

7th Edition *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*

Summary of Changes

This document summarizes the major changes made to the 7th edition of the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*. This summary does not list all changes made to the Standards; reorganization or clarified verbiage is not included unless considered to be a significant change. Refer to the final Hematopoietic Cellular Therapy Standards and the accompanying Accreditation Manual for all requirements.

Global Changes

1) Terminology

- a) The term “occurrence” was added to the 7th edition FACT-JACIE Standards. Occurrence has been defined as an instance in which an action or circumstance results in errors, accidents, deviations, adverse events, adverse reactions, or complaints. Where appropriate throughout the Standards, the generic term “occurrences” replaces “errors, accidents, deviations, adverse events, adverse reactions, or complaints.”
- b) To provide clarity, the term “planned deviation” was introduced to replace “variance”. Planned deviation is defined as an action allowed to occur with documented approval as the best course of action when adherence to the established course or accepted practice was not feasible or possible.

2) Quality Management (QM)

The 7th edition FACT-JACIE Standards Committee included a subcommittee dedicated to reviewing QM sections. In addition to revising standards to explicitly and consistently state requirements, the following changes were made:

- a) Additional document control system requirements include:
 - i. Review of all controlled documents every two years at a minimum. (B/C/D4.5.3.5)
 - ii. A version number and communication or training on the change as applicable. (B/C/D4.5.3.6)
- b) Written agreements must be reviewed on a regular basis, at least every two years. (B/C/D4.6.3)
- c) Additional required audits include:
 - i. Annual audit of documentation that external facilities performing critical contracted services have met the requirements of the written agreements. (B4.8.3.5, C4.8.3.4, D4.8.3.2)
 - ii. Periodic audit of the prescription ordering system against the protocol. (B4.8.3.7)
 - iii. Annual audit of documentation of interim assessment of donor suitability and eligibility prior to the start of the collection procedure. (C4.8.3.1)
 - iv. Annual audit of management of cellular therapy products with positive microbial culture results. (C4.8.3.3)

- d) Additional requirements for qualification include:
 - i. The Clinical Program's QM Plan must include policies and Standard Operating Procedures (SOPs) for qualification of critical manufacturers, vendors, equipment, supplies, reagents, facilities, and services. (B4.13)
 - ii. Qualification plans must include minimum acceptance criteria for performance. (B/C/D4.13.2)
 - iii. Qualification plans, results, and reports must be reviewed and approved by the Quality Manager and Clinical Program Director or designee. (B/C/D4.13.3)
- e) Risks in changes to a process must be evaluated to confirm the changes do not create an adverse impact or inherent risk elsewhere in the operation. In previous editions, the inclusion of such evaluation was limited to validation studies. (B/C/D4.15)
- f) Feedback must be obtained from associated programs and/or facilities in addition to donors and recipients or legally authorized representatives. This feedback may be obtained directly by the Clinical Program, Collection Facility, or Processing Facility; however, it is also acceptable to use hospital-wide systems provided that issues relevant to the cellular therapy program can be readily identified. (B/C/D4.16.1)
- g) QM activities must be reported, quarterly at a minimum, to representatives in key positions in all elements of the cellular therapy program to review the performance of the QM Program and its objectives. Meetings should have defined attendees, documented minutes, and assigned actions. Key performance data and review findings must be reported to staff. (B/C/D4.17)
- h) Findings from the annual review of the effectiveness of the QM Program must be made available to key personnel and appropriate Clinical Program and Facility Directors. (B/C/D4.18)

3) *ISBT 128 and Eurocode*

- a) Full Implementation (CM/C/D7.1.2, Appendix II)

The 6th edition FACT-JACIE Standards required that facilities be actively implementing ISBT 128 at a minimum. The 7th edition Standards requires that ISBT 128 or Eurocode be fully implemented. Appendix II was updated to convey requirements specific to both ISBT 128 and Eurocode. A detailed list of changes to the Appendix is below.

- b) Partial Label at Distribution for Administration (CM/C/D7.4.1, CM/C/D7.4.6)

The 7th edition Standards redefined the partial label as a label used only at the time of distribution for administration. A partial label must only be used if there are size constraints; otherwise, a full label must be applied.

For in-process identification of cellular therapy products, the 7th edition requires that, at a minimum, the product be labeled with the proper name of the product and the unique numeric or alphanumeric identifier at all times. Before distribution to another entity, the product must be labeled with a full label or a partial label that meets the requirements listed in Appendix II.

c) Changes to Appendix II Cellular Therapy Product Labeling

The changes are in red and bold font.

