FOUNDATION FOR THE ACCREDITATION OF CELLULAR THERAPY

Summary of Changes

Third Edition FACT Common Standards for Cellular Therapies

The *FACT Common Standards for Cellular Therapies, Third Edition* has been revised and updated to keep pace with the changing field of cellular therapy and maintain consistency with *FACT-JACIE International Standards for Hematopoietic Cellular Therapy, Eighth Edition*. This document summarizes the major changes, but not all changes. Reorganization or clarified verbiage is not included unless considered to be a significant change in the intent of a standard.

To clearly identify new requirements, additions to the Standards have been underlined, and some changes to existing standards have been redlined. Refer to the Standards for all revisions.

MAJOR CHANGES

1. **Tenet.**
   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 definition of "designee" is not changed from the second edition, but the term "or designee" was removed from individual standards throughout the document.

   > A2.2 Any activity can be delegated to a designee as that term is defined. The person appointing a designee retains ultimate responsibility.

2. **Definitions**
   The following definitions were added or revised in conjunction with changes to the Standards.

   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 permit tracking and tracing required by the Standards. These concepts are critical to the field of cellular therapy and facilities that will be accredited under these standards, as collection of cellular starting material, manufacturing of final product, and administration often involve several entities and personnel in different locations.

   Chain of identity [new definition]: 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 [new definition]: 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 [new definition]: 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 [new definition]: Assessment of the presence of allogeneic donor cells in a cellular therapy product recipient using any assay of informative genetic markers that distinguishes donor from recipient cells.

c. *Circular of information* [new definition]: An extension of container labels that includes the use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations. An investigator's brochure or package insert may contain this information.

d. *Continuum of care* [new definition]: The delivery of health care over a period of time. In patients with a disease, this covers all phases of illness from diagnosis to the end of life.

e. *Genetically modified cell* [new definition]: A cell that has been modified by genetic transfer for therapeutic intent.

f. *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.

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 of GxP 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 (C4.4.2.5, D4.4.2.5).

> C4.4.2.5, D4.4.2.5 Annual training in applicable current GxP appropriate to the processes performed in accordance with Applicable Law.

Good Manufacturing Practice (GMP) [revised definition]: 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 more-than-minimally ~~extensively~~ 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) [new definition]: 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 donor screening and testing, processing, storage, labeling, packaging, and distribution.

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

h. *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.

i. *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*

ISBT 128 provides a comprehensive and highly flexible system for describing products and assigning product codes. Proper terminology was required by the second edition of Common Standards. 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 collected or manufactured by the organization seeking accreditation must comply with this requirement.

a. New Standards related to ISBT 128 Coding and Labeling:

i. C7.1, D7.1 ISBT CODING AND LABELING

C7.1.1, D7.1.1 Cellular therapy products shall be identified by name according to ISBT 128 standard terminology.

C7.1.2, D7.1.2 Coding and labeling technologies shall be implemented using ISBT 128.

ii. Additional labeling changes are described in Collection and Processing sections.

b. New Definitions related to ISBT 128 Coding and Labeling:

i. *Product code* [new definition]: An eight-character ISBT 128 code that comprises the Product Description Code, a Collection Type Code, and a Division Code. The product code unambiguously describes the cellular therapy product, ensuring that it is consistently and globally understood.

ii. *Product Name* [new definition]: 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, cord blood, or other tissue.

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.

For the current list of cellular therapy products and definitions, see *ST-002 ISBT 128 Standard Terminology for Medical Products of Human Origin*, available at www.isbt128.org/standard-terminology.

