

HEMATOPOIETIC CELLULAR THERAPY

Accreditation Manual

NINTH EDITION 9.1



INTERNATIONAL STANDARDS FOR HEMATOPOIETIC CELLULAR THERAPY PRODUCT COLLECTION, PROCESSING, AND ADMINISTRATION **ACCREDITATION MANUAL**



FOUNDATION FOR THE
ACCREDITATION OF
CELLULAR THERAPY



Guidance to Accompany the FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration

Ninth Edition Version 9.1

NOTICE

This Manual and the Standards referenced herein are designed to provide minimum guidelines for programs, facilities, and individuals performing cellular therapy or providing support services for such procedures. This Manual and the Standards referenced herein 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 establish additional requirements. Each program, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with the 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.

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INTRODUCTION

This Accreditation Manual is intended to accompany the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration, Ninth Edition, 2025* (the Standards). The purpose is to explain the intent and rationale for specific Standards, to provide examples of approaches that would be considered compliant with Standards, and to detail the type of documentation that may be used to verify compliance during the accreditation process. This information is intended to be helpful to applicants for accreditation and to on-site inspectors. There are potentially many effective ways to meet the Standards. The examples and the type of documentation listed are not requirements and are not all-inclusive.

This Manual is organized in the alphanumeric order of the Standards. Each Standard is quoted in its entirety, followed by a guidance section, which includes an explanation of the applicable Standard(s), potential ways an applicant may document and an inspector may verify compliance, and examples to illustrate how the Standard may be applied. This information is intended to prepare applicants for making such evidence available to the inspector. Inspectors are not restricted to the methods or documents described for verifying compliance with Standards. Additional documentation may be requested at the discretion of the inspection team. The introduction to the ninth edition *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration* contains information that is applicable to this guidance document as well.

This Accreditation Manual does not establish new or stricter requirements than those in the Standards. If it appears there is a discrepancy between the Standards document and the Manual document, the Standards document will prevail.

Please note:

- 1) The Standards Committee's focus was to highlight those issues which may require additional explanation or examples to assist programs in attaining compliance with the Standards. For this reason, not every standard has guidance.
- 2) Updates may be made to this Manual periodically as needed to clarify the intent of the Standards. If a printed copy of this Manual differs from the version posted online at www.factglobal.org and www.ebmt.org/jacie, the web version prevails.

In the FACT-JACIE Standards, there is a deliberate and specific use of the terms "shall" and "should."

- For purposes of both the Standards and this manual, "shall" is used to indicate that the standard is a requirement to be complied with at all times. For ease of comprehension and reading, terms such as "must" or "will" are used only in this Accreditation Manual to be synonymous with "shall." An applicant must revise its practice when that practice deviates from a "shall" standard.

- The term “should” indicates an activity that is recommended, but for which there may be effective alternatives. When an applicant deviates from a “should” standard, an explanation, but no change in practice, is required.

ACCREDITATION

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

In 2025, JACIE adopted the term “certification” to describe the quality assurance activities within its processes, although “accreditation” remains the term used throughout the FACT-JACIE International Standards. This change was made in order to align with the terminology and requirements set forth in [Regulation \(EC\) No 765/2008](#), which establishes a common framework for the accreditation and oversight of conformity assessment bodies across EU Member States. This adjustment in terminology reflects a commitment to maintaining alignment with European regulatory structures while preserving clarity and consistency in the designation of JACIE’s role in promoting quality and safety in cellular therapy programs across its domain.

An accreditation cycle is three years for FACT and the certification cycle for JACIE is four years. [FACT](#) or [JACIE](#)-accredited/certified programs are listed on the websites of the respective organizations.

PART A: TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITONS

[A1:](#) Terminology

[A2:](#) Tenets

[A3:](#) Abbreviations

[A4:](#) Definitions

PART A: TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

A1 TERMINOLOGY

- A1.1 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.
- A1.2 The phrase, “policies and Standard Operating Procedures,” is used for ease of reading. When referring to a single document, either a policy or Standard Operating Procedure is sufficient.

A2 TENETS

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

- A2.1 Where Applicable Law includes more stringent requirements than these Standards, Applicable Law supersedes the Standards. Conversely, when these Standards are more stringent than Applicable Law, the Standards shall be followed.
- A2.2 Where the word “accreditation” appears in these Standards in the context of the FACT-JACIE accreditation process, “certification” shall be used instead of “accreditation” within the JACIE process.
- A2.3 Any activity can be delegated to an appropriate designee as that term is defined. The person appointing a designee retains ultimate responsibility.
- A2.4 Standards related to services not provided by the applicant do not apply to the applicant organization. The responsibility to demonstrate that a requirement is not applicable rests with the applicant’s organization.

