FOUNDATION FOR THE ACCREDITATION OF CELLULAR THERAPY

Summary of Changes

Draft Third Edition FACT Common Standards for Cellular Therapies

This document summarizes the major changes proposed in the *Third Edition FACT Common Standards for Cellular Therapies*. This summary does not list all proposed 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 second edition.

   A2.2 Any activity can be delegated to a 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

   The following definitions were added or revised in conjunction with changes to requirements in the Standards. Additional updates to the definitions bring them into conformity and consistency with the changes that were made in the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy, Eighth Edition.*

   a. *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.

b. *Chimerism and chimerism testing:*
The definitions of chimerism and chimerism testing were added to clarify the intent of the standards related to chimerism testing. The definition of chimerism testing focuses 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 cellular therapy, chimerism generally refers to the presence of allogeneic donor cells in the recipient.

"Chimerism testing" is defined as assessment of the presence of allogeneic donor cells in a recipient using any assay of informative genetic markers that distinguishes donor from recipient cells.

c. *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.

d. *Good practices:*
The definition of "*GxP"* was added in addition to the new definition of "*Good Tissue Practice (GTP)"* and the revised definition of *"Good Manufacturing Practice (GMP)"* to delineate the good practices that must be followed as applicable to the processes performed by a specific entity for a given cellular therapy.

"Good Manufacturing Practice (GMP)" is defined as the set of current practices followed by entities producing drug and biologic products, including cellular therapy products, to ensure that the products produced meet specific requirements for identity, strength, quality, and purity. In the US, GMPs are enforced under Section 501(B) of the Federal Food, Drug, and Cosmetic Act (21USC351). Cellular therapy products that ~~do not meet criteria for regulation solely under section 361 of the Public Health Services Act (see 21 CFR 1271.10(a)), and are controlled under GMP regulations.~~are more-than-minimally manipulated, are allogeneic and obtained from donors other than first or second degree relatives, or that are used for non-homologous purposes are examples of products controlled under GMP regulations. Similar requirements are delineated by the European Union as EU-GMP~~, and o~~ Other countries such as the United Kingdom, Australia, Canada, and Singapore have equally well-developed systems of regulations.

"Good Tissue Practice (GTP)" is defined as the methods used in, and the facilities and controls used for, the manufacture of cellular therapy products to prevent the introduction or transmission of communicable diseases, including all steps in collection, donor screening and testing, processing, storage, labeling, packaging, and distribution.

"GxP" is defined as 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 of GxPs 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.

e. *Packaging* [new definition]:
Placing a cellular therapy product into an appropriate secondary or outer container for shipping or transportation.

f. *Partial label at distribution for administration* [new definition]:
A label that, because of the size of the product container or other constraints, does not contain all of the required information.

g. *Preparative (conditioning) regimen* [new definition]:
The procedure used to prepare a patient for cellular therapy administration (e.g., chemotherapy, monoclonal antibody therapy, radiation therapy).

3. *ISBT 128 Coding and Labeling*

Full implementation of the ISBT 128 coding and labeling system is required in this edition. Labels for cellular therapy products manufactured by external clinical trial sponsors that do not use ISBT 128 but have been approved by the applicable regulatory authority are acceptable; however, labels for products manufactured by the organization seeking accreditation must comply with this requirement.

a. *"Product code"* is defined as an eight-character ISBT 128 code that comprises the Product Description Code, a Collection Type Code, and a Division Code. The product code makes each product from a collection unique.

b. *"Product"* is defined as the ISBT 128 Cellular Therapy Class product database name and definition (format: type of cells, comma, source of cells) for products collected from marrow, peripheral blood, and cord blood are as follows:

Subcategory 1: At collection the product code will describe the composition of the cell therapy products. It can be HPC, NC, or MNC. These products may be collected for direct infusion without further manipulation, or may be further processed into other cellular therapy classes. If they are HPCs they would retain the class name if they are used as a source of hematopoietic progenitor cells. If these products undergo modification such as cryopreservation and thawing, the class will not change but the modification is added into the product description as an attribute.

Subcategory 2: After enumeration or manufacture/processing of the collected product, the product is identified by the target cell population.

