

Summary of Changes

Eighth Edition FACT-JACIE Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration

This document summarizes the major changes in the *Eighth Edition FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*. This summary does not list all changes made to the Standards. Reorganization or clarified verbiage is not included unless considered to be a significant change in the intent of a standard. Refer to the Standards for all revisions.

To clearly identify new requirements, changes to the standards listed have been redlined.

Major Changes

1. Tenets. A tenet is a basic principle that is true throughout the Standards.

A new tenet (A2.2) was added to permit flexibility in delegation of specific activities. The term “or designee” was removed from individual standards throughout. The definition of “designee” is not changed from the seventh edition.

A2.2 Any activity can be delegated to an appropriate designee (as defined). The person appointing a designee retains ultimate responsibility.

Definition of Designee:

An individual with appropriate education, experience, or expertise who is given the authority to assume a specific responsibility. The person appointing the designee retains ultimate responsibility.

2. Definitions

- a. “*Applicable Law*” was introduced in the Eighth Edition Standards to replace “applicable law and regulations”.

- i. The phrase “*Applicable Law*” is defined as: “Any local, national, or international statute, regulation, or other governmental law that is applicable to cellular therapy product collection, processing, and administration that is relevant to the location or activities of the Clinical Program, Collection Facility, or Processing Facility.”

- b. *Cellular therapy product* [definition revised]:

Somatic cell-based product (e.g., ~~mobilized~~-HPC, mononuclear cells, cord blood cells, ~~mesenchymal stromal cells, T cells, natural killer cells~~immune effector cells, genetically modified cells, and others) that is procured from a donor and intended for processing and administration.

c. *Chain of identity and Chain of custody:*

These terms (as defined by the multi-stakeholder Chain of Identity/Chain of Custody working group of the Standards Coordinating Body) were added to the Standards Chains of identity and custody are necessary to permit tracking and tracing required by the Standards.

“Chain of identity” is defined as the permanent and transparent association of a cell or gene therapy's unique identifiers from procurement of tissue or cells throughout the full product(s) lifecycle including post treatment monitoring.

“Chain of custody” is defined as concurrent, permanent, auditable documentation illustrating the guardianship of a cell or gene therapy product from its origin through its final disposition.

d. *Chimerism and chimerism testing:*

The definition of chimerism was added to clarify the intent of the standard related to chimerism testing. The definition of chimerism testing was revised to focus on the purpose of such testing in cellular therapy, with less emphasis on the type of test.

“Chimerism” is defined as the coexistence of cells of more than one genotype in a single individual. In hematopoietic cell transplantation, chimerism generally refers to the presence of allogeneic donor hematopoietic and/or lymphoid cells in the transplant recipient.

“Chimerism testing” is defined as assessment of the presence of allogeneic donor cells in a transplant recipient using any assay of informative genetic markers that distinguishes donor from recipient cells. A diagnostic test (e.g., molecular, cytogenic, or FISH) conducted after allogeneic stem cell or bone marrow transplantation to detect the relative ratio of donor and recipient cell populations in the peripheral blood and/or bone marrow.

e. *Genetically modified cell* [new definition]:

A cell that has been modified by replacing a disease-causing gene with a healthy copy of the gene, inactivating a disease-causing gene that is not functioning properly, or introducing a new or modified gene into the body to help treat a disease.

f. *GxP* [new definition]:

Good practice following various quality standards and regulations. The “x” is variable, with further definition of good practices defined by different Applicable Law and industry standards. The type of work that is being performed will define which GxPs should be followed.

Examples include good manufacturing practice, good documentation practice, good laboratory practice, and others. Standards related to training in these areas were added to Collection and Processing sections.