A3 ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

<i>AABB</i>	Association for the Advancement of Blood & Biotherapies
<i>ABO</i>	Major human blood group including erythrocyte antigens, A, B, O
<i>Anti-</i>	Antibody to the designated antigen
<i>APP</i>	Advanced practice provider/professional

ASHI	American Society for Histocompatibility and Immunogenetics
ASTCT	American Society for Transplantation and Cellular Therapy
ATMP	Advanced Therapy Medicinal Product
BLA	Biologics License Application
BMT	Blood and marrow transplantation
CAP	College of American Pathologists
CAPA	Corrective and preventive action
CAR	Chimeric antigen receptor
CE	<i>Conformité Européene</i> or European Conformity
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CJD	Creutzfeldt-Jakob Disease
CLIA	Clinical Laboratory Improvement Amendments
CME	Continuing medical education
CMS	Centers for Medicare and Medicaid Services
CMV	Cytomegalovirus
COA	Certificate of analysis
CPD	Continuing professional development
CRS	Cytokine release syndrome
CV	Curriculum vitae
CVC	Central venous catheter
DIN	Donation identification number
DLI	Donor lymphocyte infusion
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DNV	Organization formerly known as Det Norske Veritas
EBMT	European Society for Blood and Marrow Transplantation
ECP	Extracorporeal photopheresis
ED	Emergency department
EFI	European Federation for Immunogenetics
ESH	European School of Haematology
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	United States Food and Drug Administration
G-CSF	Granulocyte colony-stimulating factor
GMP	Good manufacturing practice
GTP	Good tissue practice
GxP	Good (variable) practice
GVHD	Graft versus Host Disease
HCT/P	Human cells, tissues, and cellular and tissue-based products
HEPA	High-efficiency particulate air
HFAP	Healthcare Facilities Accreditation Program
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPC	Hematopoietic progenitor cell
HTA	Human Tissue Authority
HTLV	Human T-cell lymphotropic virus
IBC	Institutional Biosafety Committee
IBLS	Eurocode International Blood Labeling Systems
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICCBBA	International Council for Commonality in Blood Banking Automation

<i>ICU</i>	Intensive care unit
<i>IDE</i>	Investigation device exemption
<i>IEC</i>	Immune effector cell
<i>IEC-HS</i>	Immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome
<i>IND</i>	Investigational new drug
<i>IRB</i>	Institutional Review Board
<i>ISBT 128</i>	Information Standard for Blood and Transplantation – the number 128 reflects the 128 characters of the ISO/IEC 646 7-bit character set
<i>ISCT</i>	International Society for Cell & Gene Therapy
<i>ISO</i>	International Organization for Standardization
<i>JACIE</i>	Joint Assurance Committee – ISCT and EBMT
<i>kg</i>	Kilograms
<i>MNC</i>	Mononuclear cell
<i>MP</i>	Medicinal product
<i>NMDP</i>	Organization formerly known as National Marrow Donor Program
<i>OSHA</i>	Occupational Safety and Health Administration
<i>PBSC</i>	Peripheral blood stem cell
<i>PPE</i>	Personal protective equipment
<i>QM</i>	Quality management
<i>RBC</i>	Red blood cell
<i>Rh</i>	Rhesus system of human red blood cell antigens – used in this document to refer to the Rh(D) antigen only, unless otherwise specified
<i>SEC</i>	Single European Code
<i>SOP</i>	Standard operating procedure
<i>TNC</i>	Total nucleated cell count
<i>U.S.</i>	United States
<i>UK</i>	United Kingdom
<i>UL</i>	Underwriters Laboratories
<i>WMDA</i>	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 or certification, by FACT or JACIE respectively, until its expiration. At publication of these Standards, this period is three (3) years for FACT-accredited programs and four (4) years for JACIE-certified programs.

Acuity: The severity of a patient's illness or condition, indicating the level of care and resources required.

Advanced Degree: A master's degree in a biological science that is enhanced by ten years of experience in cellular therapy processing, manufacturing, laboratory management, and knowledge of applicable regulations and quality systems.

Advanced practice provider/professional (APP): 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 administration of a cellular therapy product or by the product itself.

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

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

Ambulatory care: A planned care system in which cellular therapy recipients at risk of prolonged neutropenia are based at home or in another specified accommodation. There should be specific safeguards to minimize the risk from potentially life-threatening complications of the preparative regimen.

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

And/or: Either or both may be affected or involved.

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.

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

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

Assent: The expression of approval or agreement.

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 Standard Operating 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.

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 terminology.

Cellular therapy: The administration of cellular therapy products.

Cellular therapy product: Somatic cell-based product (e.g., HPC, mononuclear cells, cord blood cells, IEC, genetically modified cells, others) that is procured from a donor and intended for processing or administration.

Chain of Custody: Concurrent, permanent, auditable documentation illustrating the guardianship of a cell or gene therapy product from its origin through its final disposition.

Chain of Identity: The permanent and transparent association of a cell or gene therapy's unique identifiers from procurement of tissue or cells throughout the full product(s) lifecycle including post treatment monitoring.

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

Chimerism testing: Assessment of the presence of allogeneic donor cells in a transplant recipient using any assay of informative genetic markers that distinguishes donor from recipient cells.

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, Standard Operating Procedures, quality management systems, clinical outcome analysis, and regular interaction among clinical sites.

Clinical Site: Any physical location where a patient or donor receives care, including inpatient, outpatient, ambulatory care facilities, and other locations. A clinical program may consist of more than one clinical site. Clinical sites can be in one or more hospitals or institutions.

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

Collection Facility: An entity providing the service of collecting the initial cellular therapy product.

Collection Site: The physical location at which cells are collected.

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; a service related to the collection, processing, storage, distribution, or administration of a cellular therapy product; or clinical care.

