



FACT-JACIE International Standards  
for **HEMATOPOIETIC**  
**CELLULAR THERAPY**  
Product Collection, Processing, and Administration

*SIXTH EDITION*

**fact** FOUNDATION FOR THE  
ACCREDITATION OF  
CELLULAR THERAPY  
AT THE UNIVERSITY OF NEBRASKA MEDICAL CENTER

  
**JACIE**  
joint accreditation committee  
isct ebmt

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# INTERNATIONAL STANDARDS FOR HEMATOPOIETIC CELLULAR THERAPY PRODUCT COLLECTION, PROCESSING, AND ADMINISTRATION

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## Sixth Edition Version 6.1

### NOTICE

These Standards are designed to provide minimum guidelines for programs, facilities, and individuals performing cellular therapy or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a program, facility, or individual should implement if the standard of practice in the community or applicable governmental laws or regulations establish additional requirements. Each program, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with these Standards is not an exclusive means of complying with the standard of care in the industry or community or with local, national, or international laws or regulations.

**The Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee – ISCT and EBMT expressly disclaim any responsibility for setting maximum standards and further expressly disclaim any responsibility, liability, or duty to member programs, directors, staff, or program donors or patients for any such liability arising out of injury or loss to any person by the failure of member programs, directors, or staff to adhere to the Standards or related guidance.**

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## INTRODUCTION

The major objective of the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration* (the Standards) is to promote quality medical and laboratory practice in hematopoietic progenitor cell transplantation and related therapies using hematopoietic-derived cellular products. These Standards apply to hematopoietic progenitor cells, defined as self-renewing and/or multi-potent stem cells capable of maturation into any of the hematopoietic lineages, lineage-restricted pluri-potent progenitor cells, and committed progenitor cells from hematopoietic sources (bone marrow, umbilical cord blood, peripheral blood, or other tissue source). These Standards also include nucleated cells, including mononuclear cells from any hematopoietic tissue source (marrow, peripheral blood, umbilical cord, and placental blood) collected for therapeutic use other than as hematopoietic progenitor cells. These Standards apply to all phases of collection, processing, storage, and administration of these cells, including donor selection and screening, in vitro manipulation such as removal or enrichment of specific cell populations, and cryopreservation. The FACT-JACIE Standards do not address the collection, processing, or administration of erythrocytes, platelets, mature granulocytes, plasma, or plasma-derived products intended for transfusion support.

For hematopoietic progenitor cells or mononuclear cells derived from umbilical cord and/or placental blood, these Standards apply only to the administration of the cellular therapy product, applying the clinical and processing standards for product preparation and transplantation as appropriate. Standards for cord blood collection and banking are available in a separate document, *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration*, available at [www.factwebsite.org](http://www.factwebsite.org).

The FACT-JACIE Standards are published under the title *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*, which accurately reflects the contributions of both organizations. The Foundation for the Accreditation of Cellular Therapy (FACT) was founded in 1996 by the American Society for Blood and Marrow Transplantation (ASBMT) and the International Society for Cellular Therapy (ISCT). The first edition of Standards was published that same year. The inspection and accreditation program based on these Standards was started in North America in 1997. The Joint Accreditation Committee of ISCT and EBMT (JACIE) was established in 1999. JACIE adopted the first edition of FACT Standards in its entirety. The second edition of FACT Standards (2002) was developed and published following joint review by FACT and JACIE. Subsequent editions of Standards have been jointly developed and approved by FACT and JACIE.

In addition, the use of *Hematopoietic* in the title is to define the scope of these standards due to an increasing number of accredited facilities that also support non-hematopoietic cellular therapies. Facilities pursuing accreditation for hematopoietic services in addition to other specialty services may consult these Standards as a single reference for all fundamental requirements.

Every effort has been made to incorporate into these Standards sound principles of quality medical and laboratory practice in cellular therapy. However, no standards can guarantee the successful outcome of such therapies. FACT-JACIE Standards are minimal guidelines that may be exceeded as deemed appropriate by the responsible personnel in individual facilities. Directors and Medical Directors of the Clinical Program, Marrow Collection Facility, Apheresis Collection Facility, and Processing Facility assume responsibility for adopting FACT-JACIE Standards as appropriate to the program or facility, and for setting more rigorous internal requirements where appropriate. Attempts have been made to conform these Standards to existing U.S. federal regulations and the requirements of the European Union Directives; however, compliance with these Standards does not guarantee compliance with all applicable regulations.

The Standards are structured to align similar standards among the three primary functions within a cellular therapy program: the Clinical Program, Collection Facility, and Processing Facility. Separate

sections exist for Marrow Collection Facilities and Apheresis Collection Facilities to recognize the inherent differences between these two facilities and the closer linkage between the Marrow Collection Facility and the Clinical Program.

Appendices are used to clarify requirements and simplify the Standards. In the sixth edition, standards requiring a minimum number of new patients were replaced by a standard requiring that the Clinical Program comply with a new appendix, the Minimum Number of New Patients for Accreditation. This change was made for clarity. No change was made to the minimum number of new patients required.

The Quality Management (QM) section for each area in the cellular therapy program was expanded in the third edition (2006) to incorporate US FDA regulatory requirements for donor screening, testing, and eligibility determination; labeling; and current Good Tissue Practices. In subsequent editions, the QM standards have been refined for clarity and realigned to reduce redundancy, but allow flexibility in the structure of quality management activities within a program. Under any structure, the Clinical Program must have assurances that QM activities are adequate in all areas that impact the patient or product. Because the clinical team usually plays a direct role in marrow collection, the Clinical Program QM requirements in Part B include marrow collection. A Marrow Collection Facility operating independently of a specific Clinical Program must comply with the QM section in Part B.

The Donor Selection, Evaluation, and Management sections in the Clinical Program and Collection Facility sections reflect the usual delineation of these responsibilities between clinical programs and collection facilities. The Collection Facility standards are focused on donor evaluation and management; the Clinical Standards have emphasis on donor selection. If a Collection Facility is primarily responsible for donor selection, that Collection Facility must comply with the applicable Clinical Program standards. The Donor Selection, Evaluation, and Management sections apply to both related and unrelated donors. Effort was made to clarify which standards apply to both allogeneic and autologous donors, and which standards apply only to allogeneic donors.

FACT-JACIE Standards require compliance with the most recent regulatory requirements and the most current resources from other initiatives in the field. This includes the Transplant Essential Data (TED) forms, the Minimum Essential Data – Form A (MED-A) forms, the Circular of Information (COI) donor testing and biohazard and warning label tables, and the ISBT 128 Standard Terminology. Links to these resources are available on the FACT website.

Both FACT and JACIE recognize the significant benefits of international standardization of coding and labeling in cellular therapy, and support the international efforts to implement ISBT 128. ISBT 128 is the global standard for terminology, identification, coding, and labeling of medical products of human origin, and has been designed to ensure accuracy and safety for the benefit of patients and donors world-wide. FACT-JACIE Standards require the use of this terminology for cellular therapy products as applicable, and require accredited programs to be actively implementing ISBT 128. Terminology current at the time of publication of these Standards is listed in A3 Definitions. Terminology is frequently updated by ICCBBA, the organization responsible for the international maintenance of the ISBT 128 standard. Accredited programs must be registered with ICCBBA, receive notification of these changes, and make appropriate revisions if needed.

Implementation of ISBT 128 will include the use of scanned information at the time of product release from collection, receipt into the laboratory, and at distribution from the processing facility. It is understood that full implementation of ISBT 128 requires a transition period, and that organizations inspected soon after publication of this edition of Standards may not have completed this process. At a minimum, “actively implementing” includes completion of most of the following:

- 1) Registration with ICCBBA;
- 2) Evidence of a written implementation plan that includes a timeline;
- 3) Implementation of the current terminology;

- 4) Identification of information technology needs and solutions;
- 5) Identification or creation of appropriate product codes;
- 6) Label designs according to the requirements of ICCBBA for Cellular Therapy Products;
- 7) Label validation;
- 8) Use of scanned information at the time of product release from collection, receipt into the laboratory, and at distribution from the processing facility.

This sixth edition of Standards includes additional significant changes. A detailed summary is available on the FACT website. Most important to note are:

- 1) Increased emphasis on outcome analysis and improvement.
  - a) Clinical Programs are required to assess at least 30 day, 100 day, and one year survival, and to compare one year survival to national or international outcome data. For US programs, at a minimum, the one year survival should be within the expected range as defined for that program by the CIBMTR Transplant Center-Specific Outcome Data. Corrective action plans will be expected if these outcomes are not achieved.
  - b) Clinical Programs must regularly assess allogeneic transplant recipients for evidence of acute and chronic graft versus host disease according to an established grading scale, and actively evaluate patients for post-transplant late effects.
  - c) Clinical Programs must also regularly assess central venous catheter infections.
- 2) Reporting of autologous transplant results is now recommended.
- 3) New requirements were added for pharmacists and physicians-in-training who are involved in the care of hematopoietic cell therapy patients.
- 4) Continuing education minimum requirements have been specifically defined as ten hours per year in topics related to hematopoietic cell therapies.
- 5) Requirements specific to immune effector cells used to modulate an immune response were added as interim standards.

These Standards (Version 6.0) are effective June 1, 2015. All accredited programs and facilities are expected to be in compliance with these Standards by that date.

## ACCREDITATION

The basis for FACT or JACIE accreditation is documented compliance with the current edition of Standards through submitted documents and an on-site inspection. Although there are joint FACT-JACIE Standards, FACT and JACIE maintain separate and parallel accreditation processes. All inspections are conducted by persons qualified by training and experience in the area of cellular therapy they inspect, and who are affiliated with an accredited facility, have completed inspector training, and have a working knowledge of FACT-JACIE Standards and of their application to various aspects of the cellular therapy program.

- 1) A clinical hematopoietic progenitor cell/therapeutic cell transplantation program may apply for accreditation alone or in conjunction with the collection facility and/or the processing facility with which it is associated. All facilities applying together should submit pre-inspection data together. A clinical program must use a collection facility and a processing facility that meet FACT-JACIE Standards and have a clearly defined contractual or reporting relationship.
  - a) Clinical Program accreditation may be for allogeneic transplantation, autologous transplantation, or both.
  - b) Clinical Program accreditation may be for transplantation of adult patients, pediatric patients, or both. As detailed in the Standards, consultants and support services appropriate to the patient population are required.

- 2) A cell collection facility or service (peripheral blood or bone marrow) may apply for accreditation as an integral part of a clinical transplant program, as an independent collection service providing cell collection services for one or more clinical transplant programs, or in conjunction with a cell processing facility if the services of collection and processing/storage are functionally linked. An accredited cell collection facility may provide services for clinical transplant programs that are or are not FACT or JACIE accredited, but shall use a processing facility that meets FACT-JACIE Standards and have a clearly defined contractual or reporting relationship.
- 3) A cell processing facility may apply for accreditation as an integral part of a clinical transplant program, as part of a collection service or facility, or as an independent cell processing facility that processes and stores products for clinical programs or collection facilities. An accredited processing facility may provide services for clinical transplant programs and/or collection services that are or are not FACT or JACIE accredited.
- 4) A clinical program that provides cellular therapy services other than hematopoietic progenitor cell transplantation in addition to hematopoietic cell transplantation requires only a single accreditation according to these Standards.
- 5) A clinical program that provides cellular therapy services other than hematopoietic progenitor cell transplantation may apply for FACT accreditation with a hematopoietic progenitor cell transplantation program provided that the definition of and requirements for a single clinical program are met. A program that utilizes the same group of physicians and serves the same patient population, with common directorship, protocols, and staffing, would meet this requirement.
- 6) A cell collection or processing facility that collects or processes hematopoietic progenitor cell therapy products in addition to other investigational products may apply for FACT accreditation for all activities and document compliance with the FACT-JACIE Standards.
- 7) If a facility does not collect or process hematopoietic cell therapy products but wishes to apply for FACT accreditation, the facility personnel should consult the current edition of the *FACT Common Standards for Cellular Therapies*.

An accreditation cycle is three years for FACT, and is four years for JACIE. Accredited facilities must complete an interim report(s) during the accreditation cycle as directed by FACT or JACIE. Accredited facilities are reinspected routinely every three years (FACT) or four years (JACIE), and may also be reinspected in response to complaints or information that a facility may be non-compliant with FACT-JACIE Standards, in response to significant changes in the program and/or facility, or as determined by FACT or JACIE. Accreditation may be suspended or terminated if a facility fails to comply with the Standards.

# **TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS**

## **PART A**

- A1 Terminology
- A2 Tenets
- A3 Abbreviations
- A4 Definitions

## **PART A: TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS**

### **A1 TERMINOLOGY**

For purposes of these Standards, the term *shall* means that the standard is to be complied with at all times. The term *should* indicates an activity that is recommended or advised, but for which there may be effective alternatives. The term *may* is permissive and is used primarily for clarity.

### **A2 TENETS**

Basic tenets for compliance with these Standards include, but are not limited to:

- A2.1 Where applicable laws and regulations include more stringent requirements than these Standards, those laws and regulations supersede the Standards. Conversely, when these Standards are more stringent than applicable laws and regulations, the Standards must be followed.
- A2.2 Applicant organizations are responsible for providing verifiable documentation of evidence of compliance with these Standards.
- A2.3 Standards related to services not provided by the applicant do not apply to the applicant organization. The burden to demonstrate that a requirement is not applicable rests with the applicant organization.

### **A3 ABBREVIATIONS**

The following abbreviations cover terms used in these Standards:

<i>ABO</i>	Major human blood group including erythrocyte antigens, A, B, O
<i>AC</i>	Accompany
<i>AF</i>	Affixed
<i>Anti-</i>	Antibody to the antigen designated
<i>APP</i>	Advanced Practice Provider/Professional
<i>ASBMT</i>	American Society for Blood and Marrow Transplantation
<i>ASFA</i>	American Society for Apheresis
<i>ASHI</i>	American Society for Histocompatibility and Immunogenetics
<i>AT</i>	Attached
<i>ATMP</i>	Advanced Therapy Medicinal Product
<i>CAR</i>	Chimeric antigen receptor
<i>CE</i>	(formerly EC) European Conforming
<i>CFR</i>	Code of Federal Regulations
<i>CIBMTR</i>	Center for International Blood and Marrow Transplant Research
<i>CLIA</i>	Clinical Laboratory Improvement Amendments
<i>CME</i>	Continuing Medical Education
<i>CMS</i>	Centers for Medicare & Medicaid Services
<i>CMV</i>	Cytomegalovirus
<i>CNS</i>	Central nervous system
<i>COA</i>	Certificate of Analysis
<i>CRS</i>	Cytokine release syndrome
<i>CTP</i>	Cellular therapy product
<i>DLI</i>	Donor lymphocyte infusion

DNA	Deoxyribonucleic acid
EBMT	European Society for Blood and Marrow Transplantation
ECP	Extracorporeal photopheresis
EFI	European Federation for Immunogenetics
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	U. S. Food and Drug Administration
GMP	Good Manufacturing Practices
GTP	Good Tissue Practices
GVHD	Graft versus Host Disease
HCT/Ps	Human cells, tissues, or cellular or tissue-based products
HLA	Human leukocyte antigen
HPC	Hematopoietic progenitor cell
IDE	Investigational Device Exemption
IND	Investigational New Drug
ISCT	International Society for Cellular Therapy
JACIE	Joint Accreditation Committee – ISCT and EBMT
MNC	Mononuclear cell
MSC	Mesenchymal stromal cell or mesenchymal stem cell
NC	Nucleated cell
NMDP	National Marrow Donor Program
OSHA	Occupational Safety and Health Administration
QM	Quality management
RBC	Red blood cell
Rh	Rhesus system of human red cell antigens; used in this document to refer to the Rh(D) antigen only, unless otherwise specified
SCTOD	Stem Cell Therapeutics Outcomes Database
SOP	Standard operating procedure
US	United States
USDA	United States Department of Agriculture
WMDA	World Marrow Donor Association

#### A4 DEFINITIONS

*Accompany:* To go, be together with, or be available to the appropriate individual(s) electronically, but not affixed or attached. Written or printed information that must accompany a cellular therapy product must be in a sealed package with, or alternatively, be attached or affixed to, the cellular therapy product container.

*Accreditation cycle:* The period of time from the awarding of accreditation until its expiration as set, and subject to change, by FACT or JACIE. At publication of these Standards, this period is three (3) years for FACT-accredited programs and four (4) years for JACIE-accredited programs.

*Advanced practice provider/professional:* Physician Assistant, Nurse Practitioner, or other licensed Advanced Practitioner authorized by the applicable legal authority to provide primary patient care with physician oversight. Physician Assistants are formally trained and licensed or certified by the applicable authority to provide diagnostic, therapeutic, and preventive health care services with physician supervision. Advanced Nurse Practitioner includes certified nurse anesthetists, nurse practitioners, certified nurse midwives, and clinical nurse specialists.

*Adverse event:* Any unintended or unfavorable sign, symptom, abnormality, or condition temporally associated with an intervention that may or may not have a causal relationship with the intervention, medical treatment, or procedure. Adverse reaction is a type of adverse event.

*Adverse reaction:* A noxious and unintended response suspected or demonstrated to be caused by the collection or infusion of a cellular therapy product or by the product itself.

*Affix:* To adhere in physical contact with the cellular therapy product container.

*Allogeneic:* The biologic relationship between genetically distinct individuals of the same species.

*Ambulatory setting:* An environment of patient care outside of an inpatient hospital.

*Apheresis:* A medical technology in which the blood of a donor is separated into its component parts, the desired component is removed, and the remaining components are returned to the donor.

*Aseptic technique:* Practices designed to reduce the risk of microbial contamination of cellular therapy products, reagents, specimens, recipients, and/or donors.

*Attach:* To fasten securely to the cellular therapy product container by means of a tie tag or comparable alternative. Any information required to be attached to a cellular therapy product container may alternatively be affixed.

*Attending physician:* The physician who is responsible for the delivery and oversight of care provided to cellular therapy recipients and who meets all qualifications defined in these Standards.

*Audit:* Documented, systematic evaluation to determine whether approved policies or procedures have been properly implemented and are being followed.

*Autologous:* Derived from and intended for the same individual.

*Available for distribution:* The time at which the cellular therapy product may leave the control of the facility.

*Biological product deviation:* Any event associated with the manufacturing of a cellular therapy product, including testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product, if that event meets the following criteria:

Either:

- Represents a deviation from current good manufacturing practice (or current good tissue practices), applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or
- Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and
  - Occurs in your facility or another facility under contract with you; and
  - Involves a distributed biological product.

*Calibrate:* To set measurement equipment against a known standard.

*CD34:* The 115 kD glycoprotein antigen, expressed by 1-2% of normal bone marrow mononuclear cells, that is defined by a specific monoclonal antibody (anti-CD34) using the standardized cluster of differentiation (CD) terminology.

*Cellular therapy:* The administration of products with the intent of providing effector cells in the treatment of disease or support of other therapy.

*Cellular therapy product:* Somatic cell-based product (e.g., mobilized HPC, mononuclear cells, cord blood cells, mesenchymal stromal cells, T cells, natural killer cells) that is procured from a donor and intended for processing and administration.

*Chimeric antigen receptor:* Artificial receptor that combines an antigen specificity domain coupled with an intracellular signaling domain typically expressed by an immune effector cell (e.g., T cell or natural killer cell).

*Chimerism testing:* A diagnostic test (e.g., molecular, cytogenetic, or FISH) conducted after allogeneic stem cell or bone marrow transplantation to detect the relative ratio of donor and recipient cell populations in the peripheral blood and/or bone marrow.

*Circular of Information:* An extension of container labels that includes the use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

*Clinical Program:* An integrated medical team housed in a defined location that includes a Clinical Program Director and demonstrates common staff training, protocols, procedures, quality management systems, clinical outcome analysis, and regular interaction among clinical sites.

*Collection:* Any procedure for procuring and labeling a cellular therapy product regardless of technique or source.

*Collection Facility:* An entity providing the service of cellular therapy product collection.

*Competency:* Ability to adequately perform a specific procedure or task according to direction.

*Complaint:* Any written, oral, or electronic communication about a problem associated with a cellular therapy product or with a service related to the collection, processing, storage, distribution, or administration of a cellular therapy product.

*Cord blood:* The whole blood, including HPC, collected from placental and umbilical cord blood vessels after the umbilical cord has been clamped.

*Corrective action:* Action taken to eliminate the root causes of an existing discrepancy or other undesirable situation to prevent recurrence.

*Courier:* An individual trained and competent in transport or shipping of cellular therapy products.

*Critical:* The quality of any element employed in cellular therapy product manufacturing to potentially change the identity, purity, potency, or safety of the cellular therapy product if altered or omitted. "Element" includes, but is not limited to, materials, equipment, personnel, documents, or facilities. For example, DMSO is a critical reagent because omitting it from the freezing medium will cause loss of cells during freezing and thawing.

*Current Good Tissue Practice:* 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.

*Current Good Manufacturing Practice:* 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, cGMPs are enforced under Section 501(B) of the Federal Food, Drug, and Cosmetic Act (21USC351). Cellular therapy products that are extensively manipulated or that are used for non-homologous purposes are examples of products controlled under cGMP regulations. Similar requirements are delineated by the European Union as EU-GMP, and other countries such as United Kingdom, Australia, Canada, and Singapore have equally well-developed systems of regulations.

*Cytokine release syndrome:* A non-antigen-specific toxicity that occurs as a result of high-level immune activation. For example, a reaction from the release of cytokines from cells targeted by an antibody or immune effector cells.

*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.

*Distribution:* Any transportation or shipment of a cellular therapy product that has been determined to meet release criteria or urgent medical need requirements.

*Donor:* A person who is the source of cells or tissue for a cellular therapy product.