4. **Genetically modified cells.**
   Due to increasing availability and use of genetically modified cellular therapy products in FACT-accredited and applicant 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 (IBC) requirements that addresses genetically modified products in compliance with Applicable Law. (D2.9)

   c. Processing Facilities utilizing genetically modified cellular therapy products shall incorporate or reference institutional or regulatory requirements related to the disposal of genetic material. (D5.1.18.1)

5. **Histocompatibility: 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

Throughout the Standards, Quality Management Standards have been revised and updated to reflect the evolution of the cellular therapy field and harmonized across all sections – Clinical, Collection, and Cell Processing. The following are the major changes and additions to Quality Management Standards:

Organizational Structure

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

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

   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, C4.3.2)

3. [The document control system shall include:] Review of controlled documents every two (2) years at a minimum. (B4.5.3.5, C4.5.3.5, D4.5.3.5)

Agreements

4. Agreements should include the responsibility of the external parties to provide clinically relevant information related to products or services. (B4.6.2.1)

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)

Outcome Analysis

Previous editions of the FACT Common Standards have included the general requirement to determine criteria and review individual and aggregate data to assess product efficacy and clinical outcomes. In this edition, requirements for outcome analysis are harmonized across the sections and can be fulfilled collaboratively.

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 collection, processing, or distribution of the cellular therapy product. (C4.7.4; D4.7.4)

Audits

Qualifications for auditors were revised to better define the competencies needed, including knowledge of the process being audited but not necessarily the technical expertise to perform it. The audit schedule was revised to annual at a minimum, and the minimal items to be audited was harmonized across the sections.

9. 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)

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

    a. ~~Periodic audit of the~~ Accuracy of clinical data. (B4.8.3.1)

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

c. ~~Annual audit of~~ Management of cellular therapy products with positive microbial culture results. (B4.8.3.3; new in C4.8.3.2 and D4.8.3.1)

d. ~~Annual audit of~~ Chain of identity and chain of custody of cellular therapy products. (B4.8.3.6, C4.8.3.5, D4.8.3.4)

e. ~~Annual audit of~~ Infectious disease resulting from cellular therapy product collection or administration. (B4.8.3.4, new in C4.8.3.3, D4.8.3.2)

11. There shall be policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency. (B4.8.4, C4.8.4, D4.8.4)

Positive Microbial Cultures

The responsibilities have been harmonized.

12. 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~~ and responsibility for the following activities at a minimum: (B4.9, C4.9, D4.9)

    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 ~~and outcome analysis~~. (B4.9.3; new to C4.9.2, D4.9.6)

    d. Follow-up of the donor, if relevant. (B4.9.4, C4.9.3; new to D4.9.7)

Occurrences

13. 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)

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

Qualification

15. 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. (B4.13, C4.13, D4.13)

    a. Qualification plans shall include minimum acceptance criteria for performance. (B4.13.1, C4.13.1, D4.13.1)

    b. Qualification shall be required following any significant changes to these items. (B4.13.2, C4.13.2, D4.13.2)

    c. Reagents that are not the appropriate grade shall undergo qualification for the intended use. (D4.13.2; new in C4.13.4)

Validation

16. Critical procedures to be validated shall include at least collection procedures, labeling, storage, ~~and~~ distribution, preparation for administration, and administration. (B4.14.1)

17. Critical procedures to be validated shall include at least 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: (B4.14.2, C4.15.2, D4.14.2)

Change Control

18. 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~~ confirm that the changes do not create an adverse impact or inherent risk elsewhere in the operation. (Change in D4.15 only; B4.15 and C4.15 are unchanged from the second edition)

    a. Evaluation of risk shall be completed for changes in critical procedures. (B4.15.1, C4.15.1, D4.15.1)

Quality Review

19. 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. (B4.16, C4.16, D4.16)

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

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

c. The Clinical Program Director/[Collection] Medical Director/Processing Facility Director ~~or designee~~ shall not ~~have oversight of~~ approve their own work. ~~if this person also performs other tasks in the Clinical Program.~~ (B4.16.3, C4.16.3, D4.16.3)

20. The Clinical Program Director/[Collection] Medical Director/Processing Facility Director ~~or designee~~ shall annually review the effectiveness of the overall Quality Management Program. (B4.17, C4.17, D4.17)

    a. The annual report and documentation of the review findings shall be made available to key personnel, the Clinical Program Director, Collection Services Director and personnel, the Processing Facility Director, and staff of the program. (B4.17.1, C4.17.1, D4.17.1)

CHANGES TO CLINICAL PROGRAM STANDARDS

General

The scope of the Standards is defined and broadened.