Consent: A process in which a healthcare professional educates a patient about the risks, benefits, and alternatives of a given procedure or intervention.

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

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.

Corrective Action Plan: A document describing the step-by-step plan of action to achieve a defined outcome or resolution of an identified occurrence or noncompliance.

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.

Cytokine release syndrome (CRS): A non-antigen-specific toxicity that occurs as a result of high-level immune activation.

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.

Deviation: The action of departing from an approved process or an established course of action.

Planned deviation: Allowed to occur with documented prior approval as the best course of action when adherence to the established course or accepted practice was not feasible or possible.

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

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

DNV: An accreditation program which directly addresses regulatory requirements for hospitals, such as the U.S. government's Centers for Medicare and Medicaid, or provides guidance and best practices for clinical specialty organizations across healthcare. DNV is now the proper name of the organization formerly known as Det Norske Veritas.

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 therapy in which lymphocytes from the original cellular therapy product donor are given to a recipient who has received an HPC transplant from the same donor.

Effective date: The day the new version of a document has been implemented and the previous version has been recalled or archived.

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 Law 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. It is recommended that cellular therapy programs use engraftment definitions from CIBMTR, EBMT, or another similar organization.

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.

Eurocode: The facility identification code (Center Code) and product coding assigned, published, and maintained by the Eurocode International Blood Labeling Systems.

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.

Extracorporeal photopheresis (ECP): A therapeutic procedure in which the buffy coat is separated from the patient's blood, treated extracorporeally with a photoactive compound (e.g., psoralens) and exposed to ultraviolet A light, then subsequently infused to the patient during the same procedure.

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 subspecialty after completing residency, usually in a hospital or academic setting.

Fresh: A cellular therapy product that has not been cryopreserved.

Genetically modified cell: A cell that has been modified by genetic transfer or edited for therapeutic intent.

Good Manufacturing Practice (GMP): 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 U.S., GMPs are enforced under Section 501(B) of the Federal Food, Drug, and Cosmetic Act ([21USC351](#)). Examples of products controlled under GMP regulations may include cellular therapy products that are more than minimally manipulated, that are allogeneic and obtained from donors other than first- or second-degree relatives, or that are used for non-homologous purposes. Equally well-developed systems of regulations are delineated by the European Union (EU-GMP), United Kingdom, Australia, Canada, and Singapore.

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

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

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 an HPC product with the intent of providing effector functions in the treatment of disease or in support of other therapy.

Hemodilution: A decreased concentration of cells and solutes in the blood caused by infusion of blood products or fluids.

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

Immune effector cell (IEC): A cell that has differentiated or manufactured 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 Applicable Law and who has identified risk factor(s) for relevant communicable disease.

Institutional Review Board (IRB) 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.

Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency interval, methods of administration, and safety monitoring procedures. The Investigator's Brochure also provides insight to support the clinical management of the study subjects during the course of the clinical trial.

ISBT 128: A global standard for the identification, labeling, and information transfer of medical products of human origin published and maintained by ICCBBA.

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 collection, 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.

New patient: An individual undergoing cellular therapy treatment (allogeneic, autologous, or syngeneic) for the first time in the Clinical Program, whether or not that patient was previously treated by that Clinical Program.

Nosocomial infection: Also known as a healthcare-associated infection or hospital-acquired infection, an infection that a patient contracts while receiving treatment for another condition in a healthcare setting.

Occurrence: An instance in which an action or circumstance results in errors, accidents, deviations, adverse events, adverse reactions, or complaints.

Organizational chart: A graphic representation of the structure, function, and reporting relationships of key personnel within an organization.

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.

Package insert: A document prepared by the drug manufacturer, approved by the applicable regulatory body, and included with drug packaging that provides drug prescribing information, details, and directions that health care providers need to prescribe a drug properly including approved uses for the drug, contraindications, potential adverse reactions, available formulations and dosage, and how to administer the drug. The package insert may be used to develop promotional or labeling materials.

Packaging: Placing a cellular therapy product into an appropriate secondary or outer container for shipping or transportation.

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

Periodic: Occurring at time intervals specifically defined by the organization as appropriate.

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.

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, lymphodepletion, 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.

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

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

Processing: All aspects of manipulation, labeling, cryopreservation, and packaging 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 code: An eight-character ISBT 128 code that comprises the Product Description Code, a Collection Type Code, and a Division Code. The product code, combined with the donation identification number and facility processing code, if applicable, makes each product globally unique.

Product name: The ISBT 128 Cellular Therapy Class product database name and definition (format: type of cells, comma, source of cells) for products of human origin. The most up-to-date list of definitions is available on ICCBBA's website at [*ISBT 128 Standard Terminology for Medical Products of Human Origin*](#).

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

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

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 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 (QM): The integration of quality assessment, assurance, control, and improvement in cellular therapy activities.

Quality Management Plan (QM Plan): A written document that describes the systems in place to implement the Quality Management Program.

Quality Management Program (QM 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.

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.

Registry: An organization responsible for the coordination of the search for cellular therapy product donors (including cord blood) unrelated to the potential recipient.

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

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

Risk assessment: The process of identifying potential hazards, evaluating the likelihood and severity of harm, and deciding on appropriate measures to control or eliminate the risk.

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.