*Donor advocate:* An individual distinct from the cellular therapy recipient's primary treating physician whose main obligation is to protect the interests, well-being, and safety of the donor. The donor advocate may help the donor understand the process, the procedures, and the potential risks and benefits of donation.

*Donor lymphocyte infusion (DLI):* A type of therapy given to a patient who has already received an allogeneic hematopoietic progenitor cell transplant from the same donor. The donor lymphocytes may kill remaining cancer cells, facilitate full donor chimerism, or provide a source of antigen specific immunity. The DLI cell source may be whole blood, bone marrow, mononuclear cells collected by apheresis with or without mobilization, cord blood, or cellular subsets purified from these source products. The active cell type may include T lymphocytes, NK cells, or B lymphocytes. May also be referred to as donor leukocyte infusion.

*Electronic record:* A record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer.

*Critical electronic record:* Electronic record system under facility control that is used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

*Eligible:* An allogeneic cellular therapy product donor for whom all the donor screening and testing have been completed in accordance with applicable laws and regulations and who has been determined to be free of risk factor(s) for relevant communicable diseases.

*Engraftment:* The reconstitution of recipient hematopoiesis with blood cells and platelets from a donor.

*Errors and Accidents:* Any unforeseen or unexpected deviations from applicable regulations, standards, or established specifications that may affect the safety, purity, or potency of a cellular therapy product.

*Establish and maintain:* A process to define, document in writing (including electronically), implement, follow, review, and, as needed, revise on an ongoing basis.

*Exceptional release:* Removal of a product that fails to meet specified criteria from quarantine or in-process status for distribution through a defined approval process.

*Expansion:* Growth of one or more cell populations in an *in vitro* culture system.

*Extracorporeal photopheresis:* An apheresis technique in which the patient's blood is collected into a specialized instrument, centrifuged, and separated into a leukocyte-depleted fraction (which is returned to the patient unmanipulated) and mononuclear "buffy coat" enriched plasma. The mononuclear cell-enriched fraction is incubated with 8-methoxypsoralen in the presence of ultraviolet A (UVA) radiation, and, upon completion of the procedure, reinfused into the patient.

*Facility:* A location where activities covered by these Standards are performed, including but not limited to determination of donor eligibility or suitability, product collection, processing, storage, distribution, issue, or administration.

*Fellow:* A physician who is in a training program in a medical specialty after completing residency, usually in a hospital or academic setting.

*Fresh:* A cellular therapy product that has never been cryopreserved.

*Hematopoietic progenitor cells (HPC):* A cellular therapy product that contains self-renewing and/or multi-potent stem cells capable of maturation into any of the hematopoietic lineages, lineage-restricted pluri-potent progenitor cells, and committed progenitor cells, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source).

*Hematopoietic progenitor cellular therapy:* The administration of HPC product with the intent of providing effector functions in the treatment of disease or in support of other therapy.

*Human cells, tissues, or cellular or tissue-based products (HCT/Ps):* Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.

*Immune effector cell:* A cell that has differentiated into a form capable of modulating or effecting a specific immune response.

*Ineligible:* An allogeneic cellular therapy product donor for whom all the donor screening and testing has been completed in accordance with the applicable laws and regulations and who has identified risk factor(s) for relevant communicable diseases.

*Institutional Review Board or Ethics Committee:* A Board or Committee established by an institution in accordance with the regulations of the relevant governmental agency to review biomedical and behavioral research that involves human subjects and is conducted at or supported by that institution.

*ISBT 128:* A global standard for the identification, labeling, and information transfer of human blood, cell, tissue, and organ products.

*Key position:* A job category with responsibilities that significantly affect the provision of service or product safety and quality.

*Label:* Written, printed, or graphic material affixed to, attached to, or accompanying a cellular therapy product container or package. Labels must contain the information as defined by applicable standards, laws, and regulations.

*Labeling:* The process of creating and applying the cellular therapy product label, including confirmation of the presence and accuracy of the required information as defined in these Standards.

*\*Late Effect:* A health problem that occurs months or years after a disease is diagnosed or after treatment has been administered. Late effects may be caused by the primary disease or its treatment, and may include physical, mental, or social problems and/or secondary cancers.

*Licensed health care professional:* An individual who has completed a prescribed program of health-care related study and has been certified, registered, or licensed by the applicable authority in the jurisdiction in which he or she is performing services to perform duties within the scope of practice of that certificate, registration, or license.

*Manipulation:* An ex vivo procedure(s) that selectively removes, enriches, expands, or functionally alters the cellular therapy product.

*Minimally Manipulated:* Processing that does not alter the relevant biological characteristics of cells or tissues. For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.

*More than minimally manipulated:* Processing that does alter the relevant biological characteristics of cells or tissues. For structural tissue, processing that does alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement. Products that are more than minimally manipulated are referred to as Advanced Therapy Medicinal Products in the European Union.

*Unmanipulated:* A cellular therapy product as obtained at collection and not subjected to any form of processing.

*Manufacturing:* Activity that includes, but is not limited to, any or all steps in the recovery, processing, packaging, labeling, storage, or distribution of any human cellular or tissue-based product, and/or the screening and testing of a cell or tissue donor.

*Marrow collection:* Harvest of bone marrow for transplantation to achieve hematopoietic reconstitution in the recipient or for further cellular therapy product manufacture. This does not include marrow aspirations intended for diagnostic purposes.

*Materials management:* An integrated process for planning and controlling all steps in the acquisition and use of goods or supply items (materials) used for the collection or processing of cellular therapy products to determine whether these materials are of adequate quality and quantity and available when needed. The materials management system combines and integrates the material selection, vendor evaluation, purchasing, expediting, storage, distribution, and disposition of materials.

*Microbial:* Related to infectious agents including bacterial and fungal organisms.

*Negative selection:* The manipulation of a cellular therapy product such that a specific cell population(s) is reduced.

*New patient:* An individual undergoing the specified type of transplantation (allogeneic, autologous, or syngeneic) for the first time in the Clinical Program, whether or not that patient was previously treated by that Clinical Program.

*Orientation:* An introduction to guide one in adjusting to new surroundings, employment, or activity.

*Outcome analysis:* The process by which the results of a therapeutic procedure are formally assessed.

*Partial label:* The minimum essential elements that must be affixed to all cellular therapy product containers at all times.

*Physician-in-training:* A physician in one of the postgraduate years of clinical training. Can be referred to as resident, fellow, registrar, or other designation, depending on the setting. The length of training varies according to the specialty.

*Policy:* A document that defines the scope of an organization, explains how the goals of the organization will be achieved, and/or serves as a means by which authority can be delegated.

*Positive selection:* The manipulation of a cellular therapy product such that a specific cell population(s) is enriched.

*Potency:* The therapeutic activity of a product as indicated by appropriate laboratory tests or adequately developed and controlled clinical data.

*Preparative (conditioning) regimen:* The treatment(s) used to prepare a patient for stem cell transplantation (e.g., chemotherapy, monoclonal antibody therapy, radiation therapy).

*Preventive action:* Action taken to eliminate the root cause and prevent occurrence of a potential discrepancy or other undesirable situation.

*Procedure:* A document that describes in detail the process or chronological steps taken to accomplish a specific task; work instructions; a procedure is more specific than a policy.

*Process:* A goal-directed, interrelated series of actions, events, or steps.

*Process control:* The standardization of processes in order to produce predictable output.

*Process development:* The series of procedures performed in order to develop a final process that achieves the required results.

*Processing:* All aspects of manipulation, cryopreservation, packaging, and labeling of cellular therapy products regardless of source, including microbial testing, preparation for administration or storage, and removal from storage. Processing does not include collection, donor screening, donor testing, storage, or distribution.

*Processing Facility:* A location where cellular therapy product processing activities are performed in support of the Clinical Program. A Processing Facility may be part of the same institution as the Clinical Program or may be part of another institution and perform these functions through contractual agreement.

*Product identity:* Unique title that identifies the cellular composition of the product in a way that can be directly tied back to a manufacturing entity or process (e.g., a protocol number, a commercial product title, or a site-defined unique identifier).

*Product sample:* A representative quantity of product removed from the cellular therapy product; an aliquot.

*\*\*Products:* 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 can be collected for direct infusion without further manipulation. HPCs may be further manipulated, but would retain the class name HPC 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.

CONCURRENT PLASMA, APHERESIS: Plasma collected from the donor as part of an apheresis cell collection procedure.

HPC, APHERESIS: A cell product containing hematopoietic progenitor cells obtained by apheresis.

HPC, CORD BLOOD: A cell product containing hematopoietic progenitor cells obtained from cord blood.

HPC, MARROW: A cell product containing hematopoietic progenitor cells obtained from bone marrow.

HPC, WHOLE BLOOD: A cell product containing hematopoietic progenitor cells obtained from whole blood.

MNC, APHERESIS: A cell product containing mononuclear cells obtained by apheresis.

MNC, UMBILICAL CORD TISSUE: A cell product containing mononuclear cells derived from umbilical cord tissue.

NC, CORD BLOOD: A cell product containing nucleated cells obtained from cord blood.

NC, MARROW: A cell product containing nucleated cells obtained from bone marrow.

NC, WHOLE BLOOD: A cell product containing nucleated cells obtained from whole blood.

Subcategory 2: After enumeration or manufacture/processing of the collected products, the product may be identified by the target cell population. These class names are based on desired cell population thought to be present in the product.

DC, APHERESIS: A cell product containing dendritic cells obtained by apheresis.

DC, CORD BLOOD: A cell product containing dendritic cells obtained from cord blood.

DC, MARROW: A cell product containing dendritic cells obtained from bone marrow.

DC, WHOLE BLOOD: A cell product containing dendritic cells obtained from whole blood.

**INVESTIGATIONAL PRODUCT:** A product for an investigational study that is accompanied by appropriate identifying study information. This class may be used for a specific product that may be part of a blinded comparison study. Products labeled as Investigational Product may include different doses or may include an active product or a placebo.

**MALIGNANT CELLS, APHERESIS:** A cell product containing malignant cells obtained by apheresis.

**MALIGNANT CELLS, MARROW:** A cell product containing malignant cells obtained from marrow.

**MALIGNANT CELLS, WHOLE BLOOD:** A cell product containing malignant cells obtained from whole blood.

**MSC, CORD BLOOD:** A cell product containing mesenchymal stromal cells derived from cord blood.

**MSC, MARROW:** A cell product containing mesenchymal stromal cells derived from bone marrow.

**MSC, WHARTON'S JELLY:** A cell product containing mesenchymal stromal cells derived from Wharton's jelly.

**NK CELLS, APHERESIS:** A cell product containing natural killer cells obtained by apheresis.

**NK CELLS, CORD BLOOD:** A cell product containing natural killer cells obtained from cord blood.

**NK CELLS, MARROW:** A cell product containing natural killer cells obtained from bone marrow.

**NK CELLS, WHOLE BLOOD:** A cell product containing natural killer cells obtained from whole blood.

**T CELLS, APHERESIS:** A cell product containing T cells obtained by apheresis.

**T CELLS, CORD BLOOD:** A cell product containing T cells obtained from cord blood.

**T CELLS, MARROW:** A cell product containing T cells obtained from bone marrow.

**T CELLS, WHOLE BLOOD:** A cell product containing T cells obtained from whole blood.

*Proficiency test:* A test to evaluate the adequacy of testing methods and equipment and the competency of personnel performing testing.

*Protocol:* A written document describing steps of a treatment or procedure in sufficient detail such that the treatment or procedure can be reproduced repeatedly without variation.

*Purity:* Relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product.

*Qualification:* The establishment of confidence that equipment, supplies, and reagents function consistently within established limits.

*Qualified person:* A person who has received training, is experienced, and has documented competence in the task assigned.

*Quality:* Conformance of a product or process with pre-established specifications or standards.

*Quality assurance:* The actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product or service are working as expected or exceed expectations individually and collectively.

*Quality assessment:* The actions, planned and performed, to evaluate all systems and elements that influence the quality of the product or service.

*Quality audit:* A documented, independent inspection and review of a facility's quality management activities to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

*Quality control:* A component of a quality management program that includes the activities and controls used to determine the accuracy and reliability of the establishment's personnel, equipment, reagents, and operations in the manufacturing of cellular therapy products, including testing and product release.

*Quality improvement:* The actions, planned and performed, to implement changes designed to improve the quality of a product or process.

*Quality management:* The integration of quality assessment, assurance, control, and improvement in cellular therapy activities.

*Quality management plan:* A written document that describes the systems in place to implement the quality management program.

*Quality management program:* An organization's comprehensive system of quality assessment, assurance, control, and improvement. A quality management program is designed to prevent, detect, and correct deficiencies that may adversely affect the quality of the cellular therapy product or increase the risk of communicable disease introduction or transmission. May also be referred to by other terms.

*Quality Unit:* The personnel responsible for Quality Management. Under good manufacturing practices, the quality unit must be independent from manufacturing, facility, and medical oversight and have final authority and oversight for the release of cellular therapy products.

*Quarantine:* The identification or storage of a cellular therapy product in a physically separate area clearly identified for such use, or through use of other procedures such as automated designation to prevent improper release of that product. Also refers to segregated storage of products known to contain infectious disease agents to reduce the likelihood of cross-contamination.

*Record:* Documented evidence that activities have been performed or results have been achieved. A record does not exist until the activity has been performed.

*Release:* Removal of a product from quarantine or in-process status when it meets specified criteria.

*Release criteria:* The requirements that must have been met before a cellular therapy product may leave the control of the Collection or Processing Facility.

*Safety:* Relative freedom from harmful effects to persons or products.

*Shipping:* The physical act of transferring a cellular therapy product within or between facilities. During shipping the product leaves the control of trained personnel at the distributing or receiving facility.

*Standard Operating Procedures (SOP) Manual:* A compilation of policies and procedures with written detailed instructions required to perform procedures. The SOP Manual may be in electronic or paper format.

*Standards:* The current edition of the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration*, which may be referred to herein as "Standards" or "FACT-JACIE Standards."

*Storage:* Holding a cellular therapy product for future processing, distribution, or administration.

*Suitable:* Donor or recipient suitability refers to issues that relate to the general health or medical fitness of the donor or recipient to undergo the collection procedure or therapy.

*Syngeneic:* The biologic relationship between identical twins.

*Target cell population:* A cell population that is expected to be affected by an action or that is believed to be mainly responsible for a given activity.

*Time of collection:* The time of day at the end of the cellular therapy product collection procedure.

*Trace:* To follow the history of a process, product, or service by review of documents.

*Track:* To follow a process or product from beginning to end.

*Transplantation:* The infusion of allogeneic, autologous, or syngeneic HPC with the intent of providing transient or permanent engraftment in support of therapy of disease.

*Transport:* The physical act of transferring a cellular therapy product within or between facilities. During transportation the product does not leave the control of trained personnel at the transporting or receiving facility.

*Unique:* Being the only one of its kind or having only one use or purpose.

*Unique identifier:* A numeric or alphanumeric sequence used to designate a given cellular therapy product with reasonable confidence that it will not be used for another purpose.

*Unplanned deviation:* The action of departing from an established course or accepted standard without intent.

*Urgent medical need:* A situation in which no comparable cellular therapy product is available and the recipient is likely to suffer death or serious morbidity without the cellular therapy product.

*Validation:* Confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process is validated by establishing, by objective evidence, that the process consistently produces a cellular therapy product meeting its predetermined specifications.

*Variance:* A planned deviation from recommended practice or standard operating procedure approved as the best course of action when adherence to the established course or accepted standard was not feasible or possible .

*Verification:* The confirmation of the accuracy of something or that specified requirements have been fulfilled.

*Verification typing:* HLA typing performed on an independently collected sample with the purpose of verifying concordance of that typing assignment with the initial HLA typing assignment. Concordance does not require identical levels of resolution for the two sets of typing but requires the two assignments be consistent with one another.

*Viability:* Living cells as defined by dye exclusion, flow cytometry, or progenitor cell culture.

*Written:* Documentation in human readable form.

*\*A portion of the definition that can be located in the National Cancer Institute at the National Institutes of Health's NCI Dictionary of Cancer Terms: <http://www.cancer.gov/dictionary?Cdrid=390292>.*

*\*\*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. Available at: [www.iccbba.org](http://www.iccbba.org) > Subject Area > Cellular Therapy > Standard Terminology.*

# CLINICAL PROGRAM STANDARDS

## PART B

- B1 General
- B2 Clinical Unit
- B3 Personnel
- B4 Quality Management
- B5 Policies and Procedures
- B6 Allogeneic and Autologous Donor Selection,  
Evaluation, and Management
- B7 Recipient Care
- B8 Clinical Research
- B9 Data Management
- B10 Records

## **PART B: CLINICAL PROGRAM STANDARDS**

### **B1: GENERAL**

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B1.1 The Clinical Program shall consist of an integrated medical team that includes a Clinical Program Director(s) housed in a defined location(s).

B1.1.1 The Clinical Program shall demonstrate common staff training, protocols, procedures, quality management systems, clinical outcome analysis, and regular interaction among all clinical sites.

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B1.2 The Clinical Program shall use cell collection and processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Clinical Program.

B1.2.1 If cellular therapy products are received directly by the Clinical Program from a third-party provider, the following responsibilities at a minimum shall be defined in a written agreement:

B1.2.1.1 Traceability and chain of custody of cellular therapy products.

B1.2.1.2 Cellular therapy product storage and distribution.

B1.2.1.3 Verification of cellular therapy product identity.

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B1.3 The Clinical Program shall abide by all applicable laws and regulations.

B1.3.1 The Clinical Program shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

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B1.4 The Clinical Program shall have a designated transplant team that includes a Clinical Program Director, a Quality Manager, and a minimum of one (1) additional attending transplant physician. The designated transplant team shall have been in place for at least twelve (12) months preceding initial accreditation.

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B1.5 The Clinical Program shall comply with the Minimum Number of New Patients for Accreditation table in Appendix I.

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## B2: CLINICAL UNIT

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- B2.1 There shall be a designated inpatient unit of appropriate location and adequate space and design that minimizes airborne microbial contamination.
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- B2.2 There shall be a designated outpatient care area that protects the patient from transmission of infectious agents and allows, as necessary, for appropriate patient isolation; confidential examination and evaluation; and administration of intravenous fluids, medications, or blood products.
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- B2.3 When the preparative regimen, cellular therapy product administration, or initial post-transplant care is provided in an ambulatory setting, there shall be a designated area with appropriate location and adequate space and design to minimize the risk of airborne microbial contamination.
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- B2.4 Facilities used by the Clinical Program shall be maintained in a clean, sanitary, and orderly manner.
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- B2.5 There shall be provisions for prompt evaluation and treatment by a transplant attending physician available on a 24-hour basis.
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- B2.6 There shall be written guidelines for communication, patient monitoring, and prompt transfer of patients to an intensive care unit, emergency department, or equivalent when appropriate.
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- B2.7 There shall be attending physician oversight if general medical physicians, physicians in training, or APPs provide care to transplant patients. The scope of responsibility of general medical physicians or APPs shall be defined.
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- B2.8 There shall be a pharmacy providing 24-hour availability of medications needed for the care of transplant patients.
- B2.8.1 Pharmacies shall have access to medications adequate to treat expected complications of immune effector cell administration, including cytokine release syndrome.
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- B2.9 There shall be access to renal support under the direction of nephrologists and trained personnel.
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- B2.10 There shall be 24-hour availability of CMV-appropriate and irradiated blood products needed for the care of transplant recipients.
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- B2.11 Clinical Programs performing allogeneic transplantation shall use HLA testing laboratories that are capable of carrying out DNA-based intermediate and high resolution HLA-typing and are appropriately accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), European Federation for Immunogenetics (EFI), or other accrediting organizations providing histocompatibility services appropriate for hematopoietic cellular therapy transplant patients.
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- B2.12 Chimerism testing shall be performed in laboratories accredited for the techniques used.
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- B2.13 There shall be an intensive care unit or equivalent coverage available.
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- B2.14 The Clinical Program shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.
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- B2.15 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 hazards.
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### **B3: PERSONNEL**

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#### **B3.1 CLINICAL PROGRAM DIRECTOR**

- B3.1.1 The Clinical Program Director shall be a physician appropriately licensed or certified to practice medicine in the jurisdiction in which the Clinical Program is located and shall have achieved specialist certification in one or more of the following specialties: Hematology, Medical Oncology, Pediatric Immunology, or Pediatric Hematology/Oncology. A physician trained prior to requirements for specialty training may serve as the Clinical Program Director if he/she has documented experience in the field of HPC transplantation extending over ten (10) years.