1. These Standards apply to all cellular therapy services provided by the Clinical Program. (B1.1.1)

    a. 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)

Clinical Unit

2. 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, radiological, electrical, or fire hazards. (B2.10)

Personnel

Changes made to this section provide clarity and update the requirements as the field evolves. Only major changes and significant additions are listed.

3. 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 minimum.~~ (B3.1.5.2)

4. Continuing education hours were not changed, but the content of the continuing education is defined.
    a. 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. (B3.1.6.1, B3.2.5.1, B3.5.3.1) Quality Managers shall also participate in continuing education related to cellular therapy, cell collection, ~~and~~ or quality management. (B3.9.2)

5. Training for Clinical Program Directors and Attending Physicians (B3.3)
    a. Specific training in each of the following areas as applicable to the Clinical Program's services:
        i. Donor selection, evaluation, and management. (B3.3.1.3)
        ii. Donor and recipient informed consent. (B3.3.1.4)
        iii. Administration of cellular therapy products and ~~patient management~~ anticipated complications. (B3.3.1.5)
        iv. Administration of preparative regimen. (B3.3.1.6)
        v. Reporting responsibilities for adverse events ~~associated with cellular therapy~~ according to Applicable Law. (B3.3.1.12)
    b. 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:
        i. Methodology and implications of testing for chimerism. (B3.3.2.4)
    c. The attending physicians shall be knowledgeable in the following procedures for cellular therapy products: (B3.3.3)
        i. Shipping and transportation. (B3.3.3.4)
        ii. Storage. (B3.3.3.5)

6. Nurses shall be trained in age-specific management of patients receiving cellular therapy. (B3.6.1.1) [Replaces specific requirements for pediatric and adult medicine training].

7. Designated staff shall include data management staff. (B3.10.1.1)

Policies and Standard Operating Procedures

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

e. Clinical Programs utilizing genetically modified cells shall incorporate or reference institutional or regulatory requirements related to biosafety, including disposal. (B5.1.13.1)
f. Response to emerging disease agents, including recipient care, donor evaluation and management, and personnel safety. (B5.1.15)
g. Each individual SOP shall include: (B5.3) A description of equipment, reagents, and supplies used. (B5.3.2)

Donor Selection, Evaluation, and Management

9. [Informed consent shall include] Intent of the collection for treatment or research. (B6.2.1.2)

10. Family members and legally authorized representatives ~~should~~ shall not serve as interpreters or translators. (B6.2.2.1)

11. The donor shall have the right to refuse to donate or withdraw consent ~~at any time~~. (B6.2.4)
    a. The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal ~~or withdrawal~~ in the event that consent is withdrawn after the recipient has begun the preparative regimen. (B6.2.4.1)

12. Donor informed consent for the cellular therapy product donation shall be obtained and documented by a licensed health care professional familiar with the collection procedure and intended use of the product. (B6.2.5)

13. For directed cellular therapy product donations, informed consent of the recipient for the cellular therapy shall be obtained before cellular therapy product collection. (B6.2.6)

14. A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to cellular therapy product collection, undergoing anesthesia, and as applicable, within seven (7) days prior to the preparation of the recipient for administration. (B6.3.3)

    a. For collection with mobilization, a pregnancy test shall be performed within seven (7) days prior to the initiation of the mobilization regimen. (B6.3.3.1) (Standard clarified)

15. Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, certified, or licensed in accordance with Applicable Law. (B6.3.4)

16. [The medical history for allogeneic donors shall include]: (B6.4.6) Questions to identify persons at increased risk of transmitting ~~inherited conditions~~ hematologic, immunologic, or genetic conditions. (B6.4.6.5)

17. Blood samples for testing for evidence of clinically relevant infection shall be ~~obtained~~ drawn and tested within timeframes required by Applicable Law. (B6.4.9)