Sinusoidal obstruction syndrome: A distinctive and potentially fatal form of hepatic injury that occurs predominantly, if not only, after drug or toxin exposure; previously known as veno-occlusive disease.

Standard Operating Procedure (SOP): A document that describes in detail the process or chronological steps taken to accomplish a specific task. Also referred to as work instructions. An SOP is more specific than a policy.

Standard Operating Procedures (SOP) Manual: A compilation of policies and Standard Operating 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 “these Standards” or “the 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 among genetically identical siblings.

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.

Third-party manufacturing: Outsourcing of part or all of the manufacturing of a cellular therapy product to a facility separate from the facilities primarily involved.

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.

Traceability: The ability to track any product through all stages of collection, processing, and administration so that tasks can be traced one step backwards and one step forward at any point in the supply chain.

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

Transplantation: The administration 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.

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.

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 to 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.

PART B: CLINICAL PROGRAM STANDARDS

- [B1:](#) General
- [B2:](#) Clinical Unit
- [B3:](#) Personnel
- [B4:](#) Quality Management
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PART B: CLINICAL PROGRAM STANDARDS

B1: GENERAL

STANDARD:

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).

Explanation:

This Standard provides the definition of a Clinical Program, an entity that can be inspected and independently accredited. A Clinical Site is any physical location where a patient or donor receives care, including inpatient, outpatient, ambulatory care facilities, and other locations. Clinical Sites can be in one or more hospitals or institutions. Virtual visits may originate from other locations.

A Clinical Program may consist of more than one Clinical Site and must be within a defined location that allows for integrated and regular interaction among all members of the medical team. Only those programs that truly function as a single integrated program may apply as one Clinical Program. Electronic medical record system access shared among multiple sites, although integrated, does not alone meet the overall intent of this Standard.

It is possible to have more than one Clinical Program in a defined location or within a single metropolitan area. Each could be accredited separately if each individually meets the criteria detailed in the Standards. There is not a limit on the total number of programs eligible for accreditation within one area.

Evidence:

The questions on the inspection application and checklist are designed to elicit the information necessary to determine if a single Clinical Program exists. Advancement in technology and travel may allow for geographically dispersed sites, but such programs would be expected to provide unequivocal evidence of integration. An organizational chart depicting the relationship between program sites will facilitate documentation of integration and site locale. No matter the distance between sites, the Clinical Program Director(s) (see section [B3](#) for a definition and description of the Clinical Program Director) should have a documented physical presence at all sites and be actively involved in daily operations to meet the intent of the Standard. Other evidence of an integrated medical team is a common Quality Management Program (QM Program) and meeting minutes demonstrating collaboration between sites on all aspects of the program at defined and regular intervals.

In the case of sites with more than one hour of traveling distance from each other or within different metropolitan areas, programs should contact the Foundation for the Accreditation of Cellular

Therapy (FACT) or Joint Assurance Committee – ISCT and EBMT (JACIE) office to verify eligibility for accreditation as a single program.

STANDARD:

B1.1.1 These Standards apply to all services provided by the Clinical Program.

Examples(s):

Accreditation of the Clinical Program is all-inclusive of transplantation and other cellular therapies. For example, if the program is accredited under these Standards and treats patients with immune effector cells (IECs) on its transplant unit, then the program will be inspected for hematopoietic progenitor cells (HPCs) and IECs.

STANDARD:

B1.1.2 The Clinical Program shall demonstrate common staff training, protocols, Standard Operating Procedures, quality management systems, clinical outcome analyses, and regular interaction among all clinical sites.

Explanation:

Clinicians accredited together as a Clinical Program must work together in readily demonstrable ways on a frequent basis and have a single director or co-directors (the Program Director[s]), responsible for these clinical activities. Individual clinical sites will be inspected as appropriate.

Several clinical sites, particularly those with different directors or outside of a defined network, joining together for the purpose of meeting criteria to qualify as a Clinical Program do not fulfill the intent of the Standards. By itself, the presence of one or more of the characteristics in this Standard does not necessarily define a single program nor meet the intent of the Standards. The FACT/JACIE Board of Directors will be the arbiter if there is a question about fulfillment of this Standard.

In the event of co-directors, the responsibilities for each Director must be clearly defined, and one must be named as the corresponding director for the accreditation activities and interaction with FACT or JACIE.

Evidence:

It is incumbent on the Clinical Program to demonstrate with evidence that there is sufficient integration. The inspector will expect to find the following if a single Clinical Program exists:

- Common or equivalent staff training programs, especially for nurses. This includes in-service training and competency testing on the same topics.

- Common or equivalent controlled documents. This includes forms, flow sheets, policies, and Standard Operating Procedures (SOPs). Example protocols include high-dose therapy and other preparative regimens, management of fever, prophylactic antibiotics, antiviral and antifungal prophylaxis, graft versus host disease (GVHD) prophylactic and/or treatment regimens (if applicable), management of IEC complications (if applicable), and administration guidelines for medications or blood components.
- Regular interaction. Regular interaction is achieved through meetings and conferences that are regularly scheduled, multidisciplinary, involve all clinical sites, and are documented in meeting minutes, including documented attendees. Regular interaction should involve physicians, nurses, coordinators, social workers, education consultants, processing staff, collection staff, and others. This should include regularly scheduled conferences on topics such as morbidity and mortality, quality assessment and improvement, protocol development, journal clubs, patient assessment and evaluation, patient outcomes, tumor boards, continuing education presentations, and interesting case presentations. Such topics could also be reported in joint manuscripts or abstracts for national meetings. The inspector should check attendance to confirm that all sites are represented and attendance is documented.