- B3.1.2 The Clinical Program Director shall have two (2) years of experience as an attending physician responsible for the direct clinical management of HPC transplant patients in the inpatient and outpatient settings.
  - B3.1.3 The Clinical Program Director shall be responsible for administrative and clinical operations, including compliance with these Standards and applicable laws and regulations.
  - B3.1.4 The Clinical Program Director shall be responsible for all elements of the design of the Clinical Program including quality management, the selection and care of patients and donors, and cell collection and processing, whether internal or contracted services.
  - B3.1.5 The Clinical Program Director shall have oversight of the medical care provided by all members of the Clinical Program.
    - B3.1.5.1 The Clinical Program Director or designee shall be responsible for verifying the knowledge and skills of members of the Clinical Program once per accreditation cycle, at minimum.
  - B3.1.6 The Clinical Program Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
    - B3.1.6.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.
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## B3.2 ATTENDING PHYSICIANS

- B3.2.1 Attending physicians shall be appropriately licensed to practice medicine in the jurisdiction of the Clinical Program and should be specialist certified or trained in one of the following specialties: Hematology, Medical Oncology, Immunology, or Pediatric Hematology/Oncology.
    - B3.2.1.1 Clinical Programs performing adult transplantation shall have at least one attending physician who has achieved specialist certification in Hematology, Medical Oncology, or Immunology.
    - B3.2.1.2 Clinical Programs performing pediatric transplantation shall have at least one attending physician who has achieved specialist certification in Pediatric Hematology/Oncology or Pediatric Immunology.
  - B3.2.2 Attending physicians shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
    - B3.2.2.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.
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### B3.3 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

- B3.3.1 Attending physicians shall each have had a minimum total of one year of supervised training in the management of transplant patients in both inpatient and outpatient settings.
- B3.3.2 Clinical training and competency shall include the management of autologous and/or allogeneic transplant recipients, as applicable.
- B3.3.3 Clinical Program Directors and attending physicians shall have received specific training and maintain competency in each of the following areas as applicable to the Clinical Program's services:
  - B3.3.3.1 Indications for HPC transplantation.
  - B3.3.3.2 Selection of suitable recipients and appropriate preparative regimens.
  - B3.3.3.3 Allogeneic and autologous donor selection, evaluation, and management.
  - B3.3.3.4 Donor and recipient informed consent.
  - B3.3.3.5 Administration of ABO incompatible cellular therapy products.
  - B3.3.3.6 Administration of preparative regimens.
  - B3.3.3.7 Administration of growth factors for HPC mobilization and for post-transplant hematopoietic cell reconstitution.
  - B3.3.3.8 HPC product infusion and patient management.
  - B3.3.3.9 Management of neutropenic fever.
  - B3.3.3.10 Diagnosis and management of infectious and non-infectious pulmonary complications of transplantation.
  - B3.3.3.11 Diagnosis and management of fungal disease.
  - B3.3.3.12 Diagnosis and management of veno-occlusive disease of the liver and other causes of hepatic dysfunction.
  - B3.3.3.13 Management of thrombocytopenia and bleeding, including recognition of disseminated intravascular coagulation.
  - B3.3.3.14 Management of hemorrhagic cystitis.
  - B3.3.3.15 Management of mucositis, nausea, and vomiting.
  - B3.3.3.16 Monitoring and management of pain.
  - B3.3.3.17 Graft versus host disease.
  - B3.3.3.18 Cytokine release syndrome.

- B3.3.3.19 Tumor lysis syndrome.
- B3.3.3.20 Macrophage activation syndrome.
- B3.3.3.21 Cardiac dysfunction.
- B3.3.3.22 Renal dysfunction.
- B3.3.3.23 Respiratory distress.
- B3.3.3.24 Neurologic toxicity.
- B3.3.3.25 Anaphylaxis.
- B3.3.3.26 Infectious and noninfectious processes.
- B3.3.3.27 Diagnosis and management of HPC graft failure.
- B3.3.3.28 Evaluation of post-transplant cellular therapy outcomes.
- B3.3.3.29 Evaluation of late effects of allogeneic and autologous transplants, including cellular, pharmacologic, and radiation therapy.
- B3.3.3.30 Documentation and reporting for patients on investigational protocols.
- B3.3.3.31 Applicable regulations and reporting responsibilities for adverse events.
- B3.3.3.32 Palliative and end of life care.
- B3.3.4 Additional specific clinical training and competency required for physicians in Clinical Programs requesting accreditation for allogeneic HPC transplantation shall include:
  - B3.3.4.1 Identification, evaluation, and selection of HPC source, including use of donor registries.
  - B3.3.4.2 Donor eligibility determination.
  - B3.3.4.3 Methodology and implications of human leukocyte antigen (HLA) typing.
  - B3.3.4.4 Management of patients receiving ABO incompatible HPC products.
  - B3.3.4.5 Diagnosis and management of immunodeficiencies and opportunistic infections.
  - B3.3.4.6 Diagnosis and management of acute graft versus host disease.
  - B3.3.4.7 Diagnosis and management of chronic graft versus host disease.
- B3.3.5 The attending physicians shall be knowledgeable in the following procedures:
  - B3.3.5.1 HPC processing.

- B3.3.5.2 HPC cryopreservation.
  - B3.3.5.3 Bone marrow harvest procedures.
  - B3.3.5.4 Apheresis collection procedures.
  - B3.3.5.5 Extracorporeal photopheresis for GVHD.
  - B3.3.5.6 Washing and diluting of cellular therapy products.
  - B3.3.5.7 Cellular therapy product administration.
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B3.4 PHYSICIANS-IN-TRAINING

- B3.4.1 Physicians-in-training shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and licensure and shall be appropriately supervised.
  - B3.4.2 Physicians-in-training shall receive specific training and develop competency in transplant-related skills, including but not limited to those listed in B3.3.3 and B3.3.4.
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B3.5 ADVANCED PRACTICE PROVIDERS/PROFESSIONALS

- B3.5.1 APPs shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and licenses.
  - B3.5.2 APPs shall have received specific training and maintain competency in the transplant-related skills that they routinely practice including but not limited to those listed in B3.3.3 and B3.3.4.
  - B3.5.3 APPs shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
    - B3.5.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.
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B3.6 CLINICAL TRANSPLANT TEAM

- B3.6.1 Clinical Programs performing pediatric transplantation shall have a transplant team trained in the management of pediatric patients.
  - B3.6.2 The Clinical Program shall have access to licensed physicians who are trained and competent in marrow collection and utilize a marrow collection facility that meets these Standards.
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- B3.6.3 The Clinical Program shall have access to personnel who are trained and competent in cellular therapy product collection by apheresis and utilize an apheresis collection facility that meets these Standards.
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B3.7 NURSES

- B3.7.1 The Clinical Program shall have nurses formally trained and experienced in the management of patients receiving cellular therapy.
- B3.7.2 Clinical Programs treating pediatric patients shall have nurses formally trained and experienced in the management of pediatric patients receiving cellular therapy.
- B3.7.3 Training and competency shall include:
- B3.7.3.1 Hematology/oncology patient care, including an overview of the cellular therapy process.
  - B3.7.3.2 Administration of preparative regimens.
  - B3.7.3.3 Administration of blood products, growth factors, cellular therapy products, and other supportive therapies.
  - B3.7.3.4 Care interventions to manage cellular therapy complications, including, but not limited to, cytokine release syndrome, tumor lysis syndrome, cardiac dysfunction, respiratory distress, neurologic toxicity, renal and hepatic failure, disseminated intravascular coagulation, anaphylaxis, neutropenic fever, infectious and noninfectious processes, mucositis, nausea and vomiting, and pain management.
  - B3.7.3.5 Recognition of cellular therapy complications and emergencies requiring rapid notification of the transplant team.
  - B3.7.3.6 Palliative and end of life care.
- B3.7.4 There shall be written policies for all relevant nursing procedures, including, but not limited to:
- B3.7.4.1 Care of immunocompromised patients.
  - B3.7.4.2 Administration of preparative regimens.
  - B3.7.4.3 Administration of cellular therapy products.
  - B3.7.4.4 Central venous access device care.
  - B3.7.4.5 Administration of blood products.
  - B3.7.4.6 Detection and management of immune effector cellular therapy complications including, but not limited to, those listed in B3.7.3.4.

- B3.7.5 There shall be an adequate number of nurses experienced in the care of transplant patients.
  - B3.7.6 There shall be a nurse/patient ratio satisfactory to manage the severity of the patients' clinical status.
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**B3.8 PHARMACISTS**

- B3.8.1 Pharmacists shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and licensure.
  - B3.8.2 Training shall include:
    - B3.8.2.1 An overview of hematology/oncology patient care, including the cellular therapy process, cytokine release syndrome, and neurological toxicities.
    - B3.8.2.2 Therapeutic drug monitoring, including, but not limited to, anti-infective agents, immunosuppressive therapy, anti-seizure medications, and anticoagulation.
    - B3.8.2.3 Monitoring for and recognition of drug/drug and drug/food interactions and necessary dose modifications.
    - B3.8.2.4 Recognition of medications that require adjustment for organ dysfunction.
  - B3.8.3 Pharmacists shall be involved in the development and implementation of guidelines or SOPs related to the pharmaceutical management of cellular therapy recipients.
  - B3.8.4 Designated transplant pharmacists shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
    - B3.8.4.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and cytokine release syndrome and neurological toxicities resulting from cellular therapies.
- 

**B3.9 CONSULTING SPECIALISTS**

- B3.9.1 The Clinical Program shall have access to certified or trained consulting specialists and/or specialist groups from key disciplines who are capable of assisting in the management of patients requiring medical care, including, but not limited to:
  - B3.9.1.1 Surgery.
  - B3.9.1.2 Pulmonary medicine.
  - B3.9.1.3 Intensive care.

- B3.9.1.4 Gastroenterology.
  - B3.9.1.5 Nephrology.
  - B3.9.1.6 Infectious disease.
  - B3.9.1.7 Cardiology.
  - B3.9.1.8 Pathology.
  - B3.9.1.9 Psychiatry.
  - B3.9.1.10 Radiology.
  - B3.9.1.11 Radiation oncology with experience in large-field (e.g., total body or total lymphoid) irradiation treatment protocols, if radiation therapy is administered.
  - B3.9.1.12 Transfusion medicine.
  - B3.9.1.13 Neurology.
  - B3.9.1.14 Ophthalmology.
  - B3.9.1.15 Obstetrics/Gynecology.
  - B3.9.1.16 Dermatology.
  - B3.9.1.17 Palliative and end of life care.
- B3.9.2 A Clinical Program treating pediatric patients shall have consultants, as defined in B3.9.1, qualified to manage pediatric patients.
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**B3.10 QUALITY MANAGER**

- B3.10.1 There shall be a Clinical Program Quality Manager to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Clinical Program.
  - B3.10.2 The Clinical Program Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.
  - B3.10.3 The Clinical Program Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy and/or quality management annually at a minimum.
    - B3.10.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.
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**B3.11 SUPPORT SERVICES STAFF**

B3.11.1 The Clinical Program shall have one or more designated staff with appropriate training and education to assist in the provision of pre-transplant patient evaluation, treatment, and post-transplant follow-up and care. Designated staff shall include:

B3.11.1.1 Dietary staff capable of providing dietary consultation regarding the nutritional needs of the recipient, including enteral and parenteral support, and appropriate dietary advice to avoid food-borne illness.

B3.11.1.2 Social Services staff.

B3.11.1.3 Psychology Services staff.

B3.11.1.4 Physical Therapy staff.

B3.11.1.5 Data Management staff sufficient to comply with B9.

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**B4: QUALITY MANAGEMENT**

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B4.1 There shall be an overall Quality Management Program that incorporates key performance data from clinical, collection, and processing facility quality management.

B4.1.1 The Clinical Program Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

B4.1.2 The Clinical Program Director shall annually review the effectiveness of the Quality Management Program.

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B4.2 The Clinical Program shall establish and maintain a written Quality Management Plan.

B4.2.1 The Clinical Program Director or designee shall be responsible for the Quality Management Plan.

B4.2.2 The Clinical Program Director or designee shall review and report to staff quality management activities, at a minimum, quarterly.

B4.2.3 The Clinical Program Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Clinical Program.

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

B4.3.1 The Quality Management Plan shall include a description of how these key positions interact to implement the quality management activities.

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B4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Clinical Program. Personnel requirements shall include at a minimum:

B4.4.1 A current job description for all staff.

B4.4.2 A system to document the following for all staff:

B4.4.2.1 Initial qualifications.

B4.4.2.2 New employee orientation.

B4.4.2.3 Initial training and retraining when appropriate for all procedures performed.

B4.4.2.4 Competency for each critical function performed.

B4.4.2.5 Continued competency at least annually.

B4.4.2.6 Continuing education.

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B4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control and management.

B4.5.1 There shall be policies and procedures for development, approval, implementation, review, revision, and archival of all critical documents.

B4.5.2 There shall be a current listing of all active critical documents that shall comply with the document control system requirements. Controlled documents shall include at a minimum:

B4.5.2.1 Policies, protocols, and Standard Operating Procedures.

B4.5.2.2 Worksheets.

B4.5.2.3 Forms.

B4.5.2.4 Labels.

B4.5.3 The document control policy shall include:

B4.5.3.1 A standardized format for policies, procedures, worksheets, and forms.

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- B4.5.3.2 Assignment of numeric or alphanumeric identifier and title to each document and document version regulated within the system.
  - B4.5.3.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.
  - B4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.
  - B4.5.3.5 A system for document change control that includes a description of the change, the signature of approving individual(s), approval date(s), effective date, and archival date.
  - B4.5.3.6 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.
  - B4.5.3.7 A system for the retraction of obsolete documents to prevent unintended use.
  - B4.5.3.8 A system for record creation, assembly, review, storage, archival, and retrieval.
- B4.5.4 There shall be a process for the regular review and assessment of records to identify recurring problems, potential points of failure, or need for process improvement.

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- B4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the clinical care of the recipient and/or donor.
- B4.6.1 Agreements shall include the responsibility of the third-party facility performing any step in collection, processing, or testing to comply with applicable laws and regulations and these Standards.
  - B4.6.2 Agreements shall be dated and reviewed on a regular basis.

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- B4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.
- B4.7.1 Criteria for cellular therapy product safety, product efficacy, and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.
  - B4.7.2 Both individual cellular therapy product data and aggregate data for each type of cellular therapy product and/or recipient type shall be evaluated.

- B4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:
- B4.7.3.1 For HPC products intended for hematopoietic reconstitution, time to engraftment following product administration.
  - B4.7.3.2 For immune effector cells, an endpoint of clinical function as approved by the Clinical Program Director.
  - B4.7.3.3 Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration.
  - B4.7.3.4 Acute GVHD grade within one hundred (100) days after allogeneic transplantation.
  - B4.7.3.5 Chronic GVHD grade within one (1) year after allogeneic transplantation.
  - B4.7.3.6 Central venous catheter infection.
- B4.7.4 Data on outcome analysis and cellular therapy product efficacy, including adverse events related to the recipient, donor, and/or product, shall be provided in a timely manner to entities involved in the collection, processing, and/or distribution of the cellular therapy product.
- B4.7.5 The Clinical Program should achieve one-year survival outcome within or above the expected range when compared to national or international outcome data.
- B4.7.5.1 If expected one-year survival outcome is not met, the Clinical Program shall submit a corrective action plan.

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- B4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a schedule for conducting, reviewing, and reporting audits of the Clinical Program's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.
- B4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.
  - B4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow up on the effectiveness of these actions in a timely manner.
  - B4.8.3 Audits shall include, at a minimum:
    - B4.8.3.1 Periodic audit of the accuracy of clinical data.
    - B4.8.3.2 Annual audit of safety endpoints and immune effector cellular therapy toxicity management.

- B4.8.3.3 Periodic audit of the accuracy of data contained in the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A Forms of the EBMT.
  - B4.8.3.4 Annual audit of donor screening and testing.
  - B4.8.3.5 Annual audit of verification of chemotherapy drug and dose against the prescription ordering system and the protocol.
  - B4.8.3.6 Annual audit of management of cellular therapy products with positive microbial culture results.
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B4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

- B4.9.1 Notification of the recipient.
  - B4.9.2 Recipient follow-up and outcome analysis.
  - B4.9.3 Follow-up of the donor, if relevant.
  - B4.9.4 Reporting to regulatory agencies if appropriate.
  - B4.9.5 Criteria for the administration of cellular therapy products with positive microbial culture results.
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B4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, biological product deviations, serious adverse events, and complaints, including the following activities at a minimum:

- B4.10.1 Detection.
  - B4.10.2 Investigation.
    - B4.10.2.1 A thorough investigation shall be conducted by the Clinical Program in collaboration with the Collection Facility, Processing Facility, and other entities involved in the manufacture of the cellular therapy product, as appropriate.
    - B4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective actions as warranted.
  - B4.10.3 Documentation.
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- B4.10.3.1 Documentation shall include a description of the event, the involved individuals and/or cellular therapy products, when the event occurred, when and to whom the event was reported, and the immediate actions taken.
  - B4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Clinical Program Director or designee and the Quality Manager.
  - B4.10.3.3 Cumulative files of errors, accidents, biological product deviations, serious adverse events, and complaints shall be maintained.
  - B4.10.3.4 Cumulative files shall include written investigation reports containing conclusions, follow-up, corrective actions, and a link to the record(s) of the involved cellular therapy products, if applicable.
- B4.10.4 Reporting.
- B4.10.4.1 When it is determined that a cellular therapy product was responsible for an adverse reaction, the reaction and results of the investigation shall be reported to the recipient's physician, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by applicable laws and regulations.
  - B4.10.4.2 Errors, accidents, biological product deviations, and complaints shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.
- B4.10.5 Corrective and preventive action.
- B4.10.5.1 Appropriate corrective action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.
  - B4.10.5.2 Follow-up audits of the effectiveness of corrective actions shall be performed in a timeframe as indicated in the investigative report.
- B4.10.6 There shall be a defined process to obtain feedback from patients or legally authorized representatives.

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B4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

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B4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event the Clinical Program's operations are interrupted.

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- B4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of supplies and validation and/or verification of the procedure for marrow collection to achieve the expected end-points, including viability of cells and cellular therapy product characteristics.
- B4.13.1 Critical reagents, supplies, equipment, and facilities used for the marrow collection procedure shall be qualified.
- B4.13.1.1 Qualification plans shall be reviewed and approved by the Clinical Program Director or designee.
- B4.13.2 The marrow collection procedure validation shall include:
- B4.13.2.1 An approved validation plan, including conditions to be validated.
- B4.13.2.2 Acceptance criteria.
- B4.13.2.3 Data collection.
- B4.13.2.4 Evaluation of data.
- B4.13.2.5 Summary of results.
- B4.13.2.6 Review and approval of the validation plan, results, and conclusion by the Marrow Collection Facility Director or designee and the Quality Manager or designee.
- B4.13.3 Changes to a process with the potential to affect the potency, viability, or purity of the cellular therapy product shall include evaluation of risk that the change might create an adverse impact anywhere in the operation and shall be validated or verified as appropriate.

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## **B5: POLICIES AND PROCEDURES**

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- B5.1 The Clinical Program shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in B4. These documents shall include all elements required by these Standards and shall address at a minimum:
- B5.1.1 Recipient evaluation, selection, and treatment.
- B5.1.2 Donor and recipient confidentiality.
- B5.1.3 Donor and recipient consent.
- B5.1.4 Donor screening, testing, eligibility determination, selection, and management.

- B5.1.5 Management of donors who require central venous access.
  - B5.1.6 Administration of the preparative regimen.
  - B5.1.7 Administration of blood products.
  - B5.1.8 Administration of HPC and other cellular therapy products, including products under exceptional release.
  - B5.1.9 Administration of ABO-incompatible products to include a description of the indication for and processing methods to be used for red cell or plasma reduction.
  - B5.1.10 Management of toxicities of immune effector cellular therapies, including cytokine release syndrome and central nervous system complications.
  - B5.1.11 Duration and conditions of cellular therapy product storage and indications for disposal.
  - B5.1.12 Hygiene and use of personal protective equipment.
  - B5.1.13 Disposal of medical and biohazard waste.
  - B5.1.14 Emergency and disaster plan, including the Clinical Program response.
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B5.2 The Clinical Program shall maintain a detailed Standard Operating Procedures Manual that includes a listing of all current Standard Operating Procedures, including title, identifier, and version.

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B5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:

- B5.3.1 A clearly written description of the objectives.
- B5.3.2 A description of equipment and supplies used.
- B5.3.3 Acceptable end-points and the range of expected results.
- B5.3.4 A stepwise description of the procedure.
- B5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.
- B5.3.6 Age-specific issues where relevant.
- B5.3.7 A reference section listing appropriate literature.

- B5.3.8 Documented approval of each procedure by the Clinical Program Director or designated physician prior to implementation and every two years thereafter.
  - B5.3.9 Documented approval of each procedural modification by the Clinical Program Director or designated physician prior to implementation.
  - B5.3.10 Reference to a current version of orders, worksheets, reports, labels, and forms.
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B5.4 Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

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B5.5 Staff training and, if appropriate, competency shall be documented before performing a new or revised procedure.

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B5.6 All personnel shall follow the Standard Operating Procedures related to their positions.

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B5.7 Variances shall be pre-approved by the Clinical Program Director and reviewed by the Quality Manager.

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## **B6: ALLOGENEIC AND AUTOLOGOUS DONOR SELECTION, EVALUATION, AND MANAGEMENT**

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B6.1 There shall be written criteria for allogeneic and autologous donor selection, evaluation, and management by trained medical personnel.

B6.1.1 Written criteria shall include criteria for the selection of allogeneic donors who are minors or elderly.

B6.1.2 Written criteria shall include criteria for the selection of allogeneic donors when more than one donor is available and suitable.

B6.1.3 Information regarding the donation process should be provided to the potential allogeneic donor prior to HLA typing.

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### **B6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT TO DONATE**

B6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

B6.2.1.1 The risks and benefits of the procedure.

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- B6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.
- B6.2.1.3 The rights of the donor or legally authorized representative to review the results of such tests according to applicable laws and regulations.
- B6.2.1.4 Alternative collection methods.
- B6.2.1.5 Protection of medical information and confidentiality.
- B6.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.
- B6.2.3 Family members and legally authorized representatives should not serve as interpreters or translators.
- B6.2.4 The donor shall have an opportunity to ask questions.
- B6.2.5 The donor shall have the right to refuse to donate.
  - B6.2.5.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.
- B6.2.6 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.
  - B6.2.6.1 Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.
- B6.2.7 In the case of a minor donor, informed consent shall be obtained from the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.
- B6.2.8 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician and/or the recipient.
- B6.2.9 The donor shall be informed of the policy for cellular therapy product discard or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product.
- B6.2.10 Documentation of consent shall be available to the Collection Facility staff prior to the collection procedure.

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B6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

- B6.3.1 There shall be criteria and evaluation policies and procedures in place to protect the safety of donors during the process of cellular therapy product collection.