Each label shall include at least the elements detailed in the following table¹:

Element ²	Label at completion of collection	Label at completion of processing	Partial label at distribution for administration ⁴	Label at distribution for administration
Unique numeric or alphanumeric identifier ³	AF	AF	AF	AF
Proper name of product ^{5,6}	AF	AF	AF	AF
Product code ⁵	AF	AF	AF	AF
Product attributes ⁵	AC	AC	AC	AF
Recipient name and/or identifier	AT	AT	AC	AT
Identity and address of collection facility or donor registry	AT	AC	AC	AC
Date, time collection ends, and (if applicable) time zone	AT	AC	AC	AC
Approximate volume	AF	AF	AF	AF
Name and quantity of anticoagulant and other additives	AF	AF	AF	AF
Recommended storage temperature range	AF	AF	AF	AF
Donor identifier and (if applicable) name	AT	AT	AC	AF
Biohazard and/or Warning Labels (as applicable, see CM7.4, C7.4, D7.4).	AT	AT	AC	AT
As applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES"	AT	AT	AC	AT
Statement "WARNING: Advise Patient of Communicable Disease Risks"	AT	AT	AC	AT
Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"	AT	AT	AC	AT
Identity and address of processing and distribution facility(ies)		AC	AC	AC
Statement "Do Not Irradiate"		AT	AC	AF
Expiration Date (if applicable)		AC	AC	AF
Expiration Time (if applicable)		AC	AC	AC
ABO and Rh of donor (if applicable)		AC	AC	AC
RBC compatibility determination (if applicable)			AC	AC
Statement indicating that leukoreduction filters shall not be used			AC	AF
Statement "FOR AUTOLOGOUS USE ONLY" (if applicable)	AT	AT	AC	AF
Date of distribution			AC	AC

AF=Affix, AT=Attach or Affix, AC=Accompany, Attach or Affix

¹Container and full package labeling requirements for licensed products or products under Investigational New Drug (IND) application shall follow applicable laws and regulations. In the U.S., see 21 CFR 312.6(a).

²Full implementation of ISBT 128 labeling requires compliance with the ISBT 128 Standard for the location of information on the label and/or the accompanying documentation.

³Overlay labels for supplementary identifiers shall not obscure the original identifier.

⁴A partial label at distribution is a label that because of the size of the product container or other constraints, does not contain all of the required information.

⁵Product proper names and attributes must be identified in words, and are listed in Chapter Three of the ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. Available at: www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology. This includes all potential attributes, in addition to the core attribute referenced in this table (Anticoagulant, Volume, Storage Temperature): Intended Use, Manipulation, Cryoprotectant, Blood Component from Third Party Donor, Preparation, Genetically Modified, Irradiation, Modification, Mobilization, Pooled Single, Cultured, Enrichment, and Reduction.

⁶Proper name of product is also referred to as class name in the ISBT 128 Standard Terminology.

4) *Additional Changes to Promote Consistency*

- a) The following requirements from the Processing Facility Standards are now explicitly stated in the Clinical Program and Collection Facility Standards:
 - i. All medical waste must be discarded in a safe manner according to written protocols for the disposal of biohazard waste and in accordance with applicable governmental laws and regulations. (B2.18, CM2.10, C2.11)
 - ii. Gloves and protective clothing must be worn while handling biological specimens. To prevent the spread of hazardous substances, personal protective equipment must be removed before leaving the workspace. (B2.19, CM2.11, C2.12)
 - iii. Cleaning and sanitation records must be retained for a minimum of three (3) years or longer in accordance with applicable laws or regulations. (B10.1.2, C11.3.2)
- b) The following requirements from the Apheresis Collection Facility Standards are now explicitly stated in the Marrow Collection Facility Standards:
 - i. The Marrow Collection Facility shall comply with B6.4.6 through B6.4.6.8 when primarily responsible for donor screening for transmissible disease. (CM6.4.3)
 - ii. The Marrow Collection Facility shall comply with B6.4.7 through B6.4.11 when primarily responsible for infectious and non-infectious disease testing of HPC donors. (CM6.4.4)
 - iii. The Marrow Collection Facility shall comply with B6.4.3, B6.4.4, and B6.4.12 through B6.4.12.4 when primarily responsible for testing for the selection of allogeneic donors. (CM6.4.5)

Changes to Clinical Program Standards

1) *Products from Third-Parties (B1.2.1)*

- a) Version 6.1 of the Standards introduced the Clinical Program's responsibilities when they directly receive a cellular therapy product for administration from a third-party. The 7th edition Standards clarify this is required when a program receives the product directly from the manufacturer or when it is routed through an intermediary facility such as a blood bank, tissue bank, or hospital pharmacy. Additional responsibilities as required by the 7th edition include:
 - i. Review and verification of product specifications provided by the manufacturer, if applicable;
 - ii. Readily available access to a summary of documents used to determine allogeneic donor eligibility; and
 - iii. Documented evidence of donor eligibility screening and testing in accordance with applicable laws and regulations.