Example(s):

Examples of a single integrated Clinical Program may include:

- A university program with an adult hospital and a pediatric hospital.
- A community program with two hospitals in the same metropolitan area.
- A National Health Service trust in the United Kingdom.
- Cancer networks.
- Any other robust organizational structure involving a center and satellite units.

A Clinical Program may have an adult unit at an adult hospital and a pediatric unit at a children's hospital. If a hospital has both adult and pediatric units that are staffed by either specialist adult or pediatric nurses, this is considered to be two sites. In contrast, a large adult unit that transplants patients in two clinical care areas (e.g., wards) with integrated nursing staff and physician coverage is considered one site.

STANDARD:

B1.2 *The Clinical Program shall abide by Applicable Law.*

Explanation:

FACT and JACIE are voluntary inspection and accreditation organizations that develop professional standards designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with the Standards does not guarantee compliance with Applicable Law. Governmental regulations must also be followed. It is the responsibility of the individual Clinical Program to

determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the facility may apply.

Compliance with other organizations' standards or governmental regulations does not ensure that the Standards have been met. Governmental regulations supersede any organization's standards if those regulations set a higher standard or are inconsistent with a specific standard. However, if a standard is more rigorous than a governmental regulation, that standard must be followed.

Evidence:

While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with Applicable Law. Evidence of compliance with the Standards will require pre-inspection information identifying prevailing governmental authorities and documentation of certificates, permits, or licenses.

Example(s):

It is the responsibility of the individual Clinical Program to determine which laws and regulations are applicable. For autologous IEC products, some of the following examples might not be applicable.

In the United States (U.S.), minimally manipulated cellular therapy products from first- or second-degree related donors are regulated under the [21 CFR Part 1271 Subpart D](#)—Current Good Tissue Practice (CGTP or GTP) regulations and section 361 of the Public Health Service Act, with the exception of products collected from bone marrow as the source of the cellular therapy product. A cellular therapy product that is extensively manipulated, obtained from an unrelated donor, combined with a drug or device, or used for non-homologous use (i.e., does not perform the same function in the recipient as in the donor) is regulated as a drug, device, and/or biological product under section 351 of the Public Health Service Act and other applicable regulations in [Title 21](#) of the Code of Federal Regulations (CFR).

In the Member States of the EU, both HPCs and T cells fall under the European [Directive 2004/23/EC](#) of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, as well as the implementing Directives [2006/17/EC](#) and [2006/86/EC](#). [Directive 2001/83/EC](#) regulates products that are classified as medicinal products (MPs). This includes somatic cellular therapy MPs and gene therapy MPs. The TMP-[Regulation \(EC\) No 1394/2007](#) entered in force on December 30, 2007, to include tissue-engineered products. The consequence of classification as an MP is that a Good Manufacturing Practice (GMP) environment is required for the production of these cells. Furthermore, each Member State in the European Union (EU) may add on additional regulations to the directives that also must be followed. Member State-specific regulations will not be detailed here. The current EU Directives will be replaced by [Regulation \(EU\) 2024/1938](#) of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application. The regulation will be fully applicable from August 7, 2027.

STANDARD:

B1.2.1 The Clinical Program shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

Explanation:

Applicable Law may require registration or certification with the government or may require accreditation from professional organizations for the activities performed within the Clinical Program.

Evidence:

Documentation of registration with the relevant governmental authorities will be sent to the FACT or JACIE office with the accreditation application materials. If such a copy is not provided to the inspector prior to the inspection, the inspector may ask to see it on site. A copy may not be immediately available at the clinical site; however, the Program Director(s) should know who in the institution is responsible for the registration and where a copy may be obtained. It is not appropriate to request a faxed copy from the regulatory authority during the on-site inspection.

Example(s):

In the U.S., Clinical Programs must have or utilize inpatient units that are located in facilities accredited by the Joint Commission, the Healthcare Facilities Accreditation Program (HFAP), or DNV (organization formerly known as Det Norske Veritas). Alternatively, U.S. Clinical Programs may choose to be directly inspected by the Centers for Medicare & Medicaid Services (CMS). In addition, U.S. Clinical Programs must be licensed as required by Applicable Law. Other countries have their own hospital certification bodies, such as the Haute Autorité de Santé (HAS) in France.

Other examples of verified compliance with regulations include current U.S. Food and Drug Administration (FDA) registration, acceptable FDA audit reports, state licensure, licensing of tissue establishments by the Member State in the EU, Clinical Laboratory Improvement Amendments (CLIA) certification, acceptable Occupational Safety and Health Administration (OSHA) inspections, or accreditation by the American Society for Histocompatibility and Immunogenetics (ASHI) or European Federation for Immunogenetics (EFI).

STANDARD:

B1.3 The Clinical Program shall have a designated cellular therapy team that includes a Clinical Program Director, a Quality Manager, and a minimum of one (1) additional transplant or cellular therapy attending physician, as applicable. The designated team shall have been in place and performing cellular therapy for at least twelve (12) months preceding initial accreditation.