- B6.3.1.1 Any abnormal finding shall be reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.
  - B6.3.1.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.
  - B6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.
  - B6.3.2 The risks of donation shall be evaluated and documented, including:
    - B6.3.2.1 Possible need for central venous access.
    - B6.3.2.2 Mobilization therapy for collection of HPC, Apheresis.
    - B6.3.2.3 Anesthesia for collection of HPC, Marrow.
  - B6.3.3 The donor should be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen.
  - B6.3.4 A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to starting the donor mobilization regimen and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.
  - B6.3.5 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, or licensed in accordance with applicable laws and regulations.
  - B6.3.6 The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.
  - B6.3.7 There shall be a written order from a physician specifying, at a minimum, timing and goals of collection and processing.
  - B6.3.8 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff prior to collection.
  - B6.3.9 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 recipient's physician.
  - B6.3.10 There shall be a policy for follow-up of donors that includes routine management and the management of collection-associated adverse events.
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## B6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

- B6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated, as those terms as defined by applicable laws.
- B6.4.2 Allogeneic donor infectious disease testing shall be performed using donor screening tests approved or cleared by the governmental authority.
- B6.4.3 Allogeneic donors and allogeneic recipients shall be tested for ABO group and Rh type using two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.
- B6.4.4 A red cell antibody screen shall be performed on allogeneic recipients.
- B6.4.5 Allogeneic donors shall be evaluated for risk factors that might result in disease transmission from the cellular therapy product by medical history, physical examination, examination of relevant medical records, and laboratory testing.
- B6.4.6 The medical history for allogeneic donors shall include at least the following:
  - B6.4.6.1 Vaccination history.
  - B6.4.6.2 Travel history.
  - B6.4.6.3 Blood transfusion history.
  - B6.4.6.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the applicable governmental authority.
  - B6.4.6.5 Questions to identify persons at risk of transmitting inherited conditions.
  - B6.4.6.6 Questions to identify persons at risk of transmitting a hematological or immunological disease.
  - B6.4.6.7 Questions to identify a past history of malignant disease.
  - B6.4.6.8 The allogeneic donor shall confirm that all the information provided is true to the best of his/her knowledge.
- B6.4.7 Allogeneic donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests required by applicable laws and regulations:
  - B6.4.7.1 Human immunodeficiency virus, type 1.
  - B6.4.7.2 Human immunodeficiency virus, type 2.
  - B6.4.7.3 Hepatitis B virus.
  - B6.4.7.4 Hepatitis C virus.
  - B6.4.7.5 *Treponema pallidum* (syphilis).

- B6.4.8 If required by applicable laws and regulations, allogeneic donors shall also be tested for evidence of clinically relevant infection by the following disease agents:
- B6.4.8.1 Human T cell lymphotropic virus I.
  - B6.4.8.2 Human T cell lymphotropic virus II.
  - B6.4.8.3 West Nile Virus.
  - B6.4.8.4 *Trypanosoma cruzi* (Chagas Disease).
- B6.4.9 Blood samples for testing for evidence of clinically relevant infection shall be drawn and tested within timeframes required by applicable laws and regulations.
- B6.4.9.1 Blood samples for communicable disease testing from allogeneic HPC donors shall be obtained within thirty (30) days prior to collection.
  - B6.4.9.2 For viable, lymphocyte rich cells, including mononuclear cells and other cellular therapy products, blood samples from allogeneic donors shall be obtained within seven (7) days prior to or after collection in the U.S. or 30 days prior to collection in European Union member states.
- B6.4.10 Allogeneic donors shall be tested for CMV (unless previously documented to be positive).
- B6.4.11 Additional tests shall be performed as required to assess the possibility of transmission of other infectious and non-infectious diseases.
- B6.4.12 Allogeneic donors and recipients shall be tested for HLA antigens by a laboratory accredited by ASHI, EFI, or other appropriate organization. Typing shall include at a minimum HLA-A, B, and DRB1 type for all allogeneic donors and also HLA-C type for unrelated allogeneic donors and related allogeneic donors other than siblings.
- B6.4.12.1 DNA high resolution molecular typing shall be used for DRB1 typing.
  - B6.4.12.2 Verification typing shall be performed on the selected allogeneic donor using an independently collected sample. Results shall be confirmed prior to administration of the preparative regimen.
  - B6.4.12.3 There shall be a procedure to confirm the identity of cord blood units if verification typing cannot be performed on attached segments.
  - B6.4.12.4 There shall be a policy for anti-HLA antibody testing for mismatched donors and recipients.
- B6.4.13 Allogeneic donor eligibility, as defined by applicable laws and regulations, shall be determined by a physician 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.
- B6.4.14 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

- B6.4.15 The use of an ineligible allogeneic donor, or an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of the rationale for his/her selection by the transplant physician, urgent medical need documentation, and the informed consent of the donor and the recipient.
- B6.4.16 Allogeneic donor eligibility shall be communicated in writing to the Collection and Processing Facilities.
- B6.4.17 There shall be a policy covering the creation and retention of allogeneic donor records.
- B6.4.17.1 Allogeneic donor records shall include donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.
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## **B7: RECIPIENT CARE**

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- B7.1 Recipient informed consent for the cellular therapy shall be obtained and documented by a licensed health care professional familiar with the proposed therapy.
- B7.1.1 The Clinical Program shall provide information regarding the risks and benefits of the proposed cellular therapy.
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- B7.2 The attending physician shall verify the availability and suitability of a donor or cellular therapy product prior to initiating the recipient's preparative regimen.
- B7.2.1 The Clinical Program shall notify the Processing Facility prior to requesting a cellular therapy product from a cord blood bank, registry, or other facility.
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- B7.3 Records shall be made concurrently with each step of recipient care in such a way that all steps may be accurately traced.
- B7.3.1 Records shall identify the person immediately responsible for each significant step, including dates and times (where appropriate) of various steps.
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- B7.4 There shall be a policy addressing safe administration of the preparative regimen.
- B7.4.1 The treatment orders shall include the patient height and weight, specific dates of administration, daily doses (if appropriate), and route of administration of each agent.

- B7.4.2 Preprinted orders or electronic equivalent shall be used for protocols and standardized regimens. These orders shall be verified and documented by an attending physician.
  - B7.4.3 The pharmacist preparing the drug shall verify and document the doses against the protocol or standardized regimen listed on the orders.
  - B7.4.4 Prior to administration of the preparative regimen, one (1) qualified person using a validated process or two (2) qualified people shall verify and document the drug and dose in the bag or pill against the orders and the protocol, and the identity of the patient to receive the therapy.
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B7.5 There shall be a policy addressing safe administration of radiation therapy.

- B7.5.1 There shall be a consultation with a radiation oncologist prior to initiation of therapy if radiation treatment is used in the preparative regimen.
  - B7.5.2 The patient's diagnosis, relevant medical history including pre-existing co-morbid conditions, and proposed preparative regimen shall be made available to the consulting radiation oncologist in writing.
  - B7.5.3 A documented consultation by a radiation oncologist shall address any prior radiation treatment the patient may have received, any other factors that may increase the toxicity of the radiation, and include a plan for delivery of radiation therapy.
  - B7.5.4 Prior to administration of each dose of radiation therapy, the dose shall be verified and documented as per radiation therapy standards.
  - B7.5.5 A final report of the details of the radiation therapy administered shall be documented in the patient medical record.
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B7.6 There shall be a policy addressing safe administration of cellular therapy products.

- B7.6.1 There shall be a policy for determining the appropriate volume and the appropriate dose of red blood cells, cryoprotectants, and other additives.
  - B7.6.2 There shall be a policy for volume of ABO-incompatible red cells in allogeneic cellular therapy products.
  - B7.6.3 There shall be consultation with the Processing Facility regarding cord blood preparation for administration.
    - B7.6.3.1 Cord blood units that have not been red cell reduced prior to cryopreservation shall be washed prior to administration.
    - B7.6.3.2 Cord blood units that have been red cell reduced prior to cryopreservation should be diluted or washed prior to administration.
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- B7.6.4 Two (2) qualified persons shall verify the identity of the recipient and the product and the order for administration prior to the administration of the cellular therapy product.
- B7.6.5 For transplants utilizing cellular therapy products from more than one donor, the first cellular therapy product shall be administered safely prior to administration of the second cellular therapy product.
- B7.6.6 There shall be documentation in the recipient's medical record of the administered cellular therapy product unique identifier, initiation and completion times of administration, and any adverse events related to administration.
- B7.6.7 A circular of information for cellular therapy products shall be available to staff.
- B7.6.8 There should be policies and procedures in place for monitoring by appropriate specialists of recipients for post-transplant late effects, including at a minimum endocrine and reproductive function, osteoporosis, cardiovascular risk factors, respiratory function, chronic renal impairment, secondary cancers, and the growth and development of pediatric patients.

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B7.7            ADDITIONAL REQUIREMENTS FOR ALLOGENEIC TRANSPLANTATION

- B7.7.1            Allogeneic recipients should be assessed regularly for evidence of acute GVHD using an established staging and grading system.
- B7.7.2            Allogeneic recipients should be assessed regularly for evidence of chronic GVHD using an established staging and grading system.
- B7.7.3            There should be policies and procedures in place for allogeneic recipient post-transplant vaccination schedules and indications.

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B7.8            The Clinical Program shall refer planned discharges and post-transplant care to facilities and health care professionals adequate for post-transplant care.

- B7.8.1            The Clinical Program shall provide or secure oversight of care that meets applicable standards.

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B7.9            There shall be a policy addressing indications for and safe administration of ECP if utilized by the Clinical Program.

- B7.9.1            There shall be a consultation with the facility or physician that performs ECP prior to initiation of therapy.
- B7.9.2            Before ECP is undertaken, there shall be a written therapy plan from an attending physician specifying the patient's diagnosis and GVHD grade, involved organs, timing of the procedure, and any other factors that may affect the safe administration of ECP.

- B7.9.3 A report of the details of ECP administered, including an assessment of the response, shall be documented in the recipient's medical record.
  - B7.9.4 The facility performing ECP shall follow written procedures appropriate for the clinical condition of the patient.
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- B7.10 There shall be policies and procedures addressing the administration of immune effector cells and management of complications.
    - B7.10.1 There shall be a consultation with the referring physician prior to initiation of immune effector cellular therapy to review the goal and plan of the treatment.
    - B7.10.2 There shall be regular assessment of the recipient to detect complications, including cytokine release syndrome and neurologic dysfunction.
    - B7.10.3 There shall be a written plan for rapid escalation of care, increased intensity of monitoring, and relevant workup to address complications.
    - B7.10.4 Communication to the clinical staff, intensive care unit, emergency department, and pharmacy shall be timely.
    - B7.10.5 The Clinical Program shall have written guidelines for management of complications, including the use of cytokine-blocking agents and corticosteroid administration.
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## **B8: CLINICAL RESEARCH**

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- B8.1 Clinical Programs shall have formal review of investigational treatment protocols and patient consent forms by a process that is approved under institutional policies and applicable laws and regulations.
    - B8.1.1 Those Clinical Programs utilizing investigational treatment protocols shall have in place a pharmacy equipped for research activities, including a process for tracking, inventory, and secured storage of investigational drugs.
    - B8.1.2 There shall be a process to manage investigational cellular therapy products.
  
  - B8.2 Documentation for all research protocols performed by the Clinical Program shall be maintained in accordance with institutional policies and applicable laws and regulations, including audits; approvals by the Institutional Review Board, Ethics Committee, or equivalent; correspondence with regulatory agencies; and any adverse events.
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- B8.3 For clinical research, informed consent shall be obtained from each research subject or legally authorized representative, in language he or she can understand, and under circumstances that minimize the possibility of coercion or undue influence.
- B8.3.1 The research subject or legally authorized representative shall be given the opportunity to ask questions and to have his/her questions answered to his/her satisfaction, and to withdraw from the research without prejudice.
- B8.3.2 Informed consent for a research subject shall contain the following elements at a minimum and comply with applicable laws and regulations:
- B8.3.2.1 An explanation of the research purposes, a description of the procedures to be followed, and the identification of investigational procedures.
- B8.3.2.2 The expected duration of the subject's participation.
- B8.3.2.3 A description of the reasonably expected risks, discomforts, benefits to the subject and others, and alternative procedures.
- B8.3.2.4 A statement of the extent to which confidentiality will be maintained.
- B8.3.2.5 An explanation of the extent of compensation for injury.
- 

- B8.4 There shall be a process in place to address the disclosure of any issues that may represent a conflict of interest in clinical research.
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## **B9: DATA MANAGEMENT**

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- B9.1 The Clinical Program shall collect all the data necessary to complete the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A forms of the EBMT.
- B9.1.1 Clinical Programs shall submit the data specified in B9.1 to a national or international database if required by applicable laws and regulations.
- B9.1.2 Clinical Programs should submit the data specified in B9.1 for allogeneic and autologous transplants to a national or international database.
- B9.1.3 Clinical Programs should collect the data specified in B9.1 for all patients for at least one year following administration of the cellular therapy product.
- B9.2 The Clinical Program should collect all the data elements included in the applicable CIBMTR Cellular Therapy forms or EBMT forms.
- B9.3 The Clinical Program shall define staff responsible for collecting data and, as appropriate, reporting data to institutional repositories and CIBMTR or EBMT.

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## **B10: RECORDS**

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B10.1 Clinical Program records related to quality control, 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 Clinical Program, or longer in accordance with applicable laws and regulations, or by a defined program or institutional policy.

B10.1.1 Employee records shall be maintained in a confidential manner and as required by applicable laws and regulations.

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B10.2 Patient and donor records including, but not limited to, consents and records of care, shall be maintained in a confidential manner as required by applicable laws and regulations 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, whichever requires the longest maintenance period.

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B10.3 Research records shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

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### **B10.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY**

B10.4.1 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

B10.4.2 The Clinical Program shall furnish outcome data, in so far as they concern the safety, purity, or potency of the cellular therapy product involved, to other facilities involved in the collection or processing of the cellular therapy product.

# **MARROW COLLECTION FACILITY STANDARDS**

## **PART CM**

- CM1 General
- CM2 Marrow Collection Facility
- CM3 Personnel
- CM4 Quality Management
- CM5 Policies and Procedures
- CM6 Allogeneic and Autologous Donor Evaluation and Management
- CM7 Coding and Labeling of Cellular Therapy Products
- CM8 Process Controls
- CM9 Cellular Therapy Product Storage
- CM10 Cellular Therapy Product Transportation and Shipping
- CM11 Records
- CM12 Direct Distribution to Clinical Program

## **PART CM: MARROW COLLECTION FACILITY STANDARDS**

### **CM1: GENERAL**

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CM1.1 These Standards apply to the Marrow Collection Facility for collection activities of all cellular therapy products collected from living donors.

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CM1.2 The Marrow Collection Facility shall use cell processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Marrow Collection Facility.

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CM1.3 The Marrow Collection Facility shall abide by all applicable laws and regulations.

CM1.3.1 The Marrow Collection Facility shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

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CM1.4 The Marrow Collection Facility shall have a Marrow Collection Facility Medical Director, a Quality Manager, and at least 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.

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CM1.5 A minimum of one (1) marrow collection procedure shall have been performed in the twelve (12) month period immediately preceding facility accreditation, and a minimum average of one (1) marrow collection procedure per year shall be performed within the accreditation cycle.

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### **CM2: MARROW COLLECTION FACILITY**

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CM2.1 There shall be appropriate designated areas for collection of cellular therapy products, for collected products, and for storage of supplies, reagents, and equipment.

CM2.1.1 The Marrow Collection Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

CM2.1.2 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all cellular therapy products prior to release or distribution.

CM2.1.3 There shall be a process for confidential donor examination and evaluation.

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- CM2.2 The Marrow Collection Facility shall provide adequate lighting, ventilation, and access to sinks to prevent the introduction, transmission, or spread of communicable disease.
- 
- CM2.3 Critical Marrow Collection Facility parameters that may affect cellular therapy product viability, integrity, contamination, sterility, or cross-contamination during collection, including temperature and humidity at a minimum, shall be assessed for risk to the cellular therapy product.
- CM2.3.1 Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.
- 
- CM2.4 Marrow Collection Facility parameters and environmental conditions shall be controlled to protect the safety and comfort of patients, donors, and personnel.
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- CM2.5 The Marrow Collection Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.
- 
- CM2.6 There shall be adequate equipment and materials for the procedures performed.
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- CM2.7 There shall be access to an intensive care unit and/or emergency services.
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- CM2.8 The Marrow Collection Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.
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- CM2.9 The Marrow Collection Facility shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to communicable disease and to chemical, biological, or radiological hazards.
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## CM3: PERSONNEL

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### CM3.1 MARROW COLLECTION FACILITY MEDICAL DIRECTOR

- CM3.1.1 There shall be a Marrow Collection Facility Medical Director who is a licensed physician with postgraduate training in cell collection and/or transplantation.
- CM3.1.2 The Marrow Collection Facility Medical Director or designee shall be responsible for the following elements:
  - CM3.1.2.1 All technical procedures.
  - CM3.1.2.2 Performance of the marrow collection procedure.
  - CM3.1.2.3 Supervision of staff.
  - CM3.1.2.4 Administrative operations.
  - CM3.1.2.5 The medical care of allogeneic and/or autologous donors undergoing marrow collection.
  - CM3.1.2.6 Pre-collection evaluation of allogeneic and/or autologous donors at the time of donation.
  - CM3.1.2.7 Care of any complications resulting from the collection procedure.
  - CM3.1.2.8 The Quality Management Program, including compliance with these Standards and other applicable laws and regulations.
- CM3.1.3 The Marrow Collection Facility Medical Director shall have at least one year experience in cellular therapy product collection procedures.
- CM3.1.4 The Marrow Collection Facility Medical Director shall have performed or supervised at least ten (10) marrow collection procedures within his/her career.
- CM3.1.5 The Marrow Collection Facility Medical Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
  - CM3.1.5.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and marrow collection.

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### CM3.2 QUALITY MANAGER

- CM3.2.1 There shall be a Marrow Collection Facility Quality Manager to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Marrow Collection Facility.

CM3.2.2 The Marrow Collection Facility Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy, cell collection, and/or quality management annually at a minimum.

CM3.2.2.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

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CM3.3 STAFF

CM3.3.1 The Marrow Collection Facility shall have access to licensed health care professionals who are trained and competent in marrow collection.

CM3.3.2 The number of trained collection personnel shall be adequate for the number of procedures performed and shall include a minimum of one designated trained individual with an identified trained backup to maintain sufficient coverage.

CM3.3.3 For Marrow Collection Facilities collecting cellular therapy products from pediatric donors, physicians and collection staff shall have documented training and experience in performing these procedures.

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**CM4: QUALITY MANAGEMENT**

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CM4.1 The Marrow Collection Facility shall comply with B4 if it operates independently of a Clinical Program.

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**CM5: POLICIES AND PROCEDURES**

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CM5.1 The Marrow Collection Facility shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in CM4. These documents shall include all elements required by these Standards and shall address at a minimum:

CM5.1.1 Donor and recipient confidentiality.

CM5.1.2 Donor consent.

CM5.1.3 Donor screening, testing, eligibility determination, and management.

CM5.1.4 Cellular therapy product collection.

CM5.1.5 Prevention of mix-ups and cross-contamination.

CM5.1.6 Labeling (including associated forms and samples).

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- CM5.1.7 Cellular therapy product expiration dates.
  - CM5.1.8 Cellular therapy product storage.
  - CM5.1.9 Release and exceptional release.
  - CM5.1.10 Transportation and shipping, including methods and conditions to be used for distribution to external facilities.
  - CM5.1.11 Critical equipment, reagent, and supply management including recalls and corrective actions in the event of failure.
  - CM5.1.12 Hygiene and use of personal protective attire.
  - CM5.1.13 Emergency and disaster plan related to the marrow collection procedure.
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CM5.2 The Marrow Collection Facility shall comply with B5.2 if it operates independently of a Clinical Program.

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CM5.3 Standard Operating Procedures required in CM5.1 shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:

- CM5.3.1 A clearly written description of the objectives.
  - CM5.3.2 A description of equipment and supplies used.
  - CM5.3.3 Acceptable end-points and the range of expected results.
  - CM5.3.4 A stepwise description of the procedure.
  - CM5.3.5 Age-specific issues where relevant.
  - CM5.3.6 Reference to other Standard Operating Procedures or policies required to perform the procedure.
  - CM5.3.7 A reference section listing appropriate literature.
  - CM5.3.8 Documented approval of each procedure by the Marrow Collection Facility Medical Director prior to implementation and every two years thereafter.
  - CM5.3.9 Documented approval of each procedural modification by the Marrow Collection Facility Medical Director or designated physician prior to implementation.
  - CM5.3.10 Reference to a current version of orders, worksheets, reports, labels, and forms.
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- CM5.4 Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.
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- CM5.5 Staff training and, if appropriate, competency shall be documented before performing a new or revised procedure.
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- CM5.6 All personnel shall follow the Standard Operating Procedures related to their positions.
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- CM5.7 Variances shall be pre-approved by the Marrow Collection Facility Medical Director, and reviewed by the Quality Manager.
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## **CM6: ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT**

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- CM6.1 There shall be written criteria for allogeneic and autologous donor evaluation and management by trained medical personnel.
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- CM6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT FOR COLLECTION
- CM6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:
- CM6.2.1.1 The risks and benefits of the procedure.
  - CM6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.
  - CM6.2.1.3 The rights of the donor or legally authorized representative to review the results of such tests according to applicable laws and regulations.
  - CM6.2.1.4 Protection of medical information and confidentiality.
- CM6.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.
- CM6.2.3 Family members and legally authorized representatives should not serve as interpreters or translators.
- CM6.2.4 The donor shall have an opportunity to ask questions.
- CM6.2.5 The donor shall have the right to refuse to donate.