3. Risk management program standards

General standards were added to address risk management program requirements for Clinical Programs utilizing licensed (or equivalent regulatory approval) cellular therapy products for which such a program is required by Applicable Law or by the manufacturer. The intent is to require Clinical Programs to establish and follow policies and Standard Operating Procedures related to any mandated risk management program.

a. Clinical Programs administering licensed, authorized, or equivalent cellular therapy products with a mandated risk management program shall have policies and Standard Operating Procedures in place for the following as required: (B7.9)

- i. Training and competency. (B7.9.1)
- ii. For each recipient of the cellular therapy product, availability of required medications to manage severe adverse events. (B7.9.2)
- iii. Reporting of adverse reactions. (B7.9.3)
- iv. Wallet cards or other means of communicating instructions to the recipient, caregivers, and other health care professionals who may provide care to the patient. (B7.9.4)

4. Addition of standards related to genetically modified cells.

Due to increasing use of genetically modified cellular therapy products in FACT-accredited organizations, the following requirements were added.

a. Administration of cellular therapy products, including HPC, IEC, genetically modified cells, and other cellular therapies. (B3.3.4.7, B3.6.2.3)

- b. Review of outcome analysis and/or product efficacy shall include at a minimum: For genetically modified HPC products, an endpoint of clinical function as approved by the Clinical Program Director. (B4.7.3.3)
 - c. When genetically modified cellular therapy products are utilized in the Clinical Program, the program shall incorporate or reference institutional or regulatory requirements relating to biosafety practices, including disposal. (B5.1.18.1)
 - d. There shall be a biosafety plan consistent with the institutional biosafety committee requirements that addresses genetically modified cellular therapy products in accordance with Applicable Law. (D2.8)
 - e. Processing Facilities utilizing genetically modified cellular therapy shall incorporate or reference institutional or regulatory requirements related to the disposal of genetic material. (D5.1.18.1)
5. Addition of training requirements in applicable GxP as required by Applicable Law for Collection and Processing Facilities. (CM3.3.4, C/D4.4.2.5)
- a. Physicians and collection staff shall have annual training in current GxP appropriate to the processes performed in accordance with Applicable Law. (CM3.3.4)
 - b. Annual training in applicable current GxP appropriate to the processes performed in accordance with Applicable Law. (C4.4.2.5)
 - c. Annual training in applicable current GxP appropriate to the processes performed in accordance with Applicable Law. (D4.4.2.5)
6. Accreditation of HLA Typing Laboratories.

The College of American Pathologists (CAP) has been approved as an accrediting organization appropriate to provide histocompatibility services for hematopoietic cellular therapy and is expressly listed in the Standards. (See B2.12; B6.4.14)

Changes Made to the Quality Management Standards

In addition to revising standards to explicitly and consistently state requirements, the following changes and additions were made:

1. Agreements should include the responsibility of the external parties to provide clinically relevant information related to products or services. (B4.6.2.1)
2. For HPC products intended for hematopoietic reconstitution, time to neutrophil and platelet engraftment following cellular therapy product administration shall be analyzed. (B4.7.3.1, C4.7.3, D4.7.3)
3. Audits shall be conducted by an individual with sufficient knowledge in the process and competence in auditing to identify problems, but who is not solely responsible for the process being audited. (B/C/D4.8.1)
4. Audits shall be performed annually at a minimum, and shall include at least the following: (B/C/D4.8.3)
5. A thorough and timely investigation shall be conducted by the Apheresis Collection Facility/Processing Facility in collaboration with the Processing Facility/Collection Facility, and the Clinical Program, and other entities involved in the manufacture of the cellular therapy product, as appropriate. (C/D4.10.2.1)
6. Occurrences shall be tracked and trended. (B/C/D4.10.2.3)
7. The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services. (B/C/D4.13)
 - a. Qualification shall be required following any significant changes to these items. (B/C/D4.13.1)
 - b. Critical equipment, software, supplies, reagents, and facilities used for the marrow collection procedure and/or other cellular collection procedures shall be qualified. (B4.13.2)
8. Critical procedures to be validated shall include at least the following: marrow or other cellular collection procedures, labeling, storage, and distribution, preparation for administration, and infusion. (B4.14.1)
 - a. Critical procedures to be validated shall include at least the following: processing techniques, cryopreservation procedures, testing, labeling, storage, and distribution, and preparation for administration. (D4.14.1)
 - b. Validation studies for a procedure shall be retained at a minimum until the procedure is no longer in use. (B4.14.2)
 - c. Each or verification shall include at a minimum: (B4.14.3, C/D4.14.2)