These definitions are as of the date of publication and use the current terminology as found in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. For the most current list of definitions, see www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology.

c. ISBT 128 CODING AND LABELING (C7.1, D7.1)
   i. Cellular therapy products shall be identified by name according to ISBT 128 standard terminology. (C7.1.1, D7.1.1)
   ii. Coding and labeling technologies shall be implemented using ISBT 128. (C7.1.2, D7.1.2)

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. Clinical Programs utilizing genetically modified cells shall incorporate or reference institutional or regulatory requirements related to biosafety, including disposal. (B5.1.13.1)

   b. There shall be a biosafety plan consistent with the institutional biosafety committee requirements that addresses genetically modified products in compliance with Applicable Law. (D2.8)

   c. Processing Facilities utilizing genetically modified cellular therapy shall incorporate or reference institutional or regulatory requirements related to the disposal of genetic material. (D5.1.19.1)

5. Addition of training requirements in applicable GxP as required by Applicable Law for collection and processing personnel. (C4.4.2.5)

   a. Annual training in applicable current GxP appropriate to the processes performed in accordance with Applicable Law. (C4.4.2.5, 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. (B2.7, B6.4.12)

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. The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions, ~~and~~ functions, and reporting relationships within the cellular therapy program, including clinical, collection, and processing activities~~, as applicable~~. (B4.3)

   a. There shall be written guidelines for communication between the Clinical Program and collection or registry personnel for the management of collection-related complications. (B4.3.2)

2. The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions, ~~and~~ functions, and reporting relationships required for collection/within the Processing Facility. (C4.3, D4.3)

3. Review of controlled documents every two (2) years at a minimum. (B4.5.3.5, C4.5.3.5, D4.5.3.5)

4. Agreements should include the responsibility of the external parties to provide clinically relevant information related to products or services. (B4.6.3)

5. Agreements shall be established when collections or other critical services are performed for external parties. (C4.6.3)

6. Agreements shall be established when the Processing Facility provides critical services to external parties. (D4.6.3)

7. Review of outcome analysis and/or product efficacy shall include at a minimum: (C4.7.3, D4.7.3)

   a. An endpoint of clinical function as approved by the Clinical Program Director. (C4.7.3.1, D4.7.3.1)

b. Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration or in accordance with Applicable Law. (C4.7.3.2, D4.7.3.2)

8. Data on outcome analysis and cellular therapy product efficacy, including adverse events related to the recipient, donor, or product, shall be provided in a timely manner to entities involved in the clinical, processing, or distribution of the cellular therapy product. (C4.7.4)

9. Data on outcome analysis and cellular therapy product efficacy, including adverse events related to the recipient, donor, or product, shall be collected and made available in a timely manner to clinical, collection, or distribution personnel as applicable. (D4.7.4)

10. Audits shall be conducted by an individual with sufficient ~~expertise~~ knowledge of the process and competence in auditing to identify problems, but who is not solely responsible for the process being audited. (B4.8.1, C4.8.1, D4.8.1)

11. Audits shall be performed annually at a minimum, and shall include at ~~a minimum~~least the following: (B4.8.3, C4.8.3, D4.8.3)

    a. ~~Annual audit of donor screening and testing~~Documentation of proper donor eligibility and suitability determination. (B4.8.3.2, C4.8.3.1)

    b. Documentation that external facilities performing critical contracted services have met the requirements of the written agreements. (D4.8.3.1)

    c. Management of cellular therapy products with positive microbial culture results. (C4.8.3.2, D4.8.3.2)

    d. ~~Annual audit of~~Chain of identity and chain of custody of cellular therapy products. (B4.8.3.6, C4.8.3.4, D4.8.3.4)

12. There shall be policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency. (C4.8.4)

13. The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results that address at a minimum: (B4.9)

    a. Notification of the recipient, recipient's physician, collection staff, processing staff, any other facility in receipt of the cellular therapy product, and, if relevant, the donor and the sponsor. (B4.9.2, C4.9.1, D4.9.5)

b. Identification of individuals authorized to approve release, including the ~~Processing Facility Director and~~ Processing Facility Medical Director at a minimum. (D4.9.4)

c. Recipient follow-up. (C4.9.2, D4.9.8)

d. Follow-up of the donor, if relevant. (D4.9.9)