- CM6.2.5.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.
- CM6.2.6 Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional familiar with the collection procedure.
  - CM6.2.6.1 Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.
- CM6.2.7 In the case of a minor donor, informed consent shall be obtained from the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.
- CM6.2.8 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician and/or the recipient.
- CM6.2.9 Documentation of consent shall be available to the Marrow Collection Facility staff prior to the collection procedure.

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CM6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

- CM6.3.1 There shall be criteria and evaluation policies and procedures in place to protect the safety of donors during the process of cellular therapy product collection.
  - CM6.3.1.1 The Marrow Collection Facility shall confirm that any abnormal findings are reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.
  - CM6.3.1.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.
  - CM6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.
- CM6.3.2 The risks of donation shall be evaluated and documented, including anesthesia for marrow collection.
- CM6.3.3 A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to starting the donor mobilization regimen and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.
- CM6.3.4 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, or licensed in accordance with applicable laws and regulations.

- CM6.3.5 The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.
  - CM6.3.6 There shall be a written order from a physician specifying, at a minimum, timing and goals of collection.
  - CM6.3.7 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 transplant physician. Collection staff shall document review of these donor safety issues.
  - CM6.3.8 There shall be written documentation of issues of donor health that pertain to the safety of the collection procedure available to the Marrow Collection Facility staff. Collection staff shall document review of these issues prior to collection.
  - CM6.3.9 There shall be a policy for follow-up of donors that includes routine management and the management of collection-associated adverse events.
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#### CM6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

- CM6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated.
  - CM6.4.2 Allogeneic donor infectious disease testing shall be performed using donor screening tests approved or cleared by the governmental authority.
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### CM7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

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#### CM7.1 ISBT 128 CODING AND LABELING

- CM7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.
  - CM7.1.2 If coding and labeling technologies have not yet been implemented, the Marrow Collection Facility shall be actively implementing ISBT 128.
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#### CM7.2 LABELING OPERATIONS

- CM7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products, product samples, and associated records.
    - CM7.2.1.1 Stocks of unused labels representing different products shall be stored in a controlled manner to prevent errors.
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- CM7.2.1.2 Obsolete labels shall be restricted from use.
- CM7.2.2 Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Marrow Collection Facility Medical Director or designee to confirm accuracy regarding identity, content, and conformity.
- CM7.2.3 Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Marrow Collection Facility Medical Director or designee.
- CM7.2.4 A system for label version control shall be employed.
- CM7.2.4.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by applicable laws and regulations, whichever is longer.
- CM7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.
- CM7.2.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.
- CM7.2.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.
- CM7.2.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.
- CM7.2.7 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process to verify the information or two (2) qualified staff members.
- CM7.2.8 Labeling elements required by applicable laws and regulations shall be present.
- CM7.2.9 All data fields on labels shall be completed.
- CM7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.
- CM7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.
- CM7.2.12 The label shall be validated as reliable for storage under the conditions in use.
-

### CM7.3 PRODUCT IDENTIFICATION

- CM7.3.1 Each cellular therapy product collection shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.
- CM7.3.1.1 The cellular therapy product, product samples, and concurrently collected samples shall be labeled with the same identifier.
- CM7.3.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.
- CM7.3.1.3 Supplementary identifiers shall not obscure the original identifier.
- CM7.3.1.4 The facility associated with each identifier shall be noted on the label.
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### CM7.4 LABEL CONTENT

- CM7.4.1 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container shall bear the information in the Cellular Therapy Product Labeling table in Appendix II.
- CM7.4.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information (COI) for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."
- CM7.4.3 Labeling at the end of collection shall occur before the cellular therapy product bag is removed from the proximity of the donor.
- CM7.4.4 Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix IV at the time of distribution.
- CM7.4.5 For 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.
- CM7.4.6 Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "For Nonclinical Use Only."
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### CM8: PROCESS CONTROLS

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- CM8.1 Collection of cellular therapy products shall be performed according to written collection procedures.
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- CM8.2 There shall be a process for inventory control that encompasses equipment, reagents, supplies, and labels.
- CM8.2.1 There shall be a system to uniquely identify and track and trace all critical equipment, reagents, supplies, and labels used in the collection of cellular therapy products.
  - CM8.2.2 Each supply and reagent used to collect cellular therapy products shall be visually examined at receipt and prior to use for damage or evidence of contamination.
  - CM8.2.3 Supplies and reagents coming into contact with cellular therapy products during collection shall be sterile and of the appropriate grade for the intended use.
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- CM8.3 Equipment for the marrow collection procedure shall conform to applicable laws and regulations.
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- CM8.4 Autologous and/or CMV-appropriate and irradiated blood components shall be available during the marrow collection procedure for all donors.
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- CM8.5 Before cell collection is undertaken, there shall be a written order from a physician specifying, at a minimum, timing and goals of collection.
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- CM8.6 There shall be peripheral blood count criteria to proceed with collection.
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- CM8.7 There shall be written documentation of an assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.
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- CM8.8 General or regional anesthesia, if required, shall be performed or supervised by a licensed, specialist-certified anesthesiologist.
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- CM8.9 Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.
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CM8.10 The Marrow Collection Facility shall utilize a process for assessing the quality of cellular therapy products to confirm product safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.

CM8.10.1 Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to confirm products meet predetermined release specifications.

CM8.10.2 Methods for collection shall employ procedures validated to result in acceptable cell viability and recovery.

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CM8.11 Collection methods shall employ aseptic technique so that cellular therapy products do not become contaminated during collection.

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CM8.12 Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures.

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CM8.13 Cellular therapy products shall be packaged in a closed sterile transfer pack appropriate for blood or marrow products.

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CM8.14 HPC, Marrow products shall be filtered to remove particulate material prior to final packaging, distribution, or administration using filters that are non-reactive with blood.

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CM8.15 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

CM8.15.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.

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## **CM9: CELLULAR THERAPY PRODUCT STORAGE**

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CM9.1 Marrow Collection Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of products.

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CM9.2 Marrow Collection Facilities shall establish policies for the duration and conditions of short-term storage prior to distribution to a Processing Facility or Clinical Program.

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## **CM10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING**

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CM10.1 Procedures for transportation and shipping of the cellular therapy product shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area.

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CM10.2 The primary cellular therapy product container shall be placed in a secondary container that is sealed to prevent leakage.

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CM10.3 The cellular therapy product shall be transported and/or shipped to the Processing Facility in a validated container at a temperature defined in a Standard Operating Procedure.

CM10.3.1 Cellular therapy products that are transported and/or shipped from the collection site to the Processing Facility shall be transported and/or shipped 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.

CM10.3.2 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.

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CM10.4 The cellular therapy product shall be transported and/or shipped with required accompanying records as defined in the transportation and shipping procedure and in compliance with CM7.4.4 and CM7.4.5.

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CM10.5 There shall be a record of the date and time of cellular therapy product distribution.

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## **CM11: RECORDS**

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CM11.1 The Marrow Collection Facility shall comply with B10 if it operates independently of a Clinical Program.

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## CM12: DIRECT DISTRIBUTION TO CLINICAL PROGRAM

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- CM12.1 Where cellular therapy products are distributed directly from the Marrow Collection Facility to the Clinical Program for administration or subsequent processing, the Standards related to labeling, documentation, distribution, transportation, and recordkeeping in Sections D7, D10, D11, D13, and the Appendices apply.

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# **APHERESIS COLLECTION FACILITY STANDARDS**

## **PART C**

- C1 General
- C2 Apheresis Collection Facility
- C3 Personnel
- C4 Quality Management
- C5 Policies and Procedures
- C6 Allogeneic and Autologous Donor Evaluation and Management
- C7 Coding and Labeling of Cellular Therapy Products
- C8 Process Controls
- C9 Cellular Therapy Product Storage
- C10 Cellular Therapy Product Transportation and Shipping
- C11 Records
- C12 Direct Distribution to Clinical Program

## **PART C: APHERESIS COLLECTION FACILITY STANDARDS**

### **C1: GENERAL**

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C1.1 These Standards apply to the Apheresis Collection Facility for collection activities of all cellular therapy products collected from living donors.

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C1.2 The Apheresis Collection Facility shall use cell processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Apheresis Collection Facility.

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C1.3 The Apheresis Collection Facility shall abide by all applicable laws and regulations.

C1.3.1 The Apheresis Collection Facility shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

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C1.4 The Apheresis Collection Facility shall have an Apheresis Collection Facility Director, an Apheresis Collection Facility Medical Director, a Quality Manager, and at least 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.

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C1.5 A minimum of ten (10) cellular therapy products shall have been collected by apheresis in the twelve (12) month period immediately preceding facility accreditation, and a minimum average of ten (10) cellular therapy products shall have been collected by apheresis per year within the accreditation cycle.

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### **C2: APHERESIS COLLECTION FACILITY**

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C2.1 There shall be appropriate designated areas for collection of cellular therapy products, for collected products, and for storage of supplies, reagents, and equipment.

C2.1.1 The Apheresis Collection Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

C2.1.2 There shall be a designated area with appropriate location and adequate space and design to minimize the risk of airborne microbial contamination in outpatient units where collection is performed.

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- C2.1.3 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all cellular therapy products prior to release or distribution.
- C2.1.4 There shall be suitable space for confidential donor examination and evaluation.
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- C2.2 The Apheresis Collection Facility shall provide adequate lighting, ventilation, and access to sinks to prevent the introduction, transmission, or spread of communicable disease.
- 
- C2.3 Apheresis Collection Facility parameters and environmental conditions shall be controlled to protect the safety and comfort of patients, donors, and personnel.
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- C2.4 Critical Apheresis Collection Facility parameters that may affect cellular therapy product viability, integrity, contamination, sterility, or cross-contamination during collection, including temperature and humidity at a minimum, shall be assessed for risk to the cellular therapy product.
- C2.4.1 Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.
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- C2.5 When using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled, monitored, and recorded, where appropriate, for air quality and surface contaminants.
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- C2.6 The Apheresis Collection Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.
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- C2.7 There shall be adequate equipment and materials for the procedures performed.
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- C2.8 There shall be access to an intensive care unit and/or emergency services.
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- C2.9 The Apheresis Collection Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.
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- C2.10 The Apheresis Collection Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease and to chemical, biological, or radiological hazards.
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### C3: PERSONNEL

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#### C3.1 APHERESIS COLLECTION FACILITY DIRECTOR

- C3.1.1 There shall be an Apheresis Collection Facility Director with a medical degree or degree in a relevant science, qualified by postgraduate training or experience for the scope of activities carried out in the Apheresis Collection Facility. The Apheresis Collection Facility Director may also serve as the Apheresis Collection Facility Medical Director, if appropriately credentialed.
- C3.1.2 The Apheresis Collection Facility Director shall be responsible for all technical procedures, performance of the collection procedure, supervision of staff, administrative operations, and the Quality Management Program, including compliance with these Standards and other applicable laws and regulations.
- C3.1.3 The Apheresis Collection Facility Director shall have at least one year experience in cellular therapy product collection procedures.
- C3.1.4 The Apheresis Collection Facility Director shall have performed or supervised a minimum of five (5) cellular therapy product apheresis collection procedures in the twelve (12) months preceding accreditation and a minimum average of five (5) cellular therapy product apheresis collection procedures per year within the accreditation cycle.
- C3.1.5 The Apheresis Collection Facility Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
- C3.1.5.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and apheresis.
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#### C3.2 APHERESIS COLLECTION FACILITY MEDICAL DIRECTOR

- C3.2.1 There shall be an Apheresis Collection Facility Medical Director who is a licensed or certified physician with postgraduate training in cell collection and/or transplantation.
- C3.2.2 The Apheresis Collection Facility Medical Director or designee shall be responsible for the medical care of donors undergoing apheresis, including the pre-collection evaluation of the donor at the time of donation and care of any complications resulting from the collection procedure.
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- C3.2.3 The Apheresis Collection Facility Medical Director shall have at least one year experience in performing and/or supervising cellular therapy product collection procedures.
- C3.2.4 The Apheresis Collection Facility Medical Director shall have performed or supervised a minimum of five (5) cellular therapy product apheresis collection procedures in the twelve (12) months preceding accreditation and a minimum average of five (5) cellular therapy product apheresis collection procedures per year within the accreditation cycle.
- C3.2.5 The Apheresis Collection Facility Medical Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
- C3.2.5.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and apheresis.
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C3.3 QUALITY MANAGER

- C3.3.1 There shall be an Apheresis Collection Facility Quality Manager to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Apheresis Collection Facility.
- C3.3.2 The Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.
- C3.3.3 The Apheresis Collection Facility Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy, cell collection, and/or quality management annually at a minimum.
- C3.3.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.
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C3.4 STAFF

- C3.4.1 The number of trained collection personnel shall be adequate for the number of procedures performed and shall include a minimum of one designated trained individual with an identified trained backup to maintain sufficient coverage.
- C3.4.2 For Apheresis Collection Facilities collecting cellular therapy products from pediatric donors, physicians and collection staff shall have documented training and experience in performing these procedures.
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## C4: QUALITY MANAGEMENT

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- C4.1 The Apheresis Collection Facility Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.
- C4.1.1 The Apheresis Collection Facility Director or designee shall annually review the effectiveness of the Quality Management Program. Documentation of the review findings shall be provided to the Clinical Program Director.
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- C4.2 The Apheresis Collection Facility shall establish and maintain a written Quality Management Plan.
- C4.2.1 The Apheresis Collection Facility Director or designee shall be responsible for the Quality Management Plan as it pertains to the Apheresis Collection Facility.
- C4.2.2 The Apheresis Collection Facility Director or designee shall review and report to staff quality management activities, at a minimum, quarterly.
- C4.2.3 The Apheresis Collection Facility Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Apheresis Collection Facility.
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- C4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions and functions within the Apheresis Collection Facility.
- C4.3.1 The Quality Management Plan shall include a description of how these key positions interact to implement the quality management activities.
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- C4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Apheresis Collection Facility. Personnel requirements shall include at a minimum:
- C4.4.1 A current job description for all staff.
- C4.4.2 A system to document the following for all staff:
- C4.4.2.1 Initial qualifications.
- C4.4.2.2 New employee orientation.
- C4.4.2.3 Initial training and retraining when appropriate for all procedures performed.
- C4.4.2.4 Competency for each critical function performed.

C4.4.2.5 Continued competency at least annually.

C4.4.2.6 Continuing education.

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C4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control and management.

C4.5.1 There shall be policies and procedures for development, approval, implementation, review, revision, and archival of all critical documents.

C4.5.2 There shall be a current listing of all active critical documents that shall comply with the document control system requirements. Controlled documents shall include at a minimum:

C4.5.2.1 Policies and Standard Operating Procedures.

C4.5.2.2 Worksheets.

C4.5.2.3 Forms.

C4.5.2.4 Labels.

C4.5.3 The document control policy shall include:

C4.5.3.1 A standardized format for policies, procedures, worksheets, forms, and labels.

C4.5.3.2 Assignment of numeric or alphanumeric identifier and title to each document and document version regulated within the system.

C4.5.3.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

C4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.

C4.5.3.5 A system for document change control that includes a description of the change, the signature of the approving individual(s), approval date, effective date, and archival date.

C4.5.3.6 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

C4.5.3.7 A system for the retraction of obsolete documents to prevent unintended use.

C4.5.3.8 A system for record creation, assembly, review, storage, archival, and retrieval.

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C4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the cellular therapy product or clinical care of the donor.

C4.6.1 Agreements shall include the responsibility of the facility performing any step in collection, processing, or testing to comply with applicable laws and regulations and these Standards.

C4.6.2 Agreements shall be dated and reviewed on a regular basis.

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C4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.

C4.7.1 Criteria for cellular therapy product safety, product efficacy, and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.

C4.7.2 Both individual cellular therapy product data and aggregate data for each type of cellular therapy product shall be evaluated.

C4.7.3 For HPC products intended for hematopoietic reconstitution, time to engraftment following product administration measured by ANC and platelet count shall be analyzed.

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C4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a schedule for conducting, reviewing, and reporting audits of the Apheresis Collection Facility's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

C4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

C4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow up on the effectiveness of these actions in a timely manner.

C4.8.3 Audits shall include the following annually at a minimum:

C4.8.3.1 Documentation of proper donor eligibility determination prior to start of the collection procedure.

C4.8.3.2 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

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C4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

C4.9.1 Notification of the recipient's physician.

C4.9.2 Investigation of cause.

C4.9.3 Follow-up of the donor, if relevant.

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C4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, biological product deviations, serious adverse events, and complaints, including the following activities at a minimum:

C4.10.1 Detection.

C4.10.2 Investigation.

C4.10.2.1 A thorough investigation shall be conducted by the Apheresis Collection Facility in collaboration with the Processing Facility and Clinical Program, as appropriate.

C4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective actions as warranted.

C4.10.3 Documentation.

C4.10.3.1 Documentation shall include a description of the event, the involved individuals and/or cellular therapy products, when the event occurred, when and to whom the event was reported, and the immediate actions taken.

C4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Apheresis Collection Facility Director, Medical Director, or designee and the Quality Manager.

C4.10.3.3 Cumulative files of errors, accidents, biological product deviations, serious adverse events, and complaints shall be maintained.

C4.10.3.4 Cumulative files shall include written investigation reports containing conclusions, follow-up, corrective actions, and a link to the record(s) of the involved cellular therapy products

C4.10.4 Reporting.

C4.10.4.1 When it is determined that a cellular therapy product was responsible for an adverse reaction, the reaction and results of the investigation shall be reported to the recipient's physician, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by applicable laws.

C4.10.4.2 Errors, accidents, biological product deviations, and complaints shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.

C4.10.5 Corrective and preventive action.

C4.10.5.1 Appropriate corrective action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.

C4.10.5.2 Follow-up audits of the effectiveness of corrective actions shall be performed in a timeframe as indicated in the investigative report.

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C4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

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C4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event the Apheresis Collection Facility's operations are interrupted.

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C4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical reagents, supplies, equipment, and facilities.

C4.13.1 Qualification plans shall be reviewed and approved by the Apheresis Collection Facility Director or designee.

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C4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of critical procedures to achieve the expected end-points, including viability of cells and cellular therapy product characteristics.

C4.14.1 Critical procedures shall include at least the following: collection procedures, labeling, storage, and distribution.

C4.14.2 Each validation shall include:

C4.14.2.1 An approved validation plan, including conditions to be validated.

C4.14.2.2 Acceptance criteria.

C4.14.2.3 Data collection.

- C4.14.2.4 Evaluation of data.
  - C4.14.2.5 Summary of results.
  - C4.14.2.6 Review and approval of the validation plan, results, and conclusion by the Apheresis Collection Facility Director or designee and the Quality Manager or designee.
- C4.14.3 Changes to a process shall include evaluation of risk to confirm that they do not create an adverse impact anywhere in the operation and shall be validated or verified as appropriate.
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## **C5: POLICIES AND PROCEDURES**

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- C5.1 The Apheresis Collection Facility shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in C4. These documents shall include all elements required by these Standards and shall address at a minimum:
- C5.1.1 Donor and recipient confidentiality.
  - C5.1.2 Donor consent.
  - C5.1.3 Donor screening, testing, eligibility determination, and management.
  - C5.1.4 Management of donors who require central venous access.
  - C5.1.5 Cellular therapy product collection.
  - C5.1.6 Administration of blood products.
  - C5.1.7 Prevention of mix-ups and cross-contamination.
  - C5.1.8 Labeling (including associated forms and samples).
  - C5.1.9 Cellular therapy product expiration dates.
  - C5.1.10 Cellular therapy product storage.
  - C5.1.11 Release and exceptional release.
  - C5.1.12 Transportation and shipping, including methods and conditions to be used for distribution to external facilities.
  - C5.1.13 Critical reagent and supply management.
  - C5.1.14 Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.

- C5.1.15 Recalls of equipment, supplies, and reagents.
  - C5.1.16 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.
  - C5.1.17 Hygiene and use of personal protective attire.
  - C5.1.18 Disposal of medical and biohazard waste.
  - C5.1.19 Emergency and disaster plan, including the Apheresis Collection Facility response.
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- C5.2 The Apheresis Collection Facility shall maintain a detailed Standard Operating Procedures Manual that includes a listing of all current Standard Operating Procedures, including title, identifier, and version.
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- C5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:
- C5.3.1 A clearly written description of the objectives.
  - C5.3.2 A description of equipment and supplies used.
  - C5.3.3 Acceptable end-points and the range of expected results.
  - C5.3.4 A stepwise description of the procedure.
  - C5.3.5 Age-specific issues where relevant.
  - C5.3.6 Reference to other Standard Operating Procedures or policies required to perform the procedure.
  - C5.3.7 A reference section listing appropriate literature.
  - C5.3.8 Documented approval of each procedure by the Apheresis Collection Facility Director or Medical Director, as appropriate, prior to implementation and every two years thereafter.
  - C5.3.9 Documented approval of each procedural modification by the Apheresis Collection Facility Director or Medical Director, as appropriate, prior to implementation.
  - C5.3.10 Reference to a current version of orders, worksheets, reports, labels, and forms.
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- C5.4 Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

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C5.5 Staff training and, if appropriate, competency shall be documented before performing a new or revised procedure.

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C5.6 All personnel shall follow the Standard Operating Procedures related to their positions.

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C5.7 Variances shall be pre-approved by the Apheresis Collection Facility Director and/or Medical Director, and reviewed by the Quality Manager.

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## **C6: ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT**

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C6.1 There shall be written criteria for allogeneic and autologous donor evaluation and management by trained medical personnel.

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### **C6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT FOR COLLECTION**

C6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

C6.2.1.1 The risks and benefits of the procedure.

C6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

C6.2.1.3 The rights of the donor or legally authorized representative to review the results of such tests according to applicable laws and regulations.