9. Evaluation of risk shall be completed for changes in critical procedures. (C/D4.15.1)
10. Meetings ~~should~~ shall have defined attendees, documented minutes, and assigned actions. (B/C/D4.17.1)
 - a. Performance data and review findings shall be reported to key positions and staff. (B/C/D4.17.2)
11. The annual report and documentation of the review findings shall be made available to key personnel, the Clinical Program Director/Collection Facility Director/Processing Facility Director, and staff of the program. (B/C/D4.18.1)

Changes to Clinical Program Standards

In addition to revising standards to explicitly and consistently state requirements, the following changes and additions were made:

1. General
 - a. These Standards apply to all services provided by the Clinical Program. (B1.1.1)
2. Clinical Unit.
 - a. There shall be 24-hour availability of CMV-appropriate and irradiated blood products or equivalent needed for the care of cellular therapy recipients. (B2.11)
 - b. The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, ~~or~~ radiological, electrical, or fire hazards. (B2.15)
3. Personnel.

Several changes were made to this section to provide clarity and update the requirements as the field evolves.

- a. Continuing education [physicians, pharmacists] shall include, but is not limited to, activities related to the field of HPC transplantation and other cellular therapies. (B3.1.6.1, B3.2.3.1, B3.7.4.1)
- b. Training for Clinical Program Directors and Attending Physicians (B3.3)
 - i. Clinical training and competency shall include the management of autologous and allogeneic transplant recipients and patients receiving immune effector cells or other cellular therapies. (B3.3.2)

- ii. Administration of cellular therapy products, including HPC, IEC, genetically modified cells, and other cellular therapies. (B3.3.4.7)
 - iii. Diagnosis and management of dermatologic complications. (B3.3.4.25)
 - c. Nurses shall have received specific training and maintain competence in the transplant and cellular therapy-related skills that they practice including: Administration of cellular therapy products, including HPC, IEC, genetically modified cells, and other cellular therapies. (B3.6.2.3)
 - d. Continuing education activities [Quality Manager] shall include ~~activities related to the field of HPC transplantation~~cellular therapy and Quality Management. (B3.9.3.1)
4. Policies and Standard Operating Procedures.
- a. The section for nursing Standard Operating Procedures was integrated into Clinical Program Standard Operating Procedures. (B5)
 - b. Data management was added as a critical aspect of the Clinical Program that must be addressed in policies and procedures. (B5.1.16)
5. Donor Selection, Evaluation, and Management.
- a. Family members and legally authorized representatives ~~shall should~~ not serve as interpreters or translators. (B6.2.2.1)
 - b. Donor informed consent for the cellular therapy product donation shall be obtained and documented by a licensed health care professional ~~familiar~~knowledgeable in the collection procedure. (B6.2.5)
 - c. The donor shall be informed of the policy for cellular therapy product storage, discard, or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product. (B6.2.8)
 - d. Appropriate mobilization should be used for the disease being treated and for the donor being collected. (B6.3.4)
 - e. Verification typing [for HLA alleles] shall be performed on the recipient and selected allogeneic donor using independently collected samples. Results shall be confirmed prior to administration of the preparative regimen, mobilization, or cellular therapy product collection, whichever is earliest. (B6.4.14.2)

- f. Allogeneic donor eligibility, as defined by Applicable Law, shall be determined by a physician licensed health care provider after history, exam, medical record review, and testing. The donor eligibility determination shall be documented in the recipient's medical record before the recipient's preparative regimen is initiated and before the allogeneic donor begins the mobilization regimen. (B6.4.15)
6. Recipient Care.
- a. Recipient informed consent for the cellular therapy shall be obtained and documented by a licensed health care professional knowledgeable in familiar with the proposed cellular therapy. (B7.1)
- i. The ~~Clinical Program~~ informed consent process shall ~~provide~~ include information regarding the risks and benefits of the proposed cellular therapy. (B7.1.1)
- b. ~~For transplants~~ When utilizing administering cellular therapy products from more than one (1) donor, ~~the first~~ each cellular therapy product shall be administered safely prior to administration of ~~the second~~ subsequent cellular therapy products. (B7.6.5)
- c. The facility performing ECP shall ~~follow written Standard Operating Procedures appropriate for the clinical condition of the patient~~ be qualified to meet FACT-JACIE requirements. (B7.11.4)
7. Clinical Research.
- a. ~~Documentation for all~~ All eClinical research protocols ~~performed by the Clinical Program~~ shall be ~~maintained~~ performed in accordance with institutional policies and ~~applicable laws and regulations~~ Applicable Law, ~~including audits; approvals by the Institutional Review Board, Ethics Committee, or equivalent; correspondence with regulatory agencies; and any adverse events and the resolution.~~ (B8.2)
- i. The Clinical Program shall maintain: (B8.2.1)
- Documentation of approval by the Institutional Review Board, Ethics Committee, or equivalent. (B8.2.1.1)
 - If applicable, documentation of approval by the institutional Biosafety Committee or equivalent. (B8.2.1.2)
 - Correspondence with regulatory agencies. (B8.2.1.3)
 - Audits and any adverse events, including their resolution. (B8.2.1.4)

