand the reach beyond the United States, the phrase “as per local regulations” was added to ensure that users follow the requirements set forth by their competent authority.
- On page 12, in Table 2, “Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States,” two additional sentences have been added to footnote “[‡]”; they read as follows: “**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, documentation should be on file to justify their use. The biohazard label may be applied per facility-specific guidance for “incomplete” eligibility status.**”
The addition of the two sentences to supplement the information concerning the need for urgent medical need strengthens the footnote focused on the column for “Urgent Medical Need.”
- On page 13, in the “Cellular Therapy Product Sources” section, subsection “HPC, Apheresis,” the final sentence has been edited to read, “**Cryopreserved** HPC(A) products may be ~~thawed and~~ washed to remove dimethyl sulfoxide (DMSO) **after thawing prior to infusion.**”
The edit has been made for clarity. The addition of “cryopreserved” reflects that the sentence is focused on frozen products. The middle of the sentence was edited to remove



“...thawed and...” and “...after thawing prior to infusion” was placed at the end of the sentence. The intent of this change has not changed the meaning of the entry.

- On page 13, in the “Cellular Therapy Product Sources” section, subsection “HPC, Cord Blood,” the first sentence has been split into two separate sentences. The edited sentences appear as follows: “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** ~~during the third stage of labor or after delivery of the placenta.~~”
The sentence was split for legibility. The wording in the new second sentence was edited for clarity.
- On page 13, in the “Cellular Therapy Product Sources” section, subsection “HPC, Cord Blood,” paragraph 1, sentence 6 has been edited to read, “~~Frozen~~ **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.”
The replacement of “Frozen” with “Cryopreserved” was for clarity and appropriate use of terminology.
- On page 14, in the “Cellular Therapy Product Sources” section, subsection “MNC, Apheresis,” paragraph 2, sentence 3 has been edited as follows, “The dose for MNC(A) is determined by institutional policies and is usually based on the number of T cells (eg, CD3+ cells), ~~nucleated cells,~~ or mononuclear cells.”
The removal of the term “nucleated cells” was for clarity.
- On page 14, in the “Cellular Therapy Product Sources” section, subsection “NC, Cord Blood,” the first sentence has been split into two separate sentences: “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** ~~during the third stage of labor or after delivery of the placenta~~ and are intended for clinical use other than as HPCs.”
The edit of the sentence was made for parallel construction with changes cited above, and for accuracy.
- On page 18, in the “Instructions for Storage and Administration of Cellular Therapy Products,” in the first bullet, the list of accreditation organizations was edited to read, “...(eg, AABB, FACT-JACIE, ~~NetCord FACT,~~ NMDP standards, or WMDA¹²⁻¹⁶).”
The removal of “NetCord FACT” was done as it was deemed redundant to “FACT-JACIE.”
- On page 20, in the “Storage” section, in paragraph 1, sentence 2, a phrase was added to read, “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).”
The addition to the sentence was made for completeness and clarity.
- On page 23 and 24, in the “Side Effects and Hazards” section, subsection “Immunologic Complications, Immediate,” subitem 1, “Acute Hemolytic Reactions,” under “Signs and symptoms of acute hemolytic reactions may include one or more of the following,” the following edits have been made:



- 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, ~~tachycardia~~.
- 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.

The decision was made to remove “tachycardia” from inclusion with “Hypotensive shock,” understanding that these two reactions are different enough to merit appearing as two separate bullet points.

“Hemoglobin” was added to the last bullet for completeness.

- On page 25, in the “Side Effects and Hazards” section, subsection “Immunologic Complications, Immediate,” subitem 3, “Allergic/Anaphylactoid/Anaphylactic Reactions,” under “Signs and symptoms of allergic reactions include,” the following edits have been made:
 - 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.

The inclusion of tachycardia was to remain consistent with the change noted above. This ensures parallel construction for the Circular.

- On page 25 and 26, in the “Side Effects and Hazards” section, subsection “Immunologic Complications, Immediate,” subitem 4, “Transfusion-Related Acute Lung Injury,” paragraph 2, the following edits have been made:

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.**

The term “may” was added to the introductory sentence, recognizing that the symptoms listed are not always a sign of TRALI.

Tachycardia has also been added to the list of potential symptoms to remain consistent with other changes throughout the Circular.

- On page 27 and 28, in the “Side Effects and Hazards” section, subsection “Immunologic Complications, Delayed,” subitem 2, “Delayed Hemolytic Reactions,” under the “Prevention” list, the following has been added:

Prevention:

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

The addition was included for completeness, recognizing that providing blood with these antigens to individuals could cause complications.

- On page 29, in the “Side Effects and Hazards” section, subsection “Nonimmunologic Complications,” subitem 2, “Septic Infusion Reactions,” in the signs and symptoms list, the following has been added:

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.

The addition of tachycardia was made to remain consistent with other additions of the same sign or symptom to other sections in the Circular.

- On page 30, in the “Side Effects and Hazards” section, subsection “Nonimmunologic Complications,” subitem 3, “Fat Emboli,” in the signs and symptoms list, the following has been added:

Signs and symptoms:

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

The addition of tachycardia was made to remain consistent with other additions of the same sign or symptom to other sections in the Circular.