C6.2.1.4 Protection of medical information and confidentiality.

C6.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.

C6.2.3 Family members and legally authorized representatives should not serve as interpreters or translators.

C6.2.4 The donor shall have an opportunity to ask questions.

C6.2.5 The donor shall have the right to refuse to donate.

C6.2.5.1 The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal.

- C6.2.6 Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional familiar with the collection procedure.
    - C6.2.6.1 Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.
  - C6.2.7 In the case of a donor who is a minor, informed consent shall be obtained from the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.
  - C6.2.8 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician and/or the recipient.
  - C6.2.9 Documentation of consent shall be available to the Apheresis Collection Facility staff prior to the collection procedure.
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C6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

- C6.3.1 There shall be criteria and evaluation policies and procedures in place to protect the safety of donors during the process of cellular therapy product collection.
  - C6.3.1.1 The Apheresis Collection Facility shall confirm that any abnormal findings are reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.
  - C6.3.1.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.
  - C6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.
- C6.3.2 The risks of donation shall be evaluated and documented, including:
  - C6.3.2.1 Possible need for central venous access.
  - C6.3.2.2 Mobilization therapy for collection of HPC, Apheresis.
- C6.3.3 The donor should be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen.
- C6.3.4 A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to starting the donor mobilization regimen and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.

- C6.3.5 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, or licensed in accordance with applicable laws and regulations.
- C6.3.6 The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.
- C6.3.7 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 transplant physician. Collection staff shall document review of these donor safety issues.
- C6.3.8 There shall be written documentation of issues of donor health that pertain to the safety of the collection procedure available to the Apheresis Collection Facility staff. Collection staff shall document review of these issues prior to collection.
- C6.3.9 There shall be a policy for follow-up of donors that includes routine management and the management of collection-associated adverse events.
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#### C6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

- C6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated.
- C6.4.2 Allogeneic donor infectious disease testing shall be performed using donor screening tests approved or cleared by the governmental authority.
- C6.4.3 The Apheresis Collection Facility shall comply with B6.4.6 through B6.4.6.8 when primarily responsible for donor screening for transmissible disease.
- C6.4.4 The Apheresis 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.
- C6.4.5 The Apheresis 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.
- C6.4.6 The Apheresis Collection Facility shall confirm that allogeneic donor eligibility, as defined by applicable laws and regulations, is determined by a physician after history, exam, medical record review, and testing before the donor begins the mobilization regimen.
- C6.4.7 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.
- C6.4.8 Collection of a cellular therapy product from an ineligible allogeneic donor, or from an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of urgent medical need that includes the rationale for the selection and documentation of the informed consent of the donor and the recipient.

C6.4.9 Allogeneic donor eligibility shall be communicated in writing to the Processing Facility.

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C6.5 There shall be a policy covering the creation and retention of donor records including at a minimum:

C6.5.1 Donor identification including at least name and date of birth.

C6.5.2 Age, gender, and medical history, and, for allogeneic donors, behavioral history.

C6.5.3 Consent to donate.

C6.5.4 Results of laboratory testing.

C6.5.5 Allogeneic donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.

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## **C7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS**

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C7.1 ISBT 128 CODING AND LABELING

C7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

C7.1.2 If coding and labeling technologies have not yet been implemented, the Apheresis Collection Facility shall be actively implementing ISBT 128.

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C7.2 LABELING OPERATIONS

C7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products, product samples, and associated records.

C7.2.1.1 Stocks of unused labels representing different products shall be stored in a controlled manner to prevent errors.

C7.2.1.2 Obsolete labels shall be restricted from use.

C7.2.2 Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Apheresis Collection Facility Director or designee to confirm accuracy regarding identity, content, and conformity.

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- C7.2.3 Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Apheresis Collection Facility Director or designee.
- C7.2.4 A system for label version control shall be employed.
  - C7.2.4.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by applicable laws and regulations, whichever is longer.
- C7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.
  - C7.2.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.
  - C7.2.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.
- C7.2.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.
- C7.2.7 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process to verify the information or two (2) qualified staff members.
- C7.2.8 Labeling elements required by applicable laws and regulations shall be present.
- C7.2.9 All data fields on labels shall be completed.
- C7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.
- C7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.
- C7.2.12 The label shall be validated as reliable for storage under the conditions in use.

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C7.3 PRODUCT IDENTIFICATION

- C7.3.1 Each cellular therapy product collection shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.
  - C7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.

- C7.3.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.
  - C7.3.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.
  - C7.3.1.4 Supplementary identifiers shall not obscure the original identifier.
  - C7.3.1.5 The facility associated with each identifier shall be noted on the label.
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#### C7.4 LABEL CONTENT

- C7.4.1 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix II.
  - C7.4.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information (COI) for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."
  - C7.4.3 Labeling at the end of collection shall occur before the cellular therapy product bag is disconnected from the donor.
  - C7.4.4 Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix IV at the time of distribution.
  - C7.4.5 For 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.
  - C7.4.6 Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "For Nonclinical Use Only."
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#### C8: PROCESS CONTROLS

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- C8.1 Collection of cellular therapy products shall be performed according to written procedures in the Apheresis Collection Facility's Standard Operating Procedures Manual.
  - C8.2 There shall be a process for inventory control that encompasses equipment, reagents, supplies, and labels.
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- C8.2.1 There shall be a system to uniquely identify and track and trace all critical equipment, reagents, supplies, and labels used in the collection of cellular therapy products.
- C8.2.2 Each supply and reagent used to collect cellular therapy products shall be visually examined at receipt and prior to use for damage or evidence of contamination.
- C8.2.3 Supplies and reagents coming into contact with cellular therapy products during collection shall be sterile and of the appropriate grade for the intended use.
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- C8.3 Equipment shall be inspected for cleanliness prior to each use and verified to be in compliance with the maintenance schedule daily prior to use. Equipment shall also be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.
- C8.3.1 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.
- C8.3.2 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.
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- C8.4 Equipment shall conform to applicable laws and regulations.
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- C8.5 Autologous and/or CMV-appropriate and irradiated blood components shall be available during the apheresis collection procedure for all donors.
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- C8.6 Before cell collection is undertaken, there shall be a written order from a physician specifying, at a minimum, timing and goals of collection.
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- C8.7 A complete blood count, including platelet count, shall be performed within 24 hours prior to each subsequent cellular therapy product collection by apheresis.
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- C8.8 There shall be peripheral blood count criteria to proceed with collection.
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- C8.9 There shall be written documentation of an assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.
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- C8.10 If required, central venous catheters shall be placed by a licensed health care professional qualified to perform the procedure.
- C8.10.1 Adequacy of central line placement shall be verified by the Apheresis Collection Facility prior to initiating the collection procedure.
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- C8.11 Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.
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- C8.12 The Apheresis Collection Facility shall utilize a process for assessing the quality of cellular therapy products to confirm product safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.
- C8.12.1 Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to confirm products meet predetermined release specifications.
- C8.12.2 Methods for collection shall employ procedures validated to result in acceptable cell viability and recovery.
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- C8.13 Collection methods shall employ aseptic technique so that cellular therapy products do not become contaminated during collection.
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- C8.14 Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures.
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- C8.15 Cellular therapy products shall be packaged in a closed sterile transfer pack appropriate for blood products.
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- C8.16 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

- C8.16.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.
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C8.17 There shall be a policy addressing safe administration of ECP.

C8.17.1 Before ECP is undertaken, there shall be a written therapy plan from a physician specifying the patient's diagnosis and GVHD grade, involved organs, indication, timing of the procedure, proposed regimen, and any other factors that may affect the safe administration of ECP.

C8.17.2 The ECP procedure shall be performed according to written standard operating procedures of the facility performing the procedure appropriate for the clinical condition of the patient.

C8.17.3 A final report of the details of ECP administered shall be documented in the patient's medical record.

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## **C9: CELLULAR THERAPY PRODUCT STORAGE**

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C9.1 Apheresis Collection Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of products.

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C9.2 Apheresis Collection Facilities shall establish policies for the duration and conditions of short-term storage prior to distribution to a Processing Facility or Clinical Program.

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## **C10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING**

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C10.1 Procedures for transportation and shipping of the cellular therapy product shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area.

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C10.2 The primary cellular therapy product container shall be placed in a secondary container that is sealed to prevent leakage.

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C10.3 The cellular therapy product shall be transported and/or shipped to the Processing Facility in a validated container at a temperature defined in a Standard Operating Procedure.

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- C10.3.1 Cellular therapy products that are transported and/or shipped from the collection site to the Processing Facility shall be transported and/or shipped 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.
- C10.3.2 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.
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C10.4 The cellular therapy product shall be transported and/or shipped with required accompanying records as defined in the transportation and shipping procedure and in compliance with C7.4.4 and C7.4.5.

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

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## **C11: RECORDS**

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### **C11.1 GENERAL REQUIREMENTS**

- C11.1.1 A records management system shall be established and maintained to facilitate the review of records.
- C11.1.1.1 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.
- C11.1.1.2 For cellular therapy products that are to be distributed for use at another institution, the Apheresis Collection Facility shall inform the receiving institution of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.
- C11.1.2 Records shall be maintained in such a way as to preserve their integrity, preservation, and retrieval.
- C11.1.3 Records shall be accurate, legible, and indelible.
- C11.1.4 Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities, and their recipients and donors, shall be established and followed in compliance with applicable laws and regulations.
-

C11.2 Apheresis Collection Facility records related to quality control, 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 Collection Facility, or longer in accordance with applicable laws and regulations, or a defined program or institution policy.

C11.2.1 Employee records shall be maintained in a confidential manner, as required by applicable laws and regulations.

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C11.3 Records to allow tracking and tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after final distribution of the product, or as required by applicable laws and regulations. These records shall include product identity, unique numeric or alphanumeric identifier, and collection date and time; and donor and recipient identification as far as known.

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C11.4 Patient and donor records including, but not limited to, consents and records of care shall be maintained in a confidential manner as required by applicable laws and regulations 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 requires the longest maintenance period.

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C11.5 Research records shall be maintained in a confidential manner as required by applicable laws and regulations for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

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C11.6 ELECTRONIC RECORDS

C11.6.1 The Apheresis Collection Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the Apheresis Collection Facility that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

C11.6.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

C11.6.3 There shall be a means by which access to electronic records is limited to authorized individuals.

C11.6.4 The critical electronic record system shall maintain unique identifiers.

C11.6.5 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

- C11.6.6 For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation in the event that critical electronic record systems are not available. The alternative system shall be validated and Apheresis Collection Facility staff shall be trained in its use.
- C11.6.7 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.
- C11.6.7.1 A method shall be established or the system shall provide for review of data before final acceptance.
- C11.6.7.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.
- C11.6.8 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.
- C11.6.9 For all critical electronic record systems, there shall be validated procedures for and documentation of:
- C11.6.9.1 Training and continued competency of personnel in systems use.
- C11.6.9.2 Monitoring of data integrity.
- C11.6.9.3 Back-up of the electronic records system on a regular schedule.
- C11.6.9.4 System assignment of unique identifiers.

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C11.7 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

- C11.7.1 The Apheresis Collection Facility shall furnish to the facility of final disposition a copy of all records relating to the collection procedures performed in so far as they concern the safety, purity, or potency of the cellular therapy product involved.
- C11.7.2 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

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**C12: DIRECT DISTRIBUTION TO CLINICAL PROGRAM**

- C12.1 Where cellular therapy products are distributed directly from the Apheresis Collection Facility to the Clinical Program for administration or for subsequent processing, the Standards related to labeling, documentation, distribution, transportation, and recordkeeping in Sections D7, D10, D11, D13, and the Appendices apply.

# **PROCESSING FACILITY STANDARDS**

## **PART D**

- D1 General
- D2 Processing Facility
- D3 Personnel
- D4 Quality Management
- D5 Policies and Procedures
- D6 Equipment, Supplies, and Reagents
- D7 Coding and Labeling of Cellular Therapy Products
- D8 Process Controls
- D9 Cellular Therapy Product Storage
- D10 Cellular Therapy Product Transportation and Shipping
- D11 Distribution and Receipt
- D12 Disposal
- D13 Records

## **PART D: PROCESSING FACILITY STANDARDS**

### **D1: GENERAL**

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

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D1.2 The Processing Facility shall abide by all applicable laws and regulations.

D1.2.1 The Processing Facility shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

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D1.3 The Processing Facility shall have a Processing Facility Director, a Processing Facility Medical Director, a Quality Manager, and at least one designated staff member actively performing cellular therapy product processing. This team shall have been in place for at least twelve (12) months preceding initial accreditation.

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### **D2: PROCESSING FACILITY**

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D2.1 The Processing Facility shall be of adequate space, design, and location, for the intended procedures.

D2.1.1 The Processing Facility shall provide adequate lighting, ventilation, and access to sinks to prevent the introduction, transmission, or spread of communicable disease.

D2.1.2 Oxygen sensors shall be appropriately placed and utilized in areas where liquid nitrogen is present.

D2.1.3 The Processing Facility shall be secure to prevent the entrance of unauthorized personnel.

D2.1.4 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 products.

D2.1.5 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all cellular therapy products prior to release or distribution.

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- D2.2 Processing Facility parameters and environmental conditions shall be controlled to protect the safety and comfort of personnel.
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- D2.3 Critical facility parameters that may affect processing, storage, or distribution, including temperature and humidity at a minimum, shall be assessed for risk to the cellular therapy product.
- D2.3.1 Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.
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- D2.4 When using procedures that may result in contamination or cross-contamination of cellular therapy products or when performing more than minimal manipulation, critical environmental conditions shall be controlled, monitored, and recorded where appropriate for air quality and surface contaminants.
- D2.4.1 The Processing Facility shall qualify environmental control systems and validate cleaning and sanitation procedures appropriate for the environmental classification and degree of manipulation performed.
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- D2.5 The Processing Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.
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- D2.6 There shall be adequate equipment and materials for the procedures performed.
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- D2.7 The Processing Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.
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- D2.8 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 hazards.
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- D2.9 All waste generated by the Processing Facility activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable laws and regulations.
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- D2.10 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.

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### D3: PERSONNEL

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#### D3.1 PROCESSING FACILITY DIRECTOR

- D3.1.1 There shall be a Processing Facility Director with a medical degree, doctoral degree, or equivalent degree in a relevant science, qualified by a minimum of two (2) years training and experience for the scope of activities carried out in the Processing Facility.
- D3.1.2 The Processing Facility Director shall be responsible for all procedures, administrative operations, and the Quality Management Program of the Processing Facility, including compliance with these Standards and other applicable laws and regulations.
- D3.1.3 The Processing Facility Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
  - D3.1.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and processing.

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#### D3.2 PROCESSING FACILITY MEDICAL DIRECTOR

- D3.2.1 There shall be a Processing Facility Medical Director who is a licensed or certified physician with a minimum of two (2) years postgraduate training and practical and relevant experience for the scope of activities carried out in the preparation and clinical use of cellular therapy products.
- D3.2.2 The Processing Facility Medical Director or designee shall be directly responsible for all medical aspects related to the Processing Facility.
- D3.2.3 The Processing Facility Medical Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.
  - D3.2.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and processing.

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#### D3.3 QUALITY MANAGER

- D3.3.1 There shall be a Processing Facility Quality Manager to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Processing Facility.

D3.3.2 The Processing Facility Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.

D3.3.3 The Processing Facility Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy processing and/or quality management annually at a minimum.

D3.3.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

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#### D3.4 STAFF

D3.4.1 The number of trained processing personnel shall be adequate for the number of procedures performed and shall include a minimum of one designated trained individual with an identified trained backup to maintain sufficient coverage.

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### D4: QUALITY MANAGEMENT

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D4.1 The Processing Facility Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

D4.1.1 The Processing Facility Director or designee shall annually review the effectiveness of the Quality Management Program. Documentation of the review findings shall be provided to the Clinical Program Director.

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D4.2 The Processing Facility shall establish and maintain a written Quality Management Plan.

D4.2.1 The Processing Facility Director or designee shall be responsible for the Quality Management Plan as it pertains to the Processing Facility.

D4.2.2 The Processing Facility Director or designee shall review and report to staff quality management activities, at a minimum, quarterly.

D4.2.3 The Processing Facility Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Processing Facility.

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D4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions and functions within the Processing Facility.

D4.3.1 The Quality Management Plan shall include a description of how these key positions interact to implement the quality management activities.

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- D4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Processing Facility. Personnel requirements shall include at a minimum:
- D4.4.1 A current job description for all staff.
  - D4.4.2 A system to document the following for all staff:
    - D4.4.2.1 Initial qualifications.
    - D4.4.2.2 New employee orientation.
    - D4.4.2.3 Initial training and retraining when appropriate for all procedures performed.
    - D4.4.2.4 Competency for each critical function performed.
    - D4.4.2.5 Continued competency at least annually.
    - D4.4.2.6 Continuing education.

- 
- D4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control and management.
- D4.5.1 There shall be policies and procedures for development, approval, implementation, review, revision, and archival of all critical documents.
  - D4.5.2 There shall be a current listing of all active critical documents that shall comply with the document control system requirements. Controlled documents shall include at a minimum:
    - D4.5.2.1 Policies and Standard Operating Procedures.
    - D4.5.2.2 Worksheets.
    - D4.5.2.3 Forms.
    - D4.5.2.4 Labels.
  - D4.5.3 The document control policy shall include:
    - D4.5.3.1 A standardized format for policies, procedures, worksheets, forms, and labels.
    - D4.5.3.2 Assignment of a numeric or alphanumeric identifier and title to each document and document version regulated within the system.
    - D4.5.3.3 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

- D4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.
  - D4.5.3.5 A system for document change control that includes a description of the change, the signature of approving individual(s), approval date(s), effective date, and archival date.
  - D4.5.3.6 Archived policies and procedures, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.
  - D4.5.3.7 A system for the retraction of obsolete documents to prevent unintended use.
  - D4.5.3.8 A system for record creation, assembly, review, storage, archival, and retrieval.
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D4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the cellular therapy product.

D4.6.1 Agreements shall include the responsibility of the facility performing any step in processing, testing, or storage to comply with applicable laws and regulations and these Standards.

D4.6.2 Agreements shall be dated and reviewed on a regular basis.

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D4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.

D4.7.1 Criteria for cellular therapy product safety, product efficacy, and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.

D4.7.2 Both individual cellular therapy product data and aggregate data for each type of cellular therapy product shall be evaluated.

D4.7.3 For HPC products intended for hematopoietic reconstitution, time to engraftment following cellular therapy product administration measured by ANC and platelet count shall be analyzed.

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D4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a schedule for conducting, reviewing, and reporting audits of the Processing Facility's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

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- D4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.
  - D4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions in a timely manner.
  - D4.8.3 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements shall be audited annually.
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D4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

- D4.9.1 Documentation and product labeling.
  - D4.9.2 Product quarantine.
  - D4.9.3 Criteria for product release.
  - D4.9.4 Identification of individuals authorized to approve release, including the Processing Facility Medical Director at a minimum.
  - D4.9.5 Investigation of cause.
  - D4.9.6 Notification of the recipient's physician, collection facility, and/or any other facility in receipt of the cellular therapy product.
  - D4.9.7 Reporting to regulatory agencies if appropriate.
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D4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, biological product deviations, serious adverse events, and complaints, including the following activities at a minimum:

- D4.10.1 Detection.
  - D4.10.2 Investigation.
    - D4.10.2.1 A thorough investigation shall be conducted by the Processing Facility in collaboration with the Collection Facility and Clinical Program, as appropriate.
    - D4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective actions as warranted.
  - D4.10.3 Documentation.
-

- D4.10.3.1 Documentation shall include a description of the event, the involved individuals and/or cellular therapy products, when the event occurred, when and to whom the event was reported, and the immediate actions taken.
- D4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Processing Facility Director, Medical Director, or designee and the Quality Manager.
- D4.10.3.3 Cumulative files of errors, accidents, biological product deviations, serious adverse events, and complaints shall be maintained.
- D4.10.3.4 Cumulative files shall include written investigation reports containing conclusions, follow-up, corrective actions, and a link to the record(s) of the involved cellular therapy products.

D4.10.4 Reporting.

- D4.10.4.1 When it is determined that a cellular therapy product was responsible for a serious adverse reaction, the reaction report and results of the investigation shall be made available to the recipient's physician, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by applicable laws.
- D4.10.4.2 Errors, accidents, biological product deviations, and complaints shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.

D4.10.5 Corrective and preventive action.

- D4.10.5.1 Appropriate corrective action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.
- D4.10.5.2 Follow-up audits of the effectiveness of corrective actions shall be performed in a timeframe as indicated in the investigative report.

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D4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

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D4.12 The Quality Management Plan shall include, or summarize and reference, policies and procedures for actions to take in the event the Processing Facility's operations are interrupted.