14. A thorough and timely investigation [of occurrences] shall be conducted by the Clinical Program/collection staff/Processing Facility in collaboration with ~~the Clinical Program, collection staff and Processing Facility, and other~~all entities involved in the collection, manufacture, testing, or administration of the cellular therapy product, as appropriate. (B4.10.2.1, C4.10.2.1, D4.10.2.1)

15. Occurrences shall be tracked and trended. (B4.10.2.3, C4.10.2.3, D4.10.2.3)

16. 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 relevant to the cellular therapy product. (B4.14, C4.14, D4.13)

    a. Qualification plans shall include minimum acceptance criteria for performance. (B4.14.1, C4.14.1, D4.13.2)

    b. Qualification shall be required following any significant changes to these items. (B4.14.2, C4.14.2, D4.13.3)

    c. Reagents that are not the appropriate grade shall undergo qualification for the intended use. (C4.14.4)

17. Critical procedures to be validated shall include at least collection procedures, labeling, storage, ~~and~~ distribution, preparation for administration, and infusion. (B4.15.1)

    a. Each validation~~-~~ or verification shall include at a minimum: (B4.15.2)

18. 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)

    a. Each validation or verification shall include at a minimum: (C4.15.2, D4.14.2)

19. The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the evaluation of risk in changes to a process to assess the effect of the change elsewhere in the operation. (C4.16)

    a. Evaluation of risk shall be completed for changes in critical procedures. (C4.16.1, D4.15.1)

20. The Clinical Program Director/Medical Director/Processing Facility Director ~~or designee~~ shall review the quality management activities with representatives in key positions in all ~~elements~~areas of the cellular therapy program, at a minimum, quarterly. (B4.17, C4.17, D4.16)

    a. ~~Key p~~Performance data and review findings shall be reported to key positions and staff. (B4.17.1, C4.17.1, D4.16.2)

    b. The meetings ~~should~~ shall have ~~designated~~ defined attendees, documented minutes, and assigned actions. (B4.17.2, C4.17.2, D4.16.1)

    c. The Clinical Program Director/Medical Director/Processing Facility Director ~~or designee~~ shall not ~~have oversight of~~ approve his/her own work~~. if this person also performs other tasks in the Clinical Program.~~ (B4.17.3, C4.17.3, D16.3)

21. The Clinical Program Director ~~or designee~~ shall annually review the effectiveness of the overall Quality Management Program. (B4.18)

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 cellular therapy services provided by the Clinical Program. (B1.1.1)

    b. The Clinical Program shall ~~use~~ verify that cell collection procedures and processing facilities ~~that~~ meet FACT Standards~~ with respect to their interactions with the Clinical Program~~. (B1.2)

2. Clinical Unit.

    a. The Clinical Program shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operation. (B2.3)

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. (B2.10)

3. Personnel.

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

a. The Clinical Program Director ~~or designee~~ shall be responsible for verifying ~~the knowledge and skills~~competency of members of the Clinical Program annually ~~once per accreditation cycle, at a min~~. (B3.1.5.2)

b. Continuing education [for the Clinical Program Director, Attending Physicians, Advanced Practice Providers/Professionals (APPs), Quality Manager] shall include, but is not limited to, activities related to the specific cellular therapy administered within the Clinical Program. Quality Managers shall also participate in continuing education related to Quality Management. (B3.1.6.1, B3.2.3.1, B3.5.3.1, B3.10.2.1)

c. Training for Clinical Program Directors and Attending Physicians (B3.3)
    i. Specific training in each of the following areas as applicable to the Clinical Program's services:
        1. Donor selection, evaluation, and management. (B3.3.1.3)
        2. Informed consent of the ~~patient~~ recipient and, if required, donor consistent with institutional policy and Applicable Law. (B3.3.1.4)
        3. Administration of cellular therapy products and anticipated complications. (B3.3.1.5)
        4. Administration of preparative regimen. (B3.3.1.6)
        5. Reporting responsibilities for adverse events according to Applicable Law. (B3.3.1.12)
    ii. If applicable to the cellular therapy product, specific clinical training and competency required for physicians in Clinical Programs requesting accreditation for allogeneic cellular therapy shall include:
        1. Methodology and implications of testing for chimerism. (B3.3.2.4)
    iii. The attending physicians shall be knowledgeable in the following procedures for cellular therapy products: (B3.3.3)
        1. Shipping and transportation. (B3.3.3.4)
        2. Storage. (B3.3.3.5)

d. Nurses shall be trained in age-specific management of patients receiving cellular therapy. (B3.7.1.1)

e. Designated staff shall include data management staff. (B3.11.1.1)