Explanation:

A Clinical Program must have sufficient experience as a team in caring for transplant and other cellular therapy recipients. A designated team does not necessarily mean that each of the individuals

has no other responsibilities or duties. It is likely that some individuals perform basic research, clinical research, other non-cellular therapy clinical care, or administrative work during the time they are not actively attending to cellular therapy donors or recipients. However, each team member must meet the training and experience requirements in [B3](#).

An attending physician may also serve as the Clinical Program Director, if appropriately credentialed. However, Clinical Programs must have an attending physician in addition to the director (i.e., a transplant team must have at least two physicians). The number of physicians overall should be proportionate to the volume of care provided. If there is a larger volume of patients, then there should be a higher number of physicians.

The Quality Manager is not required to serve the Clinical Program on a full-time basis. This position may have a fractional full-time equivalent appointment or be shared with other departments in the institution.

If an experienced team relocates to a new clinical site not encompassed within a previous Clinical Program and develops a new Clinical Program, that new program must have been in place at least 12 months. Additionally, the team must have performed a minimum number of transplants (per [Appendix I](#)) at the new location prior to accreditation of the new program. This is true regardless of the experience of the team.

Changes in key personnel or in a significant proportion of team members must be reported to the FACT or JACIE office within 90 days of the change and may require reinspection in accordance with FACT or JACIE policies. The FACT or JACIE Accreditation Committee will determine if a reinspection is required. In case of a vacancy in a key position, a qualified individual must be named to fill that position. The person so named must meet the minimal qualifications for the position, even if only filling it on an interim basis.

A Clinical Program adding cellular therapies to its services may begin pursuing accreditation prior to 12 months of adding such services, so long as the team is in place and is undergoing training and gaining experience sufficient to comply with this Standard at the time of accreditation.

Evidence:

It is the responsibility of the Clinical Program Director to contact the FACT or JACIE office if there is any question that a significant change in faculty, staff, or activities could precipitate a reinspection. It is also the responsibility of the Program Director to accurately report the information required on interim and annual report forms sent to all accredited facilities mid-cycle.

Example(s):

Changes in a Clinical Program Director do not necessarily require reinspection, especially if the majority of faculty and staff and the scope of transplant activities remain unchanged.

STANDARD:

B1.4 Clinical Programs directly responsible for cell collection or processing activities shall comply with the Standards in [Parts C](#) and [D](#) as applicable.

B1.5 The Clinical Program shall use cell collection and processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Clinical Program.

Explanation:

The Clinical Program is responsible for verifying that the collection and processing facilities from which it receives cellular therapy products meet FACT-JACIE Standards. It is not the intent of this Standard to require clinical, collection, and processing facilities to be housed in one location or services to be performed by a single legal entity. Cell collection, cell processing, or both may be integral to the Clinical Program or performed by contract by a third party. Various structures are acceptable for differing Clinical Programs. The intent of the standard is met when each component of the process demonstrates that it meets the Standards for the activities and functions it performs.

Evidence:

Collection and processing facilities that are external to the Clinical Program may choose to be formally accredited or not; however, they still must meet the FACT-JACIE Standards, submit evidence of compliance with Standards, complete an on-site inspection, and correct all deficiencies before the Clinical Program may be granted initial or renewal accreditation. The applicant Clinical Program should maintain documentation that the integrated or contracted collection and processing facilities meet the Standards.

If the collection or processing services were contracted to a new facility, reinspection would be required unless the new facility was already independently FACT or JACIE accredited or had been inspected and determined to meet the Standards.

Coordination among the Clinical Program, the collection facility, and the processing facility must be readily apparent to the inspector through documents such as a written agreement defining roles and responsibilities, SOPs, forms, and ongoing quality management (QM) documentation. If the Clinical Program uses a collection or processing facility external to its accredited program, documentation of interactions and written agreements between the Clinical Program and that collection or processing facility must be available to the inspector.

Example(s):

There are several ways FACT or JACIE accreditation may be sought, such as:

- A Clinical Program, Collection Facility, and Processing Facility may be integrally connected and be accredited together.
- A Clinical Program may contract with an independently accredited Collection Facility and/or an independently accredited Processing Facility.

- A Collection Facility may be accredited independently and collect cells for one or more Clinical Programs, which may or may not be FACT- or JACIE-accredited.
- A Collection Facility may be accredited in association with a Processing Facility and collect, process, and store cells for one or more Clinical Programs, which may or may not be FACT- or JACIE-accredited.
- A Clinical Program and a Collection Facility may be jointly accredited, with the cells processed and stored by contract at a separately accredited Processing Facility.
- An independently accredited Processing Facility may process and store cells for several Clinical Programs, which may or may not be accredited by FACT or JACIE.
- A Clinical Program may contract with an independently accredited Collection Facility for cell collection for further manufacture by a third-party manufacturer under an approved investigational new drug (IND), Biologics License Application (BLA), or equivalent.

While it is required that the Clinical Program will use cell collection facilities that meet the Standards, it is understood that the program may not always know or be able to control where an unrelated donor product, procured through the National Marrow Donor Program (NMDP) or another donor registry, has been collected. In this case, a collection center used by a registry operating in accordance with World Marrow Donor Association (WMDA) guidelines is recommended. It is expected that such products constitute a minority of the total number of products administered by any one Clinical Program.