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- D4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical supplies, manufacturers, vendors, reagents, equipment, and facilities.
- D4.13.1 Qualification plans shall be reviewed and approved by the Processing Facility Director or designee.
  - D4.13.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.
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- D4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of critical procedures to achieve the expected end-points, including viability of cells and cellular therapy product characteristics.
- D4.14.1 Critical procedures to be validated or verified shall include at least the following: processing techniques, cryopreservation procedures, labeling, storage, and distribution.
  - D4.14.2 Each validation shall include:
    - D4.14.2.1 An approved validation plan, including conditions to be validated.
    - D4.14.2.2 Acceptance criteria.
    - D4.14.2.3 Data collection.
    - D4.14.2.4 Evaluation of data.
    - D4.14.2.5 Summary of results.
    - D4.14.2.6 Review and approval of the validation plan, results, and conclusion by the Processing Facility Director or designee and the Quality Manager or designee.
  - D4.14.3 Changes to a process shall include evaluation of risk to confirm that they do not create an adverse impact anywhere in the operation and shall be validated or verified as appropriate.
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## **D5: POLICIES AND PROCEDURES**

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- D5.1 The Processing Facility shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in D4. These documents shall include all elements required by these Standards and shall address at a minimum:
- D5.1.1 Donor and recipient confidentiality.
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- D5.1.2 Cellular therapy product receipt.
  - D5.1.3 Processing and process control.
  - D5.1.4 Processing of ABO-incompatible cellular therapy products to include a description of the indication for and processing methods to be used for red cell and plasma depletion.
  - D5.1.5 Prevention of mix-ups and cross-contamination.
  - D5.1.6 Labeling (including associated forms and samples).
  - D5.1.7 Cryopreservation and thawing.
  - D5.1.8 Cellular therapy product expiration dates.
  - D5.1.9 Cellular therapy product storage to include alternative storage if the primary storage device fails.
  - D5.1.10 Release and exceptional release.
  - D5.1.11 Transportation and shipping, including methods and conditions within the Processing Facility and to and from external facilities.
  - D5.1.12 Cellular therapy product recall, to include a description of responsibilities and actions to be taken, and notification of appropriate regulatory agencies.
  - D5.1.13 Cellular therapy product disposal.
  - D5.1.14 Critical reagent and supply management.
  - D5.1.15 Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.
  - D5.1.16 Recalls of equipment, supplies, and reagents.
  - D5.1.17 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.
  - D5.1.18 Environmental control to include a description of the environmental monitoring plan.
  - D5.1.19 Hygiene and use of personal protective equipment.
  - D5.1.20 Disposal of medical and biohazard waste.
  - D5.1.21 Emergency and disaster plan, including the Processing Facility response.
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- D5.2 The Processing Facility shall maintain a detailed Standard Operating Procedures Manual that includes a listing of all current Standard Operating Procedures, including title, identifier, and version.

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- D5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:
- D5.3.1 A clearly written description of the objectives.
  - D5.3.2 A description of equipment and supplies used.
  - D5.3.3 Acceptable end-points and the range of expected results.
  - D5.3.4 A stepwise description of the procedure.
  - D5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.
  - D5.3.6 A reference section listing appropriate literature.
  - D5.3.7 Documented approval of each procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation and every two years thereafter.
  - D5.3.8 Documented approval of each procedural modification by the Processing Facility Director or Medical Director, as appropriate, prior to implementation.
  - D5.3.9 Reference to a current version of orders, worksheets, reports, labels, and forms.
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D5.4 Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.

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D5.5 Staff training and, if appropriate, competency shall be documented before performing a new or revised procedure.

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D5.6 All personnel shall follow the Standard Operating Procedures related to their positions.

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D5.7 Variances shall be pre-approved by the Processing Facility Director and/or Medical Director, and reviewed by the Quality Manager.

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## D6: EQUIPMENT, SUPPLIES, AND REAGENTS

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D6.1 Equipment, supplies, and reagents used to process cellular therapy products shall be used in a manner that maintains product function and integrity and prevents product mix-ups, contamination, and cross-contamination.

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D6.2 Supplies and reagents used in processing, testing, cryopreservation, and storage shall be controlled by a materials management system that includes requirements for the following, at a minimum:

D6.2.1 Visual examination of each supply and reagent used to manufacture cellular therapy products for damage or evidence of contamination upon receipt and acceptance into inventory.

D6.2.2 Records of receipt that shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.

D6.2.3 Storage of materials under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix up or unintended use.

D6.2.4 Use of supplies and reagents coming into contact with cellular therapy products during processing, storage, and/or administration that are sterile and of the appropriate grade for the intended use.

D6.2.5 Cleaning and sterilizing of non-disposable supplies or instruments using a procedure verified to remove infectious agents and other contaminants.

D6.2.6 Use of supplies and reagents in a manner consistent with manufacturer instructions.

D6.2.7 Process to prevent the use of expired reagents and supplies.

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D6.3 There shall be a system to uniquely identify and track all critical equipment used in the processing of cellular therapy products. The system shall identify each cellular therapy product for which the equipment was used.

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D6.4 Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.

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D6.5 The equipment shall be inspected for cleanliness prior to each use and verified to be in compliance with the maintenance schedule daily prior to use.

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D6.6 The equipment shall be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.6.1 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.

D6.6.2 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products manufactured since the last calibration.

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D6.7 There shall be a procedure that addresses the actions to take in the event of equipment malfunction or failure.

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D6.8 Equipment shall conform to applicable laws and regulations.

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D6.9 Lot numbers, expiration dates, and manufacturers of critical reagents and supplies and identification of key equipment used in each procedure shall be documented.

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D6.10 The Processing Facility shall use an inventory control system to document the availability and identity of critical reagents and supplies. This shall include at a minimum:

D6.10.1 A system to uniquely identify and track all critical reagents and supplies used to manufacture cellular therapy products.

D6.10.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.

D6.10.3 A system to maintain adequate stocks of reagents and supplies for the procedures to be performed.

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## **D7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS**

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D7.1 ISBT 128 CODING AND LABELING

D7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

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D7.1.2 If coding and labeling technologies have not yet been implemented, the Processing Facility shall be actively implementing ISBT 128.

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D7.2 LABELING OPERATIONS

D7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products, product samples, and associated records.

D7.2.1.1 Stocks of unused labels representing different cellular therapy products shall be stored in a controlled manner to prevent errors.

D7.2.1.2 Obsolete labels shall be restricted from use.

D7.2.2 Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Processing Facility Director or designee to confirm accuracy regarding identity, content, and conformity.

D7.2.3 Print-on-demand 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 A system for label version control shall be employed.

D7.2.4.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by applicable laws and regulations, whichever is longer.

D7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

D7.2.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

D7.2.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.

D7.2.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

D7.2.7 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process to verify the information or two (2) qualified staff members prior to distribution of the cellular therapy product.

D7.2.8 Labeling elements required by applicable laws and regulations shall be present.

D7.2.9 All data fields on labels shall be completed.

- D7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.
  - D7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.
  - D7.2.12 The label shall be validated as reliable for storage under the conditions in use.
- 

### D7.3 PRODUCT IDENTIFICATION

- D7.3.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.
    - D7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.
    - D7.3.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.
    - D7.3.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.
    - D7.3.1.4 Supplementary identifiers shall not obscure the original identifier.
    - D7.3.1.5 The facility associated with each identifier shall be noted on the label.
    - D7.3.1.6 If the original identifier is replaced, documentation shall link the new identifier to the original.
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### D7.4 LABEL CONTENT

- D7.4.1 At the completion of processing and at distribution for administration, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix II.
- D7.4.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."
- D7.4.3 Any container bearing a partial label shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix II. 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.

- D7.4.4 The name and address of the facility that determines that the cellular therapy product meets release criteria and the name and address of the facility that makes the product available for distribution shall either appear on the product label or accompany the product at distribution.
- D7.4.5 Cellular therapy products collected in or designated for use in the U.S. shall have the elements in the Accompanying Documents at Distribution table in Appendix IV accompany the cellular therapy product when it leaves the Processing Facility.
- D7.4.6 For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after distribution of the cellular therapy product and that the physician using the product was informed of the results of that determination.
- D7.4.7 Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "For Nonclinical Use Only."
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## D8: PROCESS CONTROLS

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- D8.1 There shall be a process for controlling and monitoring the manufacturing of cellular therapy products so that products meet predetermined release specifications.
- D8.1.1 The Processing Facility Director shall define tests and procedures for measuring and assaying cellular therapy products to assure their safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such tests and procedures shall become part of the permanent record of the product processed.
- D8.1.2 There shall be a documented system for the identification and handling of test samples so that they are accurately related to the corresponding cellular therapy product, donor, or recipient.
- D8.1.2.1 There shall be a mechanism to identify the individual obtaining the sample, the sample source, the date, and the time, if appropriate.
- D8.1.2.2 Samples obtained for testing shall be representative of the cellular therapy product to be evaluated.
- D8.1.3 There shall be the establishment of appropriate and validated assays and test procedures for the evaluation of cellular therapy products.
- D8.1.3.1 For all cellular therapy products, a total nucleated cell count and viability measurement shall be performed.
- D8.1.3.2 For HPC products intended for restoration of hematopoiesis, an assay measuring viable CD34 shall be performed.

- D8.1.3.3 For cellular therapy products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, shall be employed for evaluation of the viable target cell population before and after the processing procedures.
- D8.1.4 For tests required by these Standards performed within the Processing Facility:
- D8.1.4.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.
- D8.1.4.2 New reagent lots shall be verified to provide comparable results to current lots or to give results in agreement with suitable reference material before or concurrently with being placed into service.
- D8.1.4.3 Where available, controls shall be used each day of testing and shown to give results within the defined range established for that material.
- D8.1.4.4 Function checks shall be performed for testing instruments prior to testing donor, recipient, or cellular therapy product samples.
- D8.1.4.5 For tests performed within the Processing Facility, there shall be documentation of ongoing proficiency testing as designated by the Processing Facility Director. The results shall be reviewed by the Processing Facility Director or designee and outcomes reviewed with the staff.
- D8.1.5 Tests required by these Standards, not performed by the Processing Facility, shall be performed by a laboratory that is certified, licensed, or accredited by the appropriate laboratory regulatory agency.
- D8.1.6 Infectious disease testing required by these Standards shall be performed using screening tests approved or cleared by the governmental authority for cellular therapy product donors.
- D8.1.7 Cellular therapy products that do not meet allogeneic donor eligibility requirements, or for which allogeneic donor eligibility determination is not yet complete, shall be distributed only if there is documented urgent medical need for the product. Documentation shall include, at a minimum, the approval of the recipient's physician and the Processing Facility Medical Director or other designated physician.
- D8.1.8 Notification of the recipient's physician of nonconforming cellular therapy products and approval for their release shall be documented.
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- D8.2 Before a cellular therapy product is processed, shipped, or otherwise prepared for administration, there shall be a written request from the recipient's physician specifying the cellular therapy product type, recipient and donor identifiers, the type of processing that is to be performed, and the anticipated date of processing.
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D8.3 For allogeneic cellular therapy products, information required by the Processing Facility prior to distribution of the product shall include:

D8.3.1 A statement of donor eligibility.

D8.3.2 For ineligible donors, the reason for their ineligibility.

D8.3.3 For ineligible donors or donors for whom eligibility determination is incomplete, documentation of urgent medical need and physician approval for use.

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D8.4 Processing procedures shall be validated in the Processing Facility and documented to result in acceptable target cell viability and recovery.

D8.4.1 Published validated processes shall be verified within the Processing Facility prior to implementation.

D8.4.2 The Processing Facility shall use validated methods for preparation of cellular therapy products for administration.

D8.4.3 Cord blood units that have not been red cell reduced prior to cryopreservation shall be washed prior to administration.

D8.4.4 Cord blood units that have been red cell reduced prior to cryopreservation should be diluted or washed prior to administration.

D8.4.5 If the Processing Facility lacks experience with the type of cellular therapy product requested for a recipient, personnel shall obtain the manufacturer's instructions and follow these instructions to the extent possible.

D8.4.5.1 The Processing Facility should verify the processing procedures utilizing practice units similar to the cellular therapy product intended for administration when feasible.

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D8.5 Critical control points and associated assays shall be identified and performed on each cellular therapy product as defined in Standard Operating Procedures.

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D8.6 Methods for processing shall employ aseptic technique and cellular therapy products shall be processed in a manner that minimizes the risk of cross-contamination.

D8.6.1 Where processing of tissues and cells involves exposure to the environment, processing shall take place in an environment with specified air quality and cleanliness.

D8.6.2 The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.

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- D8.7 The Processing Facility shall monitor and document microbial contamination of cellular therapy products after processing as specified in Standard Operating Procedures.
- D8.7.1 The results of microbial cultures shall be reviewed by the Processing Facility Director or designee in a timely manner.
- D8.7.2 The recipient's physician shall be notified in a timely manner of any positive microbial cultures.
- 
- D8.8 Records shall be made concurrently with each step of the processing, testing, cryopreservation, storage, and administration or disposal/disposition/distribution of each cellular therapy product in such a way that all steps may be accurately traced.
- D8.8.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.
- D8.8.2 Records shall show the test results and the interpretation of each result, where appropriate.
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- D8.9 The Processing Facility Director or designee shall review the processing record for each cellular therapy product prior to release or distribution.
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- D8.10 There shall be documented notification to the recipient's physician and the Processing Facility Medical Director of clinically relevant processing end-points not met and remedial actions taken.
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- D8.11 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 laws and regulations.
- D8.11.1 The Processing Facility shall adhere to good manufacturing practices (GMP) appropriate for the degree of cellular therapy product manipulation.
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- D8.12 For allogeneic cellular therapy products containing red blood cells at the time of administration:
- D8.12.1 Results for ABO group and Rh type testing shall be available from two (2) independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.
- D8.12.2 Results for a red cell antibody screen on the recipient shall be available.

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D8.13 There shall be a procedure to confirm the identity of cord blood units if verification typing cannot be performed on attached segments.

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D8.14 One or more samples representing the cryopreserved cellular therapy product shall be stored.

D8.14.1 Sample(s) from cryopreserved cellular therapy products shall be stored under conditions that achieve a valid representation of the clinical product.

D8.14.2 Cryopreserved samples shall be retained according to institutional Standard Operating Procedures.

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## **D9: CELLULAR THERAPY PRODUCT STORAGE**

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D9.1 Processing Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products.

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### **D9.2 STORAGE DURATION**

D9.2.1 Processing Facilities processing, storing, and/or releasing cellular therapy products for administration shall assign an expiration date and time for non-cryopreserved products and for products thawed after cryopreservation.

D9.2.2 There shall be a written stability program that evaluates the viability and potency of cryopreserved cellular therapy products, minimally annually.

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### **D9.3 TEMPERATURE**

D9.3.1 Storage temperatures shall be defined in Standard Operating Procedures.

D9.3.2 Noncryopreserved cellular therapy products shall be maintained within a specific temperature range to maintain viability and function, to inhibit infectious agents, and for a period of time not to exceed that specified in Standard Operating Procedures.

D9.3.3 Cryopreserved cellular therapy products shall be stored within a temperature range, as defined in Standard Operating Procedures, that is appropriate for the product and cryoprotectant solution used.

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- D9.3.4 Prior to receipt of a cellular therapy product from an external facility, there shall be confirmation that the product can be appropriately stored.
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D9.4 PRODUCT SAFETY

- D9.4.1 Materials that may adversely affect cellular therapy products shall not be stored in the same refrigerators or freezers as the cellular therapy products.
- D9.4.2 For cellular therapy products immersed in liquid nitrogen, procedures to minimize the risk of cross-contamination of products shall be employed.
- D9.4.3 Processes for storing cellular therapy products in quarantine shall be defined in Standard Operating Procedures.
- D9.4.3.1 Quarantined cellular therapy products shall be easily distinguishable and stored in a manner that minimizes the risks of cross-contamination and inappropriate distribution.
- D9.4.3.2 All cellular therapy products with positive infectious disease test results for relevant communicable disease agents and/or positive microbial cultures shall be quarantined.
- D9.4.3.3 Processing Facilities storing cellular therapy products shall quarantine each product until completion of the donor eligibility determination as required by applicable laws and regulations.
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D9.5 STORAGE MONITORING

- D9.5.1 Refrigerators and freezers used for storage where cellular therapy products are not fully immersed in liquid nitrogen shall have a system to monitor the temperature continuously and to record the temperature at least every four (4) hours.
- D9.5.2 There shall be a mechanism to confirm that levels of liquid nitrogen in liquid nitrogen freezers are consistently maintained to assure that cellular therapy products remain within the specified temperature range.
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D9.6 ALARM SYSTEMS

- D9.6.1 Storage devices for cellular therapy products or reagents for cellular therapy product processing shall have alarm systems that are continuously active.
- D9.6.2 Alarm systems shall have audible and visible signals or other effective notification methods.
- D9.6.3 Alarm systems shall be checked periodically for function.
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- D9.6.4 If trained personnel are not always present in the immediate area of the storage device, a system shall be in place that alerts responsible personnel of alarm conditions on a 24-hour basis.
- D9.6.5 Alarms shall be set to activate at a temperature or level of liquid nitrogen that will allow time to salvage products.
- D9.6.6 Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.
- D9.6.6.1 Instructions shall include a procedure for notifying processing personnel.
- D9.6.7 Storage devices of appropriate temperature shall be available for cellular therapy product storage if the primary storage device fails.

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D9.7 The storage device shall be located in a secure area and accessible only to authorized personnel.

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D9.8 The Processing Facility shall use an inventory control system to identify the location of each cellular therapy product and associated samples. The inventory control system records shall include:

- D9.8.1 Cellular therapy product unique identifier.
- D9.8.2 Recipient name or unique identifier.
- D9.8.3 Storage device identifier.
- D9.8.4 Location within the storage device.

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## **D10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING**

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D10.1 Procedures for transportation and shipping of cellular therapy products shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area.

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D10.2 The primary product container for non-frozen cellular therapy products shall be placed in a secondary container and sealed to prevent leakage.

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- D10.3 Cellular therapy products that require a temperature-controlled environment and that are transported or shipped over an extended period of time shall be transported or shipped in a container validated to maintain the appropriate temperature range.
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- D10.4 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.
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- D10.5 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.
- D10.5.1 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.
- D10.5.2 The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transport or shipping.
- D10.5.2.1 The temperature of the shipping container shall be continuously monitored during shipment of cellular therapy products.
- D10.5.2.2 The shipping facility shall maintain a record of the temperature over the period of travel.
- D10.5.3 The outer container shall be secured.
- D10.5.4 The outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix III.
- D10.5.5 There shall be a document inside the outer container that includes all the information required on the outer container, in conformity with the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix III.
- D10.5.6 The outer container shall be labeled in accordance with applicable laws and regulations regarding the cryogenic material used and the transport or shipment of biological materials.
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- D10.6 The transit time shall be within time limits determined by the distributing facility in consultation with the receiving facility to maintain cellular therapy product safety.
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- D10.7 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.
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D10.8 There shall be plans for alternative means of transport or shipping in an emergency.

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D10.9 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.

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## **D11: DISTRIBUTION AND RECEIPT**

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### **D11.1 DISTRIBUTION CRITERIA**

D11.1.1 The processing, collection, and transport or shipping records for each cellular therapy product shall be reviewed by the Processing Facility Director or designee for compliance with Standard Operating Procedures and applicable laws and regulations prior to product release or distribution.

D11.1.1.1 Records shall demonstrate traceability from the donor to the recipient and from the recipient to the donor.

D11.1.2 Each cellular therapy product shall meet pre-determined release criteria prior to distribution from the Processing Facility. The release criteria shall include donor eligibility determination for allogeneic products.

D11.1.2.1 The Processing Facility Director or designee shall give specific authorization for release when the cellular therapy product does not meet technical release criteria.

D11.1.2.2 The Processing Facility Medical Director or designee shall give specific authorization for release when the cellular therapy product does not meet clinically relevant release criteria.

D11.1.2.3 Documentation of agreement of the Processing Facility Medical Director or designee and the recipient's physician consent to use any non-conforming product shall be retained in the processing record if such release is allowed by policies, procedures, or package inserts of licensed products.

D11.1.3 Each cellular therapy product issued for administration shall be visually inspected by two (2) trained personnel immediately before release to verify the integrity of the product container and appropriate labeling.

D11.1.3.1 A cellular therapy product shall not be released when the container is compromised and/or recipient or donor information is not verified unless the Processing Facility Director or designee gives specific authorization for the product's release.

D11.1.4 For each type of cellular therapy product, the Processing Facility shall maintain and distribute or make a document available to clinical staff containing the following:

- D11.1.4.1 The use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.
  - D11.1.4.2 Instructions for handling the cellular therapy product to minimize the risk of contamination or cross-contamination.
  - D11.1.4.3 Appropriate warnings related to the prevention of the transmission or spread of communicable diseases.
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D11.2 The cellular therapy product processing records shall contain a written record of product distribution including, at a minimum:

- D11.2.1 The distribution date and time.
  - D11.2.2 Unique identifier of the intended recipient.
  - D11.2.3 The proper product name and identifier.
  - D11.2.4 Documentation of donor eligibility determination.
  - D11.2.5 Identification of the facilities that requested and distributed the product.
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D11.3 Records shall permit tracing of the cellular therapy product from one facility to another, and shall include:

- D11.3.1 Date and time cellular therapy product was distributed.
  - D11.3.2 Date and time cellular therapy product was received.
  - D11.3.3 Identity of the transporting or shipping facility.
  - D11.3.4 Identity of the receiving facility.
  - D11.3.5 Identity of personnel responsible for cellular therapy product transportation or shipping and of personnel responsible for receiving the product.
  - D11.3.6 Identity of the courier.
  - D11.3.7 Documentation of any delay or problems incurred during transportation or shipping.
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D11.4 RECEIPT OF CELLULAR THERAPY PRODUCTS

- D11.4.1 Procedures shall be established and maintained for acceptance, rejection, and quarantine of cellular therapy products.
- D11.4.2 The receipt of each cellular therapy product shall include inspection to verify:

- D11.4.2.1 The integrity of the cellular therapy product container.
- D11.4.2.2 The appearance of the cellular therapy product for evidence of mishandling or microbial contamination.
- D11.4.2.3 Appropriate labeling.
- D11.4.3 If the primary container or temperature of the cellular therapy product has been compromised, the Processing Facility Director or designee shall give specific authorization to return the product to inventory.
- D11.4.4 There shall be procedures to verify that the cellular therapy product was appropriately transported or shipped.
  - D11.4.4.1 The receiving facility shall document the temperature of the outer container upon arrival.
  - D11.4.4.2 For cryopreserved cellular therapy products, receiving facility records shall include documentation of the outer container temperature during shipping.
- D11.4.5 The receiving facility shall review and verify product specifications provided by the manufacturer, if applicable.
- D11.4.6 There shall be procedures to maintain cellular therapy products in quarantine until they have been determined to meet criteria for release from quarantine.
- D11.4.7 The receiving facility shall have readily available access to a summary of documents used to determine allogeneic donor eligibility.
  - D11.4.7.1 For cellular therapy products received from an external facility, there shall be documented evidence of donor eligibility screening and testing in accordance with applicable laws and regulations.
- D11.4.8 When cellular therapy products are returned to the Processing Facility after distribution for administration, there shall be documentation in the Processing Facility records of the events requiring return, the temporary storage temperature when at the clinical facility, the results of inspection upon return, and subsequent action taken to protect product safety and viability.
  - D11.4.8.1 The Processing Facility Director or designee shall consult with the recipient's physician regarding reissue or disposal of the returned product.