8. Data Management.

- a. The Clinical Program shall collect and maintain complete and accurate~~all the~~ data necessary to complete the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A forms of the EBMT. (B9.1)
 - i. Clinical Programs ~~should~~shall submit the data specified in B9.1 for allogeneic and autologous transplants to a national or international database. (B9.1.1)
 - ii. Clinical Programs ~~should~~shall collect the data specified in B9.1 for all patients for at least one (1) year following administration of the cellular therapy product. (B9.1.2)
 - iii. Clinical Programs should meet accuracy benchmarks/criteria established by FACT, JACIE, and CIBMTR or EBMT.~~the CIBMTR, EBMT, FACT, or JACIE.~~ (B9.1.3)
- b. The Clinical Program should collect and submit all data elements included in the Cellular Immunotherapy Data Resource (CIDR) forms of the CIBMTR or the Cellular Therapy Med-A forms of the EBMT. (B9.2)

Changes to Collection Facility Standards

1. General.

- a. These Standards apply to all collection, storage, and distribution activities performed in the Marrow Collection Facility for cellular therapy products ~~obtained from living donors.~~ (CM/C1.1)

2. Collection Facility.

- a. There shall be ~~appropriate secured and controlled access to~~ designated areas for the collection ~~procedure of cellular therapy products, for collected products,~~ and for storage of equipment, supplies, and reagents. (CM/C2.1)
- b. The Collection Facility shall provide adequate lighting, ventilation, and access to sinks for handwashing and to toilets to prevent the introduction, transmission, or spread of communicable disease. (CM/C2.2)
- c. The Collection Facility shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to communicable disease and to chemical, biological, ~~or~~ radiological, electrical, or fire hazards. (CM/C2.9)

3. Personnel.

- a. There shall be a Collection Facility Medical Director who is a licensed physician with a minimum of two (2) years postgraduate certification, ~~with and~~ training and practical and relevant experience in cellular therapy product collection and transplantation. (CM3.1.1, C3.2.1)
- b. Continuing education [Medical Director] shall include, but is not limited to, activities related to the field of HPC transplantation and other cellular therapies. (CM3.1.4.1, C3.1.4.1, C3.2.4.1)
- c. The Marrow Collection Facility Quality Manager's continuing education activities shall include cellular therapy, cell collection, and Quality Management~~but is not limited to, activities related to the field of HPC transplantation~~. (CM3.2.3.1)
- d. The Apheresis Collection Facility Quality Manager's continuing education shall include cellular therapy, cell collection, and Quality Management~~but is not limited to, activities related to the field of HPC~~. (C3.3.3.1)
- e. There shall be attending physician oversight if general medical physicians, physicians in training, or APPs provide care to the cellular therapy donors. (CM3.3.5, C3.4.3)
 - i. The scope of responsibility of general medical physicians or APPs shall be defined. (CM3.3.5.1, C3.4.3.1)

4. Policies and Standard Operating Procedures [new or revised requirements]:

- a. Donor screening, testing, eligibility and suitability determination, and management. (CM/C5.1.3)
- b. Extracorporeal photopheresis if performed by the Apheresis Collection Facility. (C5.1.13)
- c. Packaging, Transportation, and shipping. (CM5.1.12, C5.1.14)
 - i. Use of additives for long duration of shipment. (CM5.1.12.2, C5.1.14.2)
- d. Disposal of medical and biohazard waste. (CM5.1.15)
- e. Cleaning and sanitation procedures, including beds and chairs and the identification of the individuals ~~responsible for~~ performing the activities. (C5.1.17)