2) *Clinical Unit (B2.4 and B2.5)*

- a) Cleaning and sanitation requirements for Clinical Programs are clarified in the 7th edition. The Clinical Program must document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations. If documentation of cleaning and sanitation is performed directly by the institutional environmental services department, the Clinical Program must have knowledge of this documentation and the ability to demonstrate that cleaning and sanitation was completed. (B2.4)
- b) There must be adequate equipment and materials for the procedures performed. (B2.5)

3) *Training and Competency in the Clinical Program*

- a) Competency and training requirements were reorganized for the Clinical Program Director and attending physicians. The following training requirements have been added: (B3.3.4)
 - i. Blood transfusion management.
 - ii. Use of irradiated blood products.
 - iii. Age-specific donor and recipient care.
- b) Age-specific considerations was added to the requirements for nursing procedures. (B3.7)
- c) Training and knowledge for designated pharmacists was expanded to include adverse events, including but not limited to, cytokine release syndrome and neurologic toxicities. (B3.8)
- d) Defined data management staff should participate in continuing education annually. (B9.3.1)

4) *Clinical Outcomes (B4.7.6)*

In addition to the requirement to meet one-year survival expectations, the Clinical Program should also set benchmarks for non-relapse mortality at 100 days after cellular therapy product administration. The Program's Quality Management Plan should describe the rationale for the benchmark selected and process for review.

5) *HLA Typing (B6.4.12.1)*

DNA high resolution typing is now required for all loci to further protect the safety of cellular therapy recipients. The Standards Committee believes improvements in technology have made this feasible for all cellular therapy programs, and this requirement does not increase the burden on programs.

6) *Recipient Care*

a) *Recipient Management and Monitoring for Complications (B7.7)*

In addition to the regular assessment for evidence of acute and chronic GVHD, the following elements were added for management of cellular therapy product recipients and monitoring for complications:

- i. Management of nausea, vomiting, pain and other discomforts;
- ii. Monitoring of blood counts and transfusion of blood products;
- iii. Monitoring of infections and use of antimicrobials;
- iv. Monitoring of organ dysfunction or failure and institution of treatment; and
- v. Monitoring of graft failure and institution of treatment.

b) *Discharges before engraftment (B7.8.1 - B7.8.1.3)*

The Clinical Program must have policies and SOPs in place for planned discharges prior to engraftment and provision of post-transplant care. When a transplant recipient is discharged prior to engraftment, the Clinical Program must verify the following are available:

- i. A consult between the attending physician and the receiving health care professionals regarding the applicable elements in Standard B7.7.
- ii. Facilities that provide appropriate location, adequate space, and protection from airborne microbial contamination.
- iii. Appropriate medications, blood products, and additional care required by the recipient.

c) Long-term Follow-up (B7.12)

The 7th edition requires that infrastructure, policies, and SOPs be in place for provision of appropriate long-term follow-up, treatment, monitoring for late effects, and plans of care for recipients.

The Clinical Program must have policies describing the transition of long-term pediatric recipients to adult care as appropriate, and the acceptance of pediatric recipients into a long-term follow-up clinic for adults.

There should be SOPs that include post-transplant vaccination schedules and indications.
(B7.9)

7) *Clinical Program Electronic Records (B10.4)*

Electronic record requirements (similar to those applicable to cellular therapy collection and processing facilities) were added to the clinical section to address systems used to support cellular therapy-specific activities. It is not the intent of these Standards to include hospital-based electronic medical records, but only those electronic systems that are under the control of the Clinical Program. Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

Changes to Collection Facility Standards

1) *Director Experience (CM3.1.3, C3.1.1, C3.2.3)*

The Facility Director and Medical Director must have at least two years of experience in cellular therapy product collection procedures.

2) *Irradiated Blood Products for Donors (CM8.4.1, C8.5.1)*

In addition to requiring autologous or CMV-appropriate and irradiated blood components be available during the collection procedure for all donors, the 7th edition recommends allogeneic blood components administered to the donor during apheresis collection be irradiated prior to transfusion. The use of irradiated blood components during the immediate post-collection period may be necessary if there is any consideration that the donor may need to donate a second product in that immediate timeframe.

3) *Records (C11.2)*

Good documentation reduces the risk of error. The Apheresis Collection Facility must define and follow good documentation practices.

Changes to Processing Facility Standards

1) *Director Experience (D3.1.3, D3.2.3)*

The Processing Facility Director and Medical Director must have performed or supervised:

- a) A minimum of five (5) cellular therapy product processing procedures in the twelve (12) months preceding initial accreditation, and
- b) A minimum average of five (5) cellular therapy product processing procedures per year within each accreditation cycle.

2) *Reagents (D6.2.4)*

The 7th edition clarifies reagent requirements. Reagents that come into contact with cellular therapy products must be clinical or pharmaceutical grade. Where there are no suitable clinical or pharmaceutical grade reagents available, reagents must undergo lot-to-lot functional verification. Verification must include acceptance criteria to confirm that new lots perform as expected compared to the previous lots.

3) *Records (D13.2)*

Good documentation reduces the risk of error. The Processing Facility must define and follow good documentation practices.