4. Policies and Standard Operating Procedures.

   a. The following changes were made to the required aspects of operations and management that must be addressed in policies or Standard Operating Procedures: (B5)
      i. Recipient evaluation, selection, and treatment across the continuum of care related to cellular therapy. (B5.1.1)
      ii. Donor and recipient informed consent related to treatment, cellular therapy product collection, and storage. (B5.1.3)
      iii. Donor search and selection, including screening, testing, eligibility determination, ~~selection,~~ and management. (B5.1.4)
      iv. Management of ABO incompatible products, if applicable. (B5.1.9)

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. 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. (B6.4.12.2)

   c. 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. (B6.4.13)

6. Recipient Care.

   a. Recipient informed consent for the cellular therapy shall be obtained and documented by a licensed health care professional knowledgeable of ~~familiar with~~ the proposed cellular therapy. (B7.1)

   b. The cellular therapy product shall be administered by a licensed healthcare professional trained in the procedure. (B7.5.1)

   c. A circular of information or investigator's brochure for cellular therapy products shall be available to staff. (B7.5.4)

7. Clinical Research.

    a. ~~Documentation for all~~All ~~c~~Clinical 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)

    b. Informed consent for a research subject shall contain the following elements at a minimum and comply with Applicable Law (B8.3.2): Contact information for the person research subjects can contact in case of questions or concerns. (B8.3.2.6)

8. Data Management.

    a. The Clinical Program shall collect and maintain complete and accurate~~all the~~ data necessary to complete the ~~Cellular Therapy Essential Data Forms of the CIBMTR for Regenerative Medicine or the Minimum Essential Data-A forms of the EBMT~~Cellular Immunotherapy Data Resource (CIDR) forms or the Cellular Therapy Med-A forms of the EBMT. (B9.1)

9. Records.
    a. Cleaning and sanitation records shall be retained for a minimum of three (3) years or longer in accordance with Applicable Law, or by a defined program or institution policy. (B10.1.2)

    b. Validation study records for a procedure shall be retained at a minimum until the procedure is no longer in use. (B10.1.3)

Changes to Collection Facility Standards

1. General.

    a. These Standards apply to all collection, storage, and distribution ~~activities~~ services performed on cellular therapy products ~~obtained from living donors~~. (C1.1)

b. Collected cellular therapy products shall be distributed to ~~cell processing~~ facilities that meet ~~the~~ FACT Standards with respect to their role in ~~the~~ cellular therapy ~~product manufacturing process~~. (C1.2)

c. Cellular collection services shall be overseen by a designated Medical Director, a Quality Manager, and a minimum of one (1) additional designated staff member. This team shall have been in place and performing cellular therapy product collections for at least twelve (12) months preceding initial accreditation. (C1.4)

d. A minimum of five (5) cellular therapy products shall have been collected prior to initial accreditation, and a minimum average of five (5) cellular therapy products shall have been collected per year within each accreditation cycle. (C1.5)

2. Collection ~~Facility~~Environment.

a. There shall be ~~appropriate~~ secured and controlled access to designated areas appropriate for collection of cellular therapy products~~, for collected products,~~ and for storage of cellular therapy products, equipment, supplies, and reagents. (C2.1)
    i. There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination. (C2.1.2)

b. There shall be adequate lighting, ventilation, and access to sinks for handwashing and to toilets to prevent the introduction, transmission, or spread of communicable disease. (C2.2)

c. There shall be attending physician oversight if general medical physicians, physicians in training, or APPs provide care to the cellular therapy donors. The scope of responsibility of general medical physicians or APPs shall be defined. (C2.8)

d. There shall be a written safety manual that includes instructions for action in case of exposure to communicable disease and to chemical, biological, ~~or~~ radiological, electrical, or fire hazards. (C2.10)

e. When a collection kit is prepared and sent to collection staff, there shall be adequate instructions and materials to collect, label, store, pack, and transport or ship the cellular therapy product and associated samples to the Processing Facility. (C2.13)
    i. The collection kit shall be transported or shipped under conditions validated to maintain the designated temperature range from the time it leaves the shipping facility until it is received by the collection staff. (C2.13.1)