Another example is an adult donor for a pediatric program located in a city where there is no FACT or JACIE-accredited adult collection center. This might require the program to utilize an adult facility for collection or an alternative collection center of a registry operating in accordance with WMDA guidelines. In all cases, it is expected that these products represent the minority of products utilized by an accredited Clinical Program.

STANDARD:

B1.6 *If the Clinical Program or an intermediary facility receives cellular therapy products directly from a third-party provider, the following responsibilities shall be defined in policies, Standard Operating Procedures, and written agreements:*

Explanation:

As Clinical Programs become involved with new approaches to standard-of-care cellular therapies or novel cellular therapies, they will likely experience increased interactions with third parties who have Investigational Device Exemptions (IDEs), IND applications, or market-approved cellular therapy products via BLA from the U.S. FDA or other equivalent regulatory pathways. The Clinical Program must have a written agreement with these third parties and other associated participating facilities, if applicable, that defines the roles and responsibilities of each.

The level of participation of the Clinical Program in manufacturing research or commercial cellular therapy products varies. Regardless of where a product is collected or manufactured, responsibilities must be clearly defined. The intent of these standards is to define the minimal elements to be included in the written agreements, but not to define the format of the agreement. Agreements meeting this standard could stand alone or be part of a larger document that exists between the entities such as relevant policies and SOPs, a contract, or a Master Service or Quality Agreement. Written agreements must also comply with FACT-JACIE QM Standards ([B4.6](#)).

By meeting the requirements of the regulatory pathways described above, the third parties are considered to be in compliance with Applicable Law, including QM systems, accreditations, and process controls as outlined in GMP and GTP regulations. If the Clinical Program is utilizing licensed or research products, the program is responsible for verifying that the manufacturer responsible for the entire manufacturing process (e.g., a commercial manufacturer, clinical trial network) possesses an approved IND or BLA in the U.S., or meets appropriate regulatory requirements if outside of the U.S.

Such regulatory approval does not, however, ensure the Clinical Program's compliance with FACT-JACIE Standards regarding their interactions with third parties, which must be defined in a written agreement. Communication with third parties regarding defined responsibilities (e.g., product ordering and handling, cell collection, scheduling, labeling, occurrence management, reporting) is critical to the safety, efficacy, and quality of the cellular therapy. The Standard applies to the Clinical Programs, their collection and processing facilities, and any other entity that performs tasks related to the cellular therapy product, even if that facility only briefly handles the product.

These Standards define specific requirements for the content of the written agreements:

- The agreement should include the process for ensuring traceability and Chain of Custody. Chain of Custody documentation should include date, time, and responsible party for each step in distribution and receipt, storage, and release for administration. The storage and distribution conditions should be defined; the Clinical Program must document that those conditions were met (e.g., temperatures during transport or shipping). The program (or receiving facility) must have a designated space with suitable and monitored equipment for receiving and storing cellular therapy products. If another entity such as the blood bank, tissue bank, or pharmacy will receive the product, this process must be defined in policies, SOPs, or a written agreement. The process and person(s) responsible for verification of the Chain of Identity on receipt must also be defined.

- When a cellular therapy product is provided to a Clinical Program from a third-party manufacturer, there should be accompanying information that includes product specifications (e.g., drug product monograph, package insert, certificates of analysis) that should be reviewed by a designated person at the time of receipt and before distribution for administration. At a minimum, this step confirms that the product expected is the product received. If applicable, there would also be a defined process related to allogeneic donor eligibility that conforms with Applicable Law.

Evidence:

The inspector will expect to review a copy of applicable written agreements and SOPs that describe the processes in place to meet these Standards. Various formats are acceptable to demonstrate effective collaboration to meet the Standards.

Example(s):

There are many ways to manage written agreements with third-party manufacturers. The following are a couple of examples:

- A third-party manufacturer may distribute a licensed or regulatory-approved cellular therapy product to a Clinical Program the day prior to expected administration. A policy and SOP shared by the Clinical Program describes the responsibilities and the process for receipt by the institutional blood bank and short-term secured storage at that location.
- A third-party manufacturer maintains a comprehensive Quality Agreement with the institution housing an IEC Clinical Program that includes responsibilities for collection and shipping of the cellular starting material collected by apheresis, and receipt and short-term storage of the finished product at the clinical site.

When a cellular therapy product is manufactured by a third party, the Clinical Program may be responsible for securing collection of the cellular source material or preparing the final product for administration. If these responsibilities are delegated to the Clinical Program in written agreements, the following examples would require compliance with [Part C](#) or [Part D](#) of the Standards as applicable:

- Evaluation of the autologous or allogeneic donor for suitability (e.g., medical fitness) to undergo the collection procedure.
- Evaluation of the allogeneic donor for donor eligibility (e.g., free of risks of transmission of infectious diseases).
- Collection of the cells and shipping to manufacturer.
- Chain of Identity and Chain of Custody information for transport, shipping, manufacturing, and storage.

- Temporary storage of the product upon receipt at the Clinical Program (in the Processing Facility or elsewhere) and distribution for administration.
- Thawing and other preparation of the product for administration to the recipient.