18. When appropriate for the cellular therapy product, allogeneic donors and recipients shall be tested for HLA loci determined by the Clinical Program Director to be of importance to the cellular therapy product by a laboratory accredited by ASHI, EFI, CAP, or other appropriate organization. (B6.4.12)

19. 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)

20. 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 is prepared for administration and before the allogeneic donor begins the mobilization regimen, if applicable. (B6.4.13)

21. The use of an ineligible allogeneic donor, or an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of urgent medical need that includes the rationale for ~~his/her~~ the selection ~~by the administering physician, urgent medical need documentation,~~ and documentation of the informed consent of the donor and the recipient. (B6.4.15)

Recipient Care

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

23. For directed cellular therapy product donations, informed consent of the recipient for the therapy shall be obtained before the product collection. (B7.1.2)

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

25. ~~Cellular therapy products shall be filtered to remove particulate material prior to administration using filters that are non-reactive.~~ (B7.5.2)
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)

26. A circular of information or Investigator's Brochure for cellular therapy products shall be available to staff. (B7.5.4)

Clinical Research

27. Clinical research protocols shall be performed in accordance with institutional policies and Applicable Law. (B8.2), including:
    a. The Clinical Program shall maintain: (B8.2.1)
        i. If applicable, documentation of approval by the Institutional Biosafety Committee (IBC) or equivalent. (B8.2.1.2)
        ii. 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):
        i. Contact information for the person research subjects can contact in case of questions or concerns. (B8.3.2.6)

Data Management

28. 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 Minimum Essential Data A forms of the EBMT~~ Cellular Immunotherapy Data Resource (CIDR) forms, Cellular Therapy Med-A forms, or other appropriate forms of the EBMT. (B9.1)

Records

29. 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)

30. 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 SERVICES STANDARDS

General

Standards for Collection Services were revised to increase the scope of collection services, reflective of the evolution of the cellular therapy field. Criteria for initial FACT accreditation have been added consistent with FACT-JACIE Hematopoietic cell Standards and appropriate to the field.

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

2. 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)

3. 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)

4. 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)

Collection ~~Activities~~ Environment

More robust environmental requirements have been added to collection standards to reflect maturation of the cellular therapy field but allow flexibility depending on the cells or tissue being collected. A controlled environment, including appropriate oversight, is required for safe collection of cellular therapy products used for administration or as starting material for further manufacturing.

5. 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)
    a. There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination. (C2.1.2)

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

7. 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)

8. 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)

9. 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)
    a. 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)

Policies and Standard Operating Procedures

The following changes were made to the required aspects of operations and management that must be addressed in policies or Standard Operating Procedures (C5):

10. Donor informed consent for cellular therapy product collection, processing and manufacturing, storage, distribution, and disposition. (C5.1.2)

11. Donor screening, testing, eligibility and suitability determination, and management. (C5.1.3)

12. Management of donors who require central venous access. (C5.1.4)

13. Packaging, transportation, and shipping. (C5.1.11)
    a. Use of additives for long duration of shipment. (C5.1.11.2)

14. Critical equipment, reagent, and supply management, including recalls and corrective actions in the event of failure. (C5.1.12)

15. Response to emerging disease agents, including donor evaluation and management and personnel safety. (C5.1.18)

16. [Each individual SOP shall include]: A description of equipment, reagents, and supplies used. (C5.3.2)

17. Staff review and, if appropriate, training and competency shall be documented before performing a new or revised Standard Operating Procedure. (C5.5)

Allogeneic and Autologous Donor Evaluation and Management

18. [Informed Consent]. The collection procedure shall be explained in terms the donor can understand and shall include the following information at a minimum: (C6.2.1)
    a. Intent of the collection for treatment or research. (C6.2.1.2)

19. Family members and legally authorized representatives ~~should~~ shall not serve as interpreters or translators. (C6.2.2.1)

20. The donor shall have the right to refuse to donate or withdraw consent ~~at any time~~. (C6.2.4)
    a. The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal ~~or withdrawal~~ in the event that consent is withdrawn after the recipient has begun the preparative regimen. (C6.2.4.1)

21. Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional ~~familiar with~~ knowledgeable in the collection procedure and intended use of the product. (C6.2.5)

22. For directed cellular therapy product donations, informed consent of the recipient for the cellular therapy shall be obtained before cellular therapy product collection. (C6.2.6)

23. 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. (New to C6.2.9; related Standard B6.2.9)

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

25. 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)

26. Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for ~~his/her~~ their selection by the administering physician and approval by the Medical Director. (C6.3.5)

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

28. 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)

29. There shall be policies covering the creation and retention of donor records including at a minimum (C6.5):
    a. Age, gender, medical history, and, for allogeneic donors, behavioral history. (C6.5.3).

Coding and Labeling of Cellular Therapy Products

30. A system of label reconciliation shall be used to ensure the final disposition of all labels allocated to a specific product is documented. (C7.2.3)

31. ~~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~~. (C7.2.4)

32. 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)

33. If the original identifier is replaced, documentation shall link the new identifier to the original. (C7.3.1.6)

34. At all stages of collection, the cellular therapy product shall be labeled with the proper name of the product and the unique numeric or alphanumeric identifier at a minimum. (C7.4.1)

35. 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)

36. 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)

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

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

Process Controls

39. There shall be a process for inventory control that encompasses equipment, containers for transport and shipping, supplies, reagents, and labels. (C8.2)
    a. Supplies and reagents shall be quarantined prior to use until verified to have met acceptance criteria. (8.2.2.1)

Process Controls: Comprehensive equipment management

Requirements have been added and streamlined for clarity.

40. There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration. (C8.3)
    a. Equipment shall be maintained in a clean and orderly manner. (C8.3.1)
        i. 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)
        ii. Equipment shall be inspected for cleanliness and documented to be clean prior to ~~each~~ use. (C8.3.1.2)

b. Maintenance shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations. (C8.3.2)
    i. The equipment shall be ~~inspected for cleanliness and~~ verified and documented to be in compliance with the maintenance schedule prior to ~~each~~ use. (C8.3.2.1)

41. 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)
    a. ~~Equipment shall be standardized and calibrated on a regularly scheduled basis and after a critical repair or move~~ 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)
    b. 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)

42. Equipment, supplies, and reagents for the collection procedure shall conform to Applicable Law. (C8.5)

Process Controls. Donor and collection: Processes have been expanded.

43. 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)

44. Methods for collection shall employ ~~aseptic technique~~ 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)

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

46. ~~Cellular therapy~~ 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) [Revised and moved from B7.5.2]

Cellular Therapy Product Storage and Transportation

New specific requirements have been added to product storage. Standards for transportation and shipping have been revised to distinguish between internal transport within a facility and transport on public roads.

47. 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)

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

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

50. The cellular therapy product~~s that require a temperature-controlled environment and that are transported or shipped over an extended period of time~~ shall be transported or shipped to the Processing Facility in a validated container within ~~the appropriate~~ a temperature range defined in a Standard Operating Procedure or written agreement. (C10.3)

51. Cellular therapy products that are transported or shipped ~~to another facility or transported on public roads~~ from the collection site to a processing facility ~~on public roads~~ shall be ~~packaged~~ in an outer container made of material adequate to withstand leakage of contents, impact shocks, pressure changes, temperature changes, puncture, and other conditions incident to ordinary handling. (C10.3.1)

52. 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 C7.4.6. (C10.4.2)

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

54. Cellular therapy products transported internally shall be packaged in a qualified, closed, and protective outer container. (C10.6)
    a. The outer container for internal transport shall be labeled as defined in Appendix II B. (C10.6.1)

55. A mechanism should be in place to allow detection if the shipping container was opened. If opened, the shipping facility should be notified. (C10.10)

Records

56. Good documentation practices shall be defined and used. (C11.2)

57. Validation studies for a collection procedure shall be retained for the duration of the use of the procedure. (C11.5.3)

58. 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. (C11.7)

59. ~~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~~s~~ shall be furnished to the facility of final disposition. ~~performed related to the safety purity, or potency of the cellular therapy product involved.~~ (C11.10.1)

CHANGES TO PROCESSING FACILITY STANDARDS

Similar to the Collection section (C1.1), the Standards have been broadened to include cellular therapy products obtained from cadaveric donors, although not all standards that may apply to cadaveric donors are included in these Standards.