5. Allogeneic and Autologous Donor Evaluation and Management.

- a. The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum: Intent of the collection for treatment or research. (CM/C6.2.1.2)
- b. Family members and legally authorized representatives ~~should~~shall not serve as interpreters or translators. (CM/C6.2.2.1)
- c. Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional ~~familiar~~knowledgeable in~~with~~ the collection procedure. (CM/C6.2.5)
- d. The donor shall be informed of the policy for cellular therapy product storage, discard, or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product. (CM/C6.2.8)
- e. For collections without mobilization, a pregnancy test shall be performed within seven (7) days prior to cellular therapy collection. (C6.3.4.1)
- f. If ~~required~~, central venous ~~catheters shall be~~access is placed~~required by a licensed health care professional qualified to perform the procedure, the rationale shall be documented in the donor's records.~~ (C6.3.7)
 - i. Adequacy of central line placement shall be verified and documented. (C6.3.8)
 - ii. Adequacy of central line placement shall be verified and documented by the Apheresis Collection Facility staff prior to initiating ~~each~~the collection procedure. (C6.3.8.1)
- g. There shall be a policy covering the creation and retention of donor records including at a minimum: (CM6.5)
 - i. Allogeneic donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination. (CM6.5.1)
 - ii. Donor identification including at least name and date of birth. (CM6.5.2)
 - iii. Age, gender, and medical history, and, for allogeneic donors, behavioral history. (CM6.5.3)
 - iv. Consent to donate. (CM6.5.4)
 - v. Results of laboratory testing. (CM6.5.5)

6. Coding and Labeling of Cellular Therapy Products.

- a. A system of label reconciliation shall be used to ensure the final disposition of all labels allocated to a specific product is documented. (CM/C7.2.2.1)

- b. ~~Print-on-demand-IL~~ label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Marrow Collection Facility Director ~~or designee~~. (CM/C7.2.3)
- c. Labeling of the cellular therapy product shall occur prior to removal of the product from the proximity of the donor. (CM7.4.2)
 - i. The identity of the donor shall be verified against the label information prior to removing the cellular therapy product from the proximity of the donor. (CM7.4.2.1)
- d. For cellular therapy products not collected, processed, and/or administered in the U.S., the appropriate Biohazard and Warning Labels shall follow Applicable Law. (CM7.4.3.1, C7.4.4.1)
- e. A cellular therapy product collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documentation table in Appendix IV at the time it leaves the control of the Apheresis Collection Facility. (C7.4.5; This was added to be consistent with the Processing Facility standard.)

7. Process Controls.

- a. There shall be a process for inventory control that encompasses equipment, ~~transport containers for transport and shipping~~, supplies, reagents, and labels. (CM/C8.2)
 - i. Supplies and reagents shall be quarantined prior to use until verified to have met acceptance criteria. (CM/C8.2.2.1)
- b. Processes for equipment management in the apheresis section (C8.3) were streamlined for clarity and added to the marrow collection section as applicable (CM8.3).
 - i. There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration. (CM/C8.3)
 - Equipment shall be maintained in a clean and orderly manner. (CM/C8.3.1)
 - Maintenance and cleaning shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations. (CM/C8.3.1.1)
 - The equipment shall be inspected for cleanliness and documented to be clean prior to use. (CM/C8.3.1.2)
 - The equipment shall be verified and documented to be in compliance with the maintenance schedule prior to use. (CM8.3.1.3)