STANDARD:

B1.6.1 Traceability and Chain of Custody of cellular therapy products.

Explanation:

Intermediary facilities may include pharmacies, blood banks, another laboratory facility, and collection facilities. The receiving facility takes responsibility for receipt of the product from the courier and provides storage until the product is needed.

STANDARD:

B1.6.2 Cellular therapy product storage and transportation (Sections [D9](#) and [D10](#) apply).

B1.6.3 Cellular therapy product distribution for administration (Section [D11](#) applies).

B1.6.4 Verification of cellular therapy product and recipient identity.

B1.6.5 Review and verification of certificate of analysis or cellular therapy product specifications provided by the manufacturer.

Explanation:

This Standard is always applicable; however, if the manufacturer does not provide the certificate of analysis (COA), the program can manage the process via a clinical risk assessment.

STANDARD:

B1.6.6 Readily available access to a summary of documents used to determine allogeneic donor eligibility.

B1.6.7 Documented evidence of allogeneic donor eligibility screening and testing in accordance with Applicable Law.

B1.7 The Clinical Program shall comply with the minimum number of new patients for accreditation as defined in [Appendix I](#).

Explanation:

[Appendix I](#) lists the minimum number of new patients who must be treated with allogeneic or autologous HPC transplantation and/or IEC therapies.

The appendix addresses multiple common organizational structures. Programs with atypical structures can work with the FACT/JACIE accreditation offices to determine how to best comply with this Standard.

Evidence:

Recipient logs with transplant and cellular therapy type will be submitted as part of the application for accreditation.

In addition, the program must indicate whether commercial or investigative cellular therapy products not intended for hematopoietic reconstitution are administered to patients in the Clinical Program. Inspectors will verify on-site that the processes associated with these products have been documented in SOPs or policies, including risk mitigation strategies and provider and patient education.

Inspectors will select at least two recipients of commercial or investigational products to follow the Chain of Identity and Chain of Custody, product administration, patient monitoring, education, adverse event management, patient discharge, and data reporting for those patients. Programs should be prepared to share results of internal audits of these patients and products.

Example(s):

The minimum number of new patients may be achieved with a combination of traditional and genetically modified HPC transplants.

STANDARD:

B1.8 There shall be a process to qualify the sites for cellular collections, including at a minimum ensuring Chain of Identity.

B1.8.1 There shall be written criteria for each collection site that define the level of donor risk that can be safely managed.

Explanation:

Clinical Programs, when sending donors (both autologous and allogeneic) for collection, must have a process to verify that the receiving Collection Site is qualified to manage the acuity of the donor. Cell collection organizations, especially apheresis centers, may collect cells for administration or for further manufacturing at various sites. Some collection sites may be within an inpatient hospital or outpatient clinic; others may be free-standing collection sites. The Standard does not require that all sites be equivalent. Collection sites may vary in capabilities, capacity, potential for donor isolation, staffing, access to transfusion services, interventional radiology, or support for pediatric patients. Some collection sites may be relatively distant from the main facility and be most appropriate for collections from healthy adult donors without central venous catheters (CVCs).

The intent of this Standard is that the Clinical Program must be aware of the type of donors that can be safely managed at the Collection Site to which donors are sent. Variables to consider should include at a minimum, ensuring Chain of Identity, expertise in central venous line management, expertise in pediatrics, availability of blood components if needed for priming an apheresis device, and ready capability to manage comorbidities such as obesity, cardiac dysfunction, or hypertension. It is acceptable to limit certain sites to specific types of donors.

Evidence:

The donor criteria for each collection site should be documented in the Clinical Program's Quality Management Plan (QM Plan), specific site description, or elsewhere.

Example(s):

The following are example statements that could indicate criteria for a collection site:

- Donors less than 25 kilograms (kg) must have collections performed at the collection site in the Pediatric Transplant Unit.
- Donors at a specific site must have a platelet count above 100,000/mm³.

STANDARD:

B1.9 Surgically collected cellular material shall be collected at an organization licensed by the appropriate regulatory agency or accredited by the Joint Commission, DNV, Accreditation Commission for Health Care, or other appropriate accrediting body.

Explanation:

For commercial products approved by the FDA or similar agency, the responsibility for collection site qualification and processes resides with the company and is not the responsibility of the Clinical Program. In these situations, the Clinical Program is only responsible for verifying that the Collection Site is appropriately accredited.

Example(s):

Some examples of the relevant European bodies include:

- [Haute Autorité de Santé](#) (HAS), France.
- [Deutsche Krebsgesellschaft](#) (DKG), Germany.
- [Care Quality Commission](#) (CQC), UK.
- [Qualicor](#), The Netherlands.

B2: CLINICAL UNIT

STANDARD:

B2.1 There shall be a designated inpatient unit of appropriate location and adequate space and design that protects the patient from transmission of infectious agents and allows for appropriate patient isolation, confidential examination, and evaluation.

Explanation:

Clinical unit facilities vary among centers based on a number of factors, including the number and type (autologous or allogeneic) of transplants performed, the patient case mix, the cell source, epidemiological factors influencing the prevalence of opportunistic infections, microbial resistance, and economic considerations including but not limited to bacteria, viruses, and fungi. Patients at high risk of infection or transmitting an infectious disease should be managed in a single occupancy room.

Consideration should be given to