3. Personnel.

    a. Continuing education [for the Medical Director of Collection Services] shall include, but is not limited to, activities related to cellular therapy product collection or the applicable therapeutic disease area. (C3.1.4.1)

    b. Continuing education [for the Quality Manager] shall include, but is not limited to, activities related to cellular therapy, cell collection, and Quality Management. (C3.2.3.1)

4. Policies and Standard Operating Procedures.

    a. The following changes were made to the required aspects of operations and management that must be addressed in policies or Standard Operating Procedures: (C5)
        i. Donor informed consent for cellular therapy product collection. (C5.1.2)
        ii. Donor screening, testing, eligibility and suitability determination, and management. (C5.1.3)
        iii. Management of donors who require central venous access. (C5.1.4)
        iv. Packaging, ~~T~~transportation, and shipping. (C5.1.11)
            - Use of additives for long duration of shipment. (C5.1.11.2)

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 (C6.2.1): Intent of the collection for treatment or research. (C6.2.1.2)

    b. Family members and legally authorized representatives ~~should~~ shall not serve as interpreters or translators. (6.2.2.1)

    c. Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional ~~familiar~~ knowledgeable in the collection procedure. (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. (C6.2.8)

    e. Autologous donors shall be evaluated and tested as required by Applicable Law. (C6.3.1.3)

    f. For collection with mobilization, a pregnancy test shall be performed within seven (7) days prior to the initiation of the mobilization regimen. (C6.3.3.1)

g. Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the administering physician and approval by the Medical Director. ~~Collection staff shall document review of these donor safety issues.~~ (C6.3.5)
    i. ~~There shall be written documentation of i~~Issues of donor health that pertain to the safety of the collection procedure shall be available to the collection staff. Collection staff shall document review of these issues prior to collection. (C6.3.5.1)

h. Hemodilution in the donor prior to collection of blood samples for infectious disease testing and acceptance criteria shall be assessed. (C6.4.2.1)

i. Collection staff shall confirm that allogeneic donor eligibility, as defined by Applicable Law, is determined by a ~~physician~~ licensed health care provider after history, exam, medical record review, and testing ~~within seven (7) days of collection~~before the donor begins the mobilization regimen, if mobilization is utilized. (C6.4.6)

j. There shall be policies covering the creation and retention of donor records including at a minimum: Age, gender, medical history, and, for allogeneic donors, behavioral history. (C6.5.3)

6. Coding and Labeling of Cellular Therapy Products.

    a. ~~Print-on-demand l~~Label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Medical Director ~~or designee~~. (C7.2.3)

    b. If cellular therapy products from the same donor are pooled, the identifier on the pooled product shall allow tracing to the original products. (C7.3.1.3)

    c. At all stages of collection, the cellular therapy product label shall minimally contain the proper name of the product and the unique numeric or alphanumeric identifier. (C7.4.1)

    d. Any container bearing a partial label at the time of distribution shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix I. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product. (C7.4.6)

e. For allogeneic cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after ~~the use of the product~~distribution of the cellular therapy product and that the physician using the product was informed of the results of that determination. (C7.4.7)

f. Cellular therapy products for third-party manufacturers shall be labeled with product labels that conform to FACT requirements or Applicable Law. (C7.4.8)

g. Cellular therapy products distributed for nonclinical purposes shall be designated and labeled as not for clinical use. (C7.4.9)

7. Process Controls.

a. There shall be a process for inventory control that encompasses equipment, containers for transport and shipping, supplies, reagents, and labels. (C8.2)
    i. Supplies and reagents shall be quarantined prior to use until verified to have met acceptance criteria. (C8.2.2.1)

b. Requirements for equipment management in the apheresis section were streamlined for clarity. (C8.3)
    i. There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration. (C8.3)
        - Equipment shall be maintained in a clean and orderly manner. (C8.3.1)
            - Cleaning shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations. (C8.3.1.1)
            - Equipment shall be inspected for cleanliness and documented to be clean prior to use. (C8.3.1.2)
        - ~~Equipment~~ Maintenance shall be ~~standardized and calibrated on a regularly scheduled basis and after a critical repair or move~~performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations. (C8.3.2)
            - The equipment shall be verified and documented to be in compliance with the maintenance schedule prior to use. (C8.3.2.1)