General

1. 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)

Processing Facility

Processing Facility standards have been reorganized, expanded, and clarified to include the rationale for the Standard.

2. There shall be secured and controlled access to designated areas for the processing procedure and for storage of equipment, supplies, and reagents. (D2.1)
    a. The designated area for processing shall be in an appropriate location of adequate space and design to minimize the risk of airborne microbial contamination. (D2.1.1)

3. There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of cellular therapy products. (D2.1.3)

4. 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)

5. 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.~~ (D2.5)

6. 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, radiological, electrical, or fire hazards. (D2.8)

7. There shall be a biosafety plan consistent with the Institutional Biosafety Committee (IBC) requirements that addresses genetically modified products in compliance with Applicable Law. (D2.9)

Personnel

8. 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)

9. 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)

Policies and Standard Operating Procedures.

The following issues that must be addressed in policies or Standard Operating Procedures were added: (D5)

10. Appropriate processing procedures for specific cellular therapy products, including cryopreservation and thawing. (D5.1.3.1)

11. Packaging, transportation, and shipping, including methods and conditions within the Processing Facility and to and from external facilities. (D5.1.10)

12. Critical equipment, reagent, and supply management, including recalls and corrective actions in the event of failure. (D5.1.13)

13. Processing Facilities utilizing genetically modified cellular therapy products shall incorporate or reference institutional or regulatory requirements related to the disposal of genetic material. (D5.1.18.1)

14. Response to emerging disease agents, including donor evaluation, product assessment and labeling, and personnel safety. (D5.1.20)

15. [Each individual Standard Operating Procedure shall include:] A description of equipment, reagents, and supplies used. (D5.3.2)

Equipment, Supplies, and Reagents

16. 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)

Coding and Labeling

17. 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)

18. ~~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)

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

20. 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)

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

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

Process Controls

23. ~~If the Processing Facility lacks experience with the type of cellular therapy product requested for a recipient, personnel shall obtain~~ Preparation for administration of cellular therapy products manufactured by third parties shall follow the instructions provided by the manufacturer. (D8.4.3)
    a. If relabeling of prepared third-party products is required, the label shall follow Applicable Law. (D8.4.3.2)

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

25. Documentation of the approvals by the Institutional Review Board, Ethics Committee, or equivalent and the Institutional Biosafety Committee or equivalent shall be maintained. (D8.12.1)

Cellular Therapy Product Storage

26. Processing and storage facilities shall be secured and controlled to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products. (D9.1)

27. Conditions and duration of storage of all cellular therapy products shall be validated. (D9.2.1)

28. 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)

Cellular Therapy Product Transportation and Shipping

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

30. A mechanism should be in place to allow detection if the shipping container was opened. If opened, the shipping facility should be notified. (D10.10)

Records

31. The processing facility shall define and follow good documentation practices. (D13.2)

32. Safeguards to secure the confidentiality of all records and communications among 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. (D13.4)

33. The Processing Facility shall define and follow good documentation practices. (D13.2)

34. 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. (D13.6.1)

35. 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. (D13.6.1.3)

36. Records to allow tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after administration, ~~final~~ distribution, disposition, or expiration of the cellular therapy 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. (D13.6.2)

37. 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. (D13.6.4)

38. The Processing Facility shall ~~furnish~~ provide to the facility of final disposition a ~~copy~~ summary 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. (D13.7.2)

Appendix I: CELLULAR THERAPY PRODUCT LABELING

39. Appendix I

    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.

40. Appendix II

    Appendix II is new to define labeling requirements for internal transport of cellular therapy products.

    B: CELLULAR THERAPY PRODUCT LABELS FOR INTERNAL TRANSPORT

    Each container for internal transport shall include an internal transport label with at least the elements detailed in the following table:

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