- On page 34 in the References section, the following updates and edits have been made:
 2. **Food and Drug Administration. Current good tissue practice (CGTP) and additional requirements for manufacturers of human cells, tissues and cellular and tissue-based products (HCT/Ps). December 30, 2011. Fed Regist 2011;76:82308-9.** ~~Food and Drug Administration. Current good tissue practice for human cell, tissue, and cellular and tissue-based product establishments; inspection and enforcement; final rule (November 24, 2004). Fed Regist 2004;69:68612-88.~~
The reference has been updated to the most recent version of the FDA Guidance.
 3. Food and Drug Administration. Eligibility determination for donors of human cells, tissues, and cellular and tissue-based products (**HCT/Ps**); final rule (**February 28, 2007**). Fed Regist 2007;72:9009-8(~~May 25, 2004~~). Fed Regist 2004;62:29786-834.
The reference has been updated to the most recent version of the FDA Guidance.
 4. Food and Drug Administration. Human cells, tissues, and cellular and tissue-based products; donor screening and testing, and related labeling; interim final rule (**June 19, 2007**) (~~May 25, 2005~~). Fed Regist **2007;72:33667-69**. 2005;70:29949-52.
The reference has been updated to the most recent version of the FDA Guidance.
 5. Food and Drug Administration. Human cells, tissues, and cellular and tissue-based products; establishment registration and listing; **interim** final rule (**January 27, 2004**) (~~May 25, 2001~~). Fed Regist **2004;69:3823-6**. 2001;66:5447-69.
The reference has been updated to the most recent version of the FDA Guidance.

- On page 35 in the References section, the following updates and edits have been made:
 8. Ruiz R, ed. Standard terminology for medical products of human origin (**ST-002**). Version **7.67** ~~7.50~~. San Bernardino, CA: ICCBBA, 2021. [**Available at: https://www.isbt128.org/standard-terminology (accessed September 29, 2023).** ~~https://www.iccbba.org/uploads/92/2a/922aaf6d4a2752109eed39b7f60207e/Standard-Terminology-for-Medical-Products-of-Human-Origin-v7.50.pdf (accessed April 27, 2021).~~]
The reference was updated to the most recent version of the ISBT 128 terminology.
 9. Cabana E, ed. United States consensus guidance for the uniform labeling of cellular therapy products using ISBT 128. Version 1.3.1. San Bernardino, CA: ICCBBA, 2015. [**Cabana, E, Ed, ISBT 128 Standard Labeling of Cellular Therapy Products (ST-004) https://www.isbt128.org/ST-004 (accessed September 29, 2023)** Available at: ~~http://www.iccbba.org/tech-library/iccbba-documents/guidance-documents (accessed April 13, 2016).~~]
The reference was updated to the most recent version of the guidance for labeling cellular therapy products with ISBT 128 terminology.
 10. **Freire M, Distler P**, ed. Implementation guide: Product coding [Data Structures 003 and 032] - cellular therapy. Version **1.3.0**. ~~1.2.0~~, San Bernardino, CA: ICCBBA, **2023** ~~2015~~. [Available at **https://www.isbt128.org/IG-022 (accessed September 29, 2023).**]
The reference was updated to the most recent version of the guidance for labeling cellular therapy products with ISBT 128 terminology.



11. Food and Drug Administration. Testing donors of human cells, tissues, and cellular and tissue-based products (HCT/P): Specific requirements. Silver Spring, MD: CBER Office of Communication, Outreach, and Development, 2019. [Available at: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-donors-human-cells-tissues-and-cellular-and-tissue-based-products-hctp-specific-requirements> (accessed September 29, 2023)].

<https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm> (accessed April 27, 2021)]

The reference has been updated to the most recent version of the FDA Guidance's web address.

12. **Brown K** Haspel R, ed. Standards for cellular therapy services. **11⁹**th ed. Bethesda, MD: AABB, **2023**~~2017~~.

The reference has been updated to the most recent version of the Standards.

13. FACT-JACIE international standards for cellular therapy product collection, processing, and administration. **Version 8.1**~~7~~th ed. Omaha, NE: Foundation for the Accreditation of Cellular Therapy, **2021**~~2018~~.

The reference has been updated to the most recent version.

14. NetCord-FACT international standards for cord blood collection, processing, and release for administration. **7**~~6~~th ed. Omaha, NE: Foundation for the Accreditation of Cellular Therapy, **2021**~~2016~~.

The reference has been updated to the most recent version.

15. NMDP standards. **25**~~24~~th ed. Minneapolis, MN: NMDP, **2023**~~2018~~.

The reference has been updated to the most recent version.

16. WMDA international standards for **unrelated** hematopoietic stem cell donor registries, **2020**~~2017~~. **Leiden, the Netherlands: World Marrow Donor Association, 2019.** [Available at: <https://wmda.info/wp-content/uploads/2020/02/WMDA-Standards-2020-copyright-version-Final-table-of-content-.pdf> (accessed September 29, 2023).]

The reference has been updated to the most recent version.