- ii. All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented. (CM/C8.3.2)
 - Calibration shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations. (CM/C8.3.2.1)
 - When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products collected since the last calibration. (CM8.3.2.2)
 - iii. Equipment, supplies, and reagents [for the marrow collection procedure] shall conform to Applicable Law. (CM/C8.3.3)
- c. Autologous or CMV-appropriate and irradiated blood products or equivalent components shall be available during the marrow/apheresis collection procedure for all donors. (CM/C8.4)
- i. Allogeneic blood components-products administered to the donor during marrow collection ~~should~~ shall be CMV-appropriate and irradiated or equivalent prior to transfusion. (CM8.4.1)
 - ii. Allogeneic blood components-products administered to the donor during apheresis collection or used during priming procedures ~~should~~ shall be CMV-appropriate and irradiated or equivalent prior to transfusion. (C8.4.1)
- d. Appropriate mobilization should be used for the disease being treated and for the donor being collected. (C8.9.1)
- e. Methods for collection shall employ procedures that minimize the risk of microbial contamination and be validated to result in acceptable cell viability, ~~sterility,~~ and recovery. (CM/C8.10.1)
- f. Collection methods ~~for pediatric donors~~ shall employ appropriate age and size adjustments to the procedures. (CM/C8.11)
- g. There shall be policies addressing safe treatment with ECP, if applicable. (C8.14)
~~The ECP shall be performed according to written standard operating procedures of the facility performing the procedure appropriate for the clinical condition of the patient.(C8.17.2)~~
- i. A final report of the ~~details of the~~ ECP treatment, including procedure ~~shall~~ details, shall be documented in the patient's medical record. (C8.14.2)

8. Cellular Therapy Product Storage.

- a. Marrow Collection Facilities shall control and secure storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of cellular therapy products. (CM/C9.1)

- b. Conditions and duration of storage of all cellular therapy products shall be validated. (CM/C9.2.1)
- c. Marrow/Apheresis Collection Facilities collecting, storing, or releasing cellular therapy products for administration or further manufacturing shall assign an expiration date and time. (CM/C9.2.2)

9. Cellular Therapy Product Transportation and Shipping.

- a. Additives to the cellular therapy product should be used for shipping over a long duration of time. (CM/C10.1.1)
- b. The Collection Facility shall perform a risk assessment to evaluate the need for continuous temperature monitoring during transportation or shipment of cellular therapy products. (CM/C10.3.2)

10. Records.

- a. Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities, and health care providers and their recipients and donors, shall be established and followed in compliance with Applicable Law. (C11.1.5)
- b. Validation studies for a collection procedure shall be retained for the duration of the use of the procedure. (C11.3.3)
- c. The Apheresis Collection Facility shall furnish to the facility of final disposition a copy of all cellular therapy product records relating to the collection procedures performed related to the safety, purity, or potency integrity of the cellular therapy product involved. (C11.8.1)

Changes to Processing Facility Standards

1. General.

- a. These Standards apply to all processing, storage, and distribution activities performed in the Processing Facility on cellular therapy products ~~obtained from living donors.~~ (D1.1)

2. Processing Facility.

- a. There shall be secured and controlled access to designated areas for processing and for storage of equipment, supplies, and reagents. (D2.1)
 - i. The designated area for processing shall be in an appropriate location ofThe Processing Facility shall be of adequate space, and design, and location for the intended procedures to minimize the risk of airborne microbial contamination. (D2.1.1)
- b. The Processing Facility shall provide adequate lighting, ventilation, and access to sinks for hand washing and to toilets to prevent the introduction, transmission, or spread of communicable disease. (D2.2)
- c. There shall be a written assessment of critical Processing Facility parameters that may affect cellular therapy product viability, integrity, or contamination or cross-contamination during processing, storage, or distribution. (D2.4)
- d. The Processing Facility shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, or radiological, electrical, or fire hazards. (D2.7)

3. Personnel.

- a. Continuing education [Director, Medical Director] shall include, but is not limited to, activities related to the field of HPC transplantation and other cellular therapies. (D3.1.4.1, D3.2.4.1)
- b. The Processing Facility Quality Manager's continuing education activities shall include, but is not limited to, activities related to the field of HPC cellular therapy, cell processing, and Quality Management. (D3.3.3.1)

4. Policies and Standard Operating Procedures [new and revised standards].

- a. Appropriate processing procedures for specific products, including cryopreservation and thawing. (D5.1.3.1)
- b. Processing of ABO-incompatible cellular therapy products to include a description of the indication for and processing methods to be used for red blood cell and plasma depletionreduction. (D5.1.4)
- c. Packaging, Ttransportation, and shipping, including methods and conditions within the Processing Facility and to and from external facilities. (D5.1.10)