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. (C8.4)
    - Calibration shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations. (C8.4.1)
    - 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. (C8.4.2)

iii. Equipment, supplies, and reagents shall conform to Applicable Law. (C8.5)

c. Administration of appropriate mobilization agents if required shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents. (C8.7)

d. There shall be a written order from a physician specifying, at a minimum, an anticipated date and goals of collection. (C8.8)

e. Methods for collection shall employ procedures that minimize the risk of microbial contamination and are validated to result in acceptable cell viability and~~, if applicable, recovery~~ yield. (C8.9.1)

f. ~~Collection methods shall employ aseptic technique so that cellular therapy products do not become contaminated during collection. (C8.8)~~

g. Collection methods ~~for pediatric donors~~ shall employ appropriate age and size adjustments to the procedures when required. (C8.10)

h. Marrow products shall be filtered to remove particulate material prior to final packaging, distribution, or administration using filters that are non-reactive with blood. (C8.11) [Moved from section B]

8. Cellular Therapy Product Storage.

a. Storage areas shall be secure and controlled in a manner to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of cellular therapy products. (C9.1)

b. Conditions and duration of storage for all cellular therapy products shall be validated. (C9.2.1)

c. When collecting, storing, or releasing cellular therapy products for administration or further manufacturing, an expiration date and time shall be assigned. (C9.2.2)

9. Cellular Therapy Product Transportation and Shipping.

    a. ~~Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping~~The cellular therapy product shall be transported or shipped to the Processing Facility in a validated container within a temperature range defined in a Standard Operating Procedure or written agreement. (C10.3)

    b. The cellular therapy product shall be transported or shipped with required accompanying records as defined in the transportation and shipping Standard Operating Procedures and in compliance with C7.4.5 and C7.4.7. (C10.4.2)

    c. There shall be a record of the date and time of cellular therapy product distribution. (C10.5)

    d. The cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually. (C10.8)
        i. There should be a mechanism in place to notify the shipping facility if the shipping container was opened. (C10.8.1)

10. Records.

    a. Good documentation practices shall be defined and used. (C11.1.2)
        i. Records shall be accurate and legible. (C11.1.2.1)
        ii. Written records shall be indelible. (C11.1.2.2)

    b. Safeguards to secure the confidentiality of all records and communications among the collection staff, processing~~,~~ and clinical facilities, and health care providers and their recipients and donors~~,~~ shall be established and followed in compliance with Applicable Law. (C11.1.4)

    c. Validation studies for a collection procedure shall be retained for the duration of the use of the procedure. (C11.2.3)

    d. Recipient and ~~D~~donor records including, but not limited to, consents and records of care shall be maintained in a confidential manner as required by Applicable Law for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration of the product, whichever is latest. (C11.4)

e. ~~The collection staff shall furnish to the facility of final disposition a~~A copy of all cellular therapy product records relating to the collection procedure shall be furnished to the facility of final disposition. ~~performed related to the safety, purity, or potency of the cellular therapy product involved.~~ (C11.7.1)

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 ~~P~~processing ~~Facility~~ shall be in an appropriate location of adequate space~~,~~ and design to minimize the risk of airborne microbial contamination.~~, and location for the intended procedures~~. (D2.1.1)
      ii. The Processing Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy or genetically modified products. (D2.1.2)
      iii. There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of cellular therapy products. (D2.1.3)

   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 ~~of the cellular therapy product~~. (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 [for the Processing Facility Director and the Processing Facility Medical Director] shall include, but is not limited to, activities related to cellular therapy product processing or the applicable therapeutic disease area. (D3.1.3.1, D3.2.3.1)

    b. Continuing education [for the Processing Facility Quality Manager] shall include, but is not limited to, activities related to cellular therapy, cell processing, and Quality Management. (D3.3.3.1)