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## **D12: DISPOSAL**

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- D12.1 Disposal of cellular therapy products shall include the following requirements:

- D12.1.1 A pre-collection written agreement between the storage facility and the designated recipient or the donor defining the length of storage and the circumstances for disposal of cellular therapy products.
- D12.1.2 The option to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.
- D12.1.3 Documentation of no further need for the cellular therapy product before any product is discarded.
  - D12.1.3.1 For HPC products, this shall include documentation of the designated recipient's death, if applicable.
- D12.1.4 Approval by the Processing Facility Medical Director or the recipient's physician for cellular therapy product discard or other disposition, and method of disposal.
- D12.1.5 A method of disposal and decontamination that meets applicable laws and regulations for disposal of biohazardous materials and/or medical waste.
- D12.1.6 Processing Facilities, in consultation with the Clinical Program, shall establish policies for the duration and conditions of storage and indications for disposal.
  - D12.1.6.1 Recipients, donors, and associated Clinical Programs should be informed about policies for directed cellular therapy products as part of the informed consent process and before the cellular therapy product collection.
- D12.1.7 If there is no pre-existing agreement describing conditions for cellular therapy product storage and/or discard or if the intended recipient is lost to follow-up, the storage facility shall make a documented effort to notify the donor, cellular therapy product manufacturer, or designated recipient's physician and facility about product disposition, including disposal or transfer.

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- D12.2 The records for discarded or transferred cellular therapy products shall indicate the product was discarded or transferred, date of discard or transfer, disposition, and method of disposal or transfer.
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## **D13: RECORDS**

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- D13.1 There shall be a records management system for quality and cellular therapy product record creation, assembly, review, storage, archival, and retrieval.
  - D13.1.1 The records management system shall facilitate the review of records pertaining to a particular cellular therapy product prior to distribution and for follow-up evaluation or investigation.

- D13.1.2 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.
- D13.1.3 For cellular therapy products that are to be distributed for use at another institution, the Processing Facility shall inform the receiving institution of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.
- D13.1.4 Records shall be maintained in such a way as to secure their integrity, preservation, and retrieval.
- D13.1.5 Records shall be accurate, legible, and indelible.
- D13.1.6 Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities and their recipients and donors shall be established and followed in compliance with applicable laws and regulations.

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D13.2 ELECTRONIC RECORDS

- D13.2.1 The Processing Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the Processing Facility that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.
- D13.2.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.
  - D13.2.2.1 There shall be a means by which access to electronic records is limited to authorized individuals.
  - D13.2.2.2 The critical electronic record system shall maintain unique identifiers.
  - D13.2.2.3 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.
- D13.2.3 For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation of the Processing Facility in the event that critical electronic record systems are not available. The alternative system shall be validated and Processing Facility staff shall be trained in its use.
- D13.2.4 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.
  - D13.2.4.1 A method shall be established or the system shall provide for review of data before final acceptance.

- D13.2.4.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.
  - D13.2.5 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.
  - D13.2.6 For all critical electronic record systems, there shall be validated procedures for and documentation of:
    - D13.2.6.1 Systems development.
    - D13.2.6.2 Numerical designation of system versions, if applicable.
    - D13.2.6.3 Prospective validation of systems, including hardware, software, and databases.
    - D13.2.6.4 Installation of the system.
    - D13.2.6.5 Training and continued competency of personnel in systems use.
    - D13.2.6.6 Monitoring of data integrity.
    - D13.2.6.7 Back-up of the electronic records system on a regular schedule.
    - D13.2.6.8 System maintenance and operations.
    - D13.2.6.9 System assignment of unique identifiers.
  - D13.2.7 All system modifications shall be authorized, documented, and validated prior to implementation.
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### D13.3 RECORDS TO BE MAINTAINED

- D13.3.1 Processing Facility records related to quality control, 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 applicable laws or regulations, or with a defined program or institution policy.
  - D13.3.1.1 Facility maintenance records pertaining to facility cleaning and sanitation shall be retained for at least three (3) years or longer in accordance with applicable laws or regulations, or with defined program or institution policy. All other facility maintenance records shall be retained as in D13.3.1.

- D13.3.2 Records to allow tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after final distribution of the product, or as required by applicable laws and regulations. These records shall include collection and processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product identity, and donor and recipient information as found on the original container.
- D13.3.3 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 laws and regulations or institutional policy, whichever requires the longest maintenance period.

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D13.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

- D13.4.1 The Processing Facility shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a cellular therapy product.
- D13.4.2 The Processing Facility shall furnish to the facility of final disposition a copy of all records relating to the collection, processing, and storage procedures performed in so far as the records concern the safety, purity, or potency of the cellular therapy product involved.
- D13.4.3 If two (2) or more facilities participate in the collection, processing, or distribution of the cellular therapy product, the records of the Processing Facility shall show plainly the extent of its responsibility.

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**MINIMUM NUMBER OF NEW PATIENTS FOR ACCREDITATION**

Clinical Programs shall transplant at least the following number of new patients<sup>1</sup> before initial accreditation and annually thereafter:

Transplant Population	Clinical Site(s)	Type of Transplant	Twelve (12) Months Prior to Initial Accreditation	Average Per Year Within Accreditation Cycle
Adult OR Pediatric (only one of these two)	Single Clinical Site	Autologous only	5 autologous	5 autologous
		Allogeneic and Autologous	10 allogeneic recipients	10 allogeneic recipients
	Multiple Clinical Sites	Autologous only	5 autologous recipients at each site	5 autologous recipients at each site
		Allogeneic and Autologous	5 allogeneic recipients at each applicable site <sup>2</sup> 5 autologous at each applicable site <sup>2</sup>	5 allogeneic recipients at each applicable site <sup>2</sup> 5 autologous at applicable each applicable site <sup>2</sup>
Combined Adult AND Pediatric	Single Clinical Site	Autologous only	5 adult autologous And 5 pediatric autologous recipients	5 adult autologous and 5 pediatric autologous recipients
		Allogeneic and Autologous	5 adult allogeneic recipients 5 pediatric allogeneic recipients	5 adult allogeneic recipients 5 pediatric allogeneic recipients
	Multiple Clinical Sites	Autologous only	5 adult autologous at each applicable site 5 pediatric autologous recipients at each applicable site	5 adult autologous recipients at each applicable site 5 pediatric autologous recipients at each applicable site
		Allogeneic and Autologous	5 adult allogeneic recipients at each applicable site 5 pediatric allogeneic recipients at each applicable site 5 adult autologous at each applicable site <sup>2</sup> 5 pediatric autologous at each applicable site <sup>2</sup>	5 adult allogeneic recipients at each site 5 pediatric allogeneic recipients at each site 5 adult autologous at each applicable site <sup>2</sup> 5 pediatric autologous at each applicable site <sup>2</sup>

<sup>1</sup>The term “new allogeneic patient” or “new autologous patient” includes only a patient who received his/her first transplant of that type during the period of time in question.

<sup>2</sup>Programs performing allogeneic and autologous transplantation that have more than one clinical site may or may not perform both types of transplant at each site. The requirement for five autologous transplant recipients per site only applies to those sites that do not perform allogeneic transplant.

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## APPENDIX II

### CELLULAR THERAPY PRODUCT LABELING

Each label shall include at least the elements detailed in the following table<sup>1</sup>:

Element <sup>2</sup>	Partial label	Label at completion of collection	Label at completion of processing	Label at distribution for administration <sup>4</sup>
Unique numeric or alphanumeric identifier <sup>3</sup>	AF	AF	AF	AF
Proper name of product <sup>5</sup>	AF	AF	AF	AF
Product attributes <sup>5</sup>			AC	AC
Recipient name and/or identifier		AT	AT	AT
Identity and address of collection facility or donor registry		AT	AC	AC
Date, time collection ends, and (if applicable) time zone		AT	AC	AC
Approximate volume		AT	AT	AT
Name and quantity of anticoagulant and other additives		AC	AC	AC
Donor identifier and (if applicable) name		AT	AT	AT
Recommended storage temperature range		AT	AT	AT
Biohazard and/or Warning Labels (as applicable, see CM7.4, C7.4, D7.4).		AT	AT	AT
As applicable: <ul style="list-style-type: none"> <li>• Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES"</li> <li>• Statement "WARNING: Advise Patient of Communicable Disease Risks"</li> <li>• Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"</li> </ul>		AT	AT	AT
Identity and address of processing and distribution facility(ies)			AC	AC
Statement "Do Not Irradiate"			AT	AT
Expiration Date (if applicable)			AC	AC
Expiration Time (if applicable)			AC	AC
ABO and Rh of donor (if applicable)			AC	AC
RBC compatibility determination (if applicable)				AC
Statement indicating that leukoreduction filters shall not be used.				AT
Statement "FOR AUTOLOGOUS USE ONLY" (if applicable)		AT	AT	AT
Date of distribution				AC

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

<sup>1</sup>Container 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).

<sup>2</sup>Facilities registered with ICCBBA who have fully implemented ISBT 128 labeling shall follow the ISBT 128 Standard for the location of information on the label and/or the accompanying documentation.

<sup>3</sup>Overlay labels for supplementary identifiers shall not obscure the original identifier.

<sup>4</sup>Products thawed at the bedside do not require a new label unless repackaged into a new container.

<sup>5</sup>Product proper names and attributes are listed in Chapter Three of the ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. Available at: [www.iccbba.org](http://www.iccbba.org) > Subject Area > Cellular Therapy > Standard Terminology.

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**CELLULAR THERAPY PRODUCT LABELS FOR SHIPPING AND TRANSPORT ON PUBLIC ROADS**

Each container for shipping and transport on public roads shall include a document on the inside of the container and a label on the exterior of the container with at least the elements detailed in the following table:

Element	Inner container document	Outer container label
Date of distribution	AC	AC
Time <sup>1</sup> of distribution, if appropriate	AC	AC
Statement "Do Not X-Ray" and /or "Do Not Irradiate", if applicable	AC	AF
Statements "Human Cells for Administration" or equivalent and "Handle with Care"	AC	AF
Shipper handling instructions	AC	AF
Shipping facility name, street address, contact person, and phone number	AC	AF
Receiving facility name, street address, contact person, and phone number	AC	AF
Biohazard and/or Warning Labels (as applicable, see CM7.4.2, C7.4.2, D7.4.2).	AC	
If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES"	AC	
Statement "WARNING: Advise Patient of Communicable Disease Risks"	AC	
Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"	AC	

AC= Accompany, AF=Affix

<sup>1</sup>Time shall include the time zone when shipping or transport of the cellular therapy product involves crossing time zones.

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ACCOMPANYING DOCUMENTS AT DISTRIBUTION

Products collected in or designated for use in the U.S. shall be accompanied upon leaving the Collection or Processing Facility with at least the elements detailed in the following table<sup>1</sup>:

Documentation	Allogeneic Donors-Eligible	Allogeneic Donor-Ineligible <sup>2</sup>	Allogeneic Donor-Incomplete <sup>2</sup>
Statement that the donor has been determined to be either eligible or ineligible, based upon results of donor screening and testing	X	X	
Summary of records used to make the donor-eligibility determination <sup>3</sup>	X	X	
Name and address of the establishment that made the donor-eligibility determination	X	X	
Listing and interpretation of the results of all communicable disease testing performed	X	X	X
Statement that the communicable disease testing was performed by a laboratory meeting regulatory requirements <sup>4</sup>	X	If applicable	If applicable
Statement noting the reason(s) for the determination of ineligibility		X	
Statement that the donor-eligibility determination has not been completed			X
Statement that the product must not be transplanted or infused until completion of the donor-eligibility determination, except under condition of urgent medical need			X
Listing of any required screening or testing that has not yet been completed			X
Results of donor screening and testing that has been performed			X
Documentation that the physician using the cellular therapy product was notified of incomplete testing or screening			X
Instructions for product use to prevent the introduction, transmission, or spread of communicable diseases <sup>1</sup>	X	X	X
Instructions for reporting serious adverse reactions or events to the distributing facility <sup>1,5</sup>	X	X	X

<sup>1</sup>For autologous cellular therapy products, instructions for product use to prevent the introduction, transmission, or spread of communicable diseases and for reporting serious adverse reactions or events to the distributing facility are always required for autologous products. Furthermore, a donor eligibility determination is not required by FDA. However, if any donor screening or testing is performed and risk factors or reactive test results are identified, accompanying documentation shall be provided.

<sup>2</sup>May only be distributed after release by the Processing Facility Medical Director due to urgent medical need. For ineligible cellular therapy products or incomplete donor eligibility determination, the product shall be shipped in quarantine. For products distributed prior to completion of donor eligibility, determination shall be completed and the physician shall be informed of the results.

<sup>3</sup> Access (electronic or otherwise) to the source documents by the distributing facility and/or receiving facility is sufficient.

<sup>4</sup>This includes laboratories certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 or those laboratories that have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services, or those that have met equivalent non-U.S. requirements.

<sup>5</sup> Access to the Clinical Program SOPs and forms could suffice when the distributing and clinical facilities are within the same facility.

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CHANGES TO SIXTH EDITION STANDARDS

The table below outlines the changes made to the *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration* with each version of the sixth edition of these Standards.<sup>1</sup>

Version Number <sup>2</sup>	Standard	Change
6.1	A3	<u>CAR (Chimeric antigen receptor)</u>
6.1	A3	<u>CNS (Central nervous system)</u>
6.1	A3	<u>CRS (Cytokine release syndrome)</u>
6.1	A3	<u>MSC (Mesenchymal stromal cell or mesenchymal stem cell)</u>
6.1	A3	<u>NC (Nucleated cell)</u>
6.1	A4	Cellular therapy product: Somatic cell-based product (e.g., mobilized HPC, mononuclear cells, cord blood cells, mesenchymal stromal cells, <u>T cells, natural killer cells</u> ) that is procured from a donor and intended for processing and administration.
6.1	A4	<u>Chimeric antigen receptor: Artificial receptor that combines an antigen specificity domain coupled with an intracellular signaling domain typically expressed by an immune effector cell (e.g., T cell or natural killer cell).</u>
6.1	A4	Corrective action: Action taken to eliminate the <u>root causes</u> of an existing discrepancy or other undesirable situation to prevent recurrence.
6.1	A4	<u>Cytokine release syndrome: A non-antigen-specific toxicity that occurs as a result of high-level immune activation. For example, a reaction from the release of cytokines from cells targeted by an antibody or immune effector cells.</u>
6.1	A4	<u>Immune effector cell: A cell that has differentiated into a form capable of modulating or effecting a specific immune response.</u>
6.1	A4	Preventive action: Action taken to eliminate the <u>root cause</u> and prevent occurrence of a potential discrepancy or other undesirable situation.
6.1	A4	<u>Product identity: Unique title that identifies the cellular composition of the product in a way that can be directly tied back to a manufacturing entity or process (e.g., a protocol number, a commercial product title, or a site-defined unique identifier).</u>

<b>Version Number<sup>2</sup></b>	<b>Standard</b>	<b>Change</b>
6.1	A4	Quality assurance: The actions, planned and performed, to provide confidence that all systems and elements that influence the quality of the product or service are working as expected <u>or exceed expectations</u> individually and collectively.
6.1	B1.2.1	<u>If cellular therapy products are received directly by the Clinical Program from a third-party provider, the following responsibilities at a minimum shall be defined in a written agreement:</u>
6.1	B1.2.1.1	<u>Traceability and chain of custody of cellular therapy products.</u>
6.1	B1.2.1.2	<u>Cellular therapy product storage and distribution.</u>
6.1	B1.2.1.3	<u>Verification of cellular therapy product identity.</u>
6.1	B2.6	There shall be written guidelines for communication, patient monitoring, and prompt transfer of patients to an intensive care unit, <u>emergency department</u> , or equivalent when appropriate.
6.1	B2.8.1	<u>Pharmacies shall have access to medications adequate to treat expected complications of immune effector cell administration, including cytokine release syndrome.</u>
6.1	B3.3.3	Clinical Program Directors and attending physicians shall have received specific training and maintain competency in each of the following areas <u>as applicable to the Clinical Program's services:</u>
6.1	B3.3.3.12	Diagnosis and management of veno-occlusive disease of the liver <u>and other causes of hepatic dysfunction.</u>
6.1	B3.3.3.13	Management of thrombocytopenia and bleeding, <u>including recognition of disseminated intravascular coagulation.</u>
6.1	B3.3.3.17	<u>Graft versus host disease.</u>
6.1	B3.3.3.18	<u>Cytokine release syndrome.</u>
6.1	B3.3.3.19	<u>Tumor lysis syndrome.</u>
6.1	B3.3.3.20	<u>Macrophage activation syndrome.</u>
6.1	B3.3.3.21	<u>Cardiac dysfunction.</u>
6.1	B3.3.3.22	<u>Renal dysfunction.</u>
6.1	B3.3.3.23	<u>Respiratory distress.</u>
6.1	B3.3.3.24	<u>Neurologic toxicity.</u>
6.1	B3.3.3.25	<u>Anaphylaxis.</u>
6.1	B3.3.3.26	<u>Infectious and noninfectious processes.</u>
6.1	B3.3.5.7	<u>Cellular therapy product administration.</u>

<b>Version Number<sup>2</sup></b>	<b>Standard</b>	<b>Change</b>
6.1	B3.7.3.4	Care interventions to manage <del>transplant</del> <u>cellular therapy complications, including, but not limited to, cytokine release syndrome, tumor lysis syndrome, cardiac dysfunction, respiratory distress, neurologic toxicity, renal and hepatic failure, disseminated intravascular coagulation, anaphylaxis, neutropenic fever, infectious and noninfectious processes, mucositis, nausea and vomiting, and pain management.</u>
6.1	B3.7.4.6	<u>Detection and management of immune effector cellular therapy complications including, but not limited to, those listed in B3.7.3.4.</u>
6.1	B3.8.2.1	An overview of hematology/oncology patient care, including the cellular therapy process, <u>cytokine release syndrome, and neurological toxicities.</u>
6.1	B3.8.3	Pharmacists <del>should</del> <u>shall</u> be involved in the development and implementation of guidelines or SOPs related to the pharmaceutical management of <del>transplant</del> <u>cellular therapy recipients.</u>
6.1	B3.8.4.1	Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation <u>and cytokine release syndrome and neurological toxicities resulting from cellular therapies.</u>
6.1	B3.10.2	<u>The Clinical Program Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.</u>
6.1	B4.7.3.2	<u>For immune effector cells, an endpoint of clinical function as approved by the Clinical Program Director.</u>
6.1	B4.7.3.3	Overall and treatment-related morbidity and mortality at <u>thirty (30) days, one hundred (100) days, and one (1) year after transplantation cellular therapy product administration.</u>
6.1	B4.8.3.1	<u>Periodic audit of the accuracy of clinical data.</u>
6.1	B4.8.3.2	<u>Annual audit of safety endpoints and immune effector cellular therapy toxicity management.</u>
6.1	B4.10.2.1	A thorough investigation shall be conducted by the Clinical Program in collaboration with the Collection Facility, <del>and</del> <u>Processing Facility, and other entities involved in the manufacture of the cellular therapy product, as appropriate.</u>
6.1	B5.1.10	<u>Management of toxicities of immune effector cellular therapies, including cytokine release syndrome and central nervous system complications.</u>

<b>Version Number<sup>2</sup></b>	<b>Standard</b>	<b>Change</b>
6.1	B6.3.9	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 <del>transplant</del> <u>recipient's</u> physician.
6.1	B7.10	<u>There shall be policies and procedures addressing the administration of immune effector cells and management of complications.</u>
6.1	B7.10.1	<u>There shall be a consultation with the referring physician prior to initiation of immune effector cellular therapy to review the goal and plan of the treatment.</u>
6.1	B7.10.2	<u>There shall be regular assessment of the recipient to detect complications, including cytokine release syndrome and neurologic dysfunction.</u>
6.1	B7.10.3	<u>There shall be a written plan for rapid escalation of care, increased intensity of monitoring, and relevant workup to address complications.</u>
6.1	B7.10.4	<u>Communication to the clinical staff, intensive care unit, emergency department, and pharmacy shall be timely.</u>
6.1	B7.10.5	<u>The Clinical Program shall have written guidelines for management of complications, including the use of cytokine-blocking agents and corticosteroid administration.</u>
6.1	B8.1.2	<u>There shall be a process to manage investigational cellular therapy products.</u>
6.1	B9.2	<u>The Clinical Program should collect all the data elements included in the applicable CIBMTR Cellular Therapy forms or EBMT forms.</u>
6.1	B9.3	<u>The Clinical Program shall define staff responsible for collecting data and, as appropriate, reporting data to institutional repositories and CIBMTR or EBMT.</u>
6.1	C3.3.2	<u>The Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.</u>
6.1	D3.3.2	<u>The Processing Facility Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.</u>

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<sup>1</sup> This appendix does not include minor numbering or reorganization changes that were a result of the substantive changes listed above.

<sup>2</sup> The effective date of version 6.1 is March 1, 2017.

## ACKNOWLEDGEMENTS

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