5. Equipment, Supplies, and Reagents.

- a. There shall be adequate equipment and materials for the procedures performed. (D6.2)

6. Coding and Labeling.

- a. A system of label reconciliation shall be used to ensure the final disposition of all labels allocated to a specific product is documented. (D7.2.3)
- b. ~~Print-on-demand-IL~~ label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Processing Facility Director ~~or designee~~. (D7.2.4)
- c. For cellular therapy products not collected, processed, and/or administered in the U.S., the appropriate Biohazard and Warning Labels shall follow Applicable Law. (D7.4.4.1)

7. Process Controls.

- a. ~~For tests performed within the Processing Facility, t~~here shall be documentation of ongoing proficiency testing as designated by the Processing Facility Director. The results shall be reviewed by the Processing Facility Director ~~or designee~~ and outcomes reviewed with the staff. (D8.1.4.5)
- b. There shall be a written request from the recipient's physician specifying the cellular therapy product type, recipient and donor identifiers, the type of processing that is to be performed, and the anticipated date of processing before a cellular therapy product is processed, shipped, or otherwise prepared for administration. ~~there shall be a written request from the recipient's physician specifying the cellular therapy product type, recipient and donor identifiers, the type of processing that is to be performed, and the anticipated date of processing.~~ (D8.2)
- c. Preparation for administration of cellular therapy products manufactured by third-partiesthird parties, shall follow the instructions provided by the manufacturer. ~~lacks experience with the type of cellular therapy product requested for a recipient, personnel shall obtain the manufacturer's instructions and follow these instructions to the extent possible.~~ (D8.4.5)
 - i. The Processing Facility should verify the processing preparation procedures utilizing practice units similar to the cellular therapy product intended for administration when feasible. (D8.4.5.1)
 - ii. If relabeling of prepared third-party products is required, the label shall follow Applicable Law. (D8.4.5.2)
- d. Critical calculations shall be verified and documented where appropriate. (D8.6)

- e. Processing using more-than-minimal manipulation shall only be performed in accordance with institutional policies and Applicable Law; with Institutional Review Board or Ethics Committee approval, and with the written informed consent of the donor, if applicable, and the recipient of the cellular therapy product, ~~and in compliance with applicable laws and regulations.~~ (D8.12)
 - i. Documentation of approvals by the Institutional Review Board, Ethics Committee, or equivalent; and the Institutional Biosafety Committee, or equivalent shall be maintained. (D8.12.1)
8. Cellular Therapy Product Storage.
- a. Processing Facilities shall control and secure storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products. (D9.1)
 - b. Conditions and duration of storage of all cellular therapy products shall be validated. (D9.2.1)
 - c. Samples [for stability studies] should include those representative of all processing methods and those representative of maximum storage duration. (D9.2.3.1)
9. Cellular Therapy Product Transportation and Shipping.
- a. Cellular therapy products transported internally shall be packaged in a closed and rigid outer container. (D10.6)
 - i. The outer container for internal transport shall be labeled as defined in Appendix III B. (D10.6.1)
10. Records.
- a. Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities, and health care providers and their recipients and donors, shall be established and followed in compliance with Applicable Law. (D13.1.7)
 - b. Processing Facility records related to quality control, investigational protocols, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, or the creation of the cellular therapy product record, whichever is latest, or according to Applicable Law. (D13.4.1)

i. Validation studies for a current processing procedure shall be retained at a minimum until no products manufactured using that procedure remain in inventory. (D13.4.1.3)

c. The Processing Facility shall furnish to the facility of final disposition a summary ~~copy~~ of ~~all~~ records relating to the collection, processing, and storage procedures performed related to the safety, purity, or potency of the cellular therapy product involved. (D13.5.2)

11. Appendix III

B: CELLULAR THERAPY PRODUCT LABELS FOR INTERNAL TRANSPORT

<u>Element</u>	<u>Internal transport label</u>
<u>Statements "Human Cells for Administration" or equivalent and "Handle with Care"</u>	<u>AF</u>
<u>Emergency contact person name and phone number</u>	<u>AF</u>