4. Policies and Standard Operating Procedures.

    a. The following changes were made to the required aspects of operations and management that must be addressed in policies or Standard Operating Procedures: (D5)
        i. Appropriate processing procedures for specific products, including cryopreservation and thawing. (D5.1.3.1)
        ii. Packaging, ~~T~~transportation, and shipping, including methods and conditions within the Processing Facility and to and from external facilities. (D5.1.11)

5. Equipment, Supplies, and Reagents.

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

    b. Lot-to-lot functional verification shall include acceptance criteria to confirm that new lots perform as expected compared to the previous lots. (D6.3.4.3)

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 l~~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. If the original identifier is replaced, documentation shall link the new identifier to the original. (D7.3.1.6)

d. At all stages of processing, the cellular therapy product shall be labeled with the proper name of the product and the unique numeric or alphanumeric identifier, at a minimum. (D7.4.1)

e. Cellular therapy products from third-party manufacturers shall be labeled with product labels that conform to Applicable Law. (D7.4.8)

f. Cellular therapy products distributed for nonclinical purposes shall be designated and labeled as "not for clinical use." (D7.4.9)

7. Process Controls.

a. Preparation for administration of cellular therapy products manufactured by third parties, ~~If the Processing Facility~~ 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.~~ (D8.4.3)
    i. The Processing Facility should verify the~~processing~~ preparation procedures utilizing practice ~~products~~ materials similar to the cellular therapy product intended for administration when feasible. (D8.4.3.1)
    ii. If relabeling of prepared third-party products is required, the label shall follow Applicable Law. (D8.4.3.2)

b. Critical calculations shall be verified and documented where appropriate. (D8.6)

c. Processing using more-than-minimal manipulation shall only be performed ~~with Institutional Review Board or Ethics Committee approval, with the written informed consent of the donor, if applicable, and the recipient of the cellular therapy product, and in compliance with Applicable Law~~in accordance with institutional policies and Applicable Law and with the written informed consent of the donor, if applicable, and the recipient of the cellular therapy product. (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)

d. One or more retention samples representing the cryopreserved cellular therapy product shall be stored under conditions that achieve a valid representation of the clinical product and in accordance with institutional Standard Operating Procedures. (D8.14)

8. Cellular Therapy Product Storage.

    a. Processing and storage ~~F~~facilities shall be secured and controlled ~~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. All cellular therapy products with positive infectious disease test results for relevant communicable disease agents or positive microbial cultures shall be quarantined. Disposition shall be documented. (D9.4.3.2)

9. Cellular Therapy Product Transportation and Shipping.

    a. Cellular therapy products transported internally shall be packaged in a qualified, closed, and protective outer container. (D10.6)
        i. The outer container for internal transport shall be labeled as defined in Appendix II B. (D10.6.1)

10. Records.

    a. Safeguards to secure the confidentiality of all records and communications between the collection staff, processing facilities, ~~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. The Processing Facility shall define and follow good documentation practices. (D13.2)

    c. 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 ~~by the Processing Facility, or longer in accordance with~~after the creation of the cellular therapy product record or date of the cellular therapy product's distribution, disposition, or expiration, whichever is latest, or according to Applicable Law. (D13.4.1)
        i. Validation study records for a processing procedure shall be retained for a minimum of ten (10) years after distribution of the final products manufactured using that procedure. (D13.4.1.3)

d. Records to allow tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after administration, distribution, disposition, or expiration of the cellular therapy product~~after final distribution of the product~~, or as required by Applicable Law. These records shall include collection and processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product ~~identity~~code, and donor and recipient information as known. (D13.4.2)

e. All records pertaining to the processing, testing, storage, or distribution of cellular therapy products shall be maintained for a minimum of ten (10) years after the date of administration, or if the date of administration is not known, then 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 most recent, or according to Applicable Law or institutional policy, whichever is latest. (D13.4.3)

f. Research records shall be maintained in a confidential manner as required by Applicable Law or for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest. (D13.4.4)

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

11. Appendix I: CELLULAR THERAPY PRODUCT LABELING

    Multiple updates were made to the cellular therapy labeling requirements to be harmonized with ISBT 128 labeling and to clarify requirements for partial labels at distribution for administration. Consult the table for the full details.

12. Appendix II
    B: CELLULAR THERAPY PRODUCT LABELS FOR INTERNAL TRANSPORT

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

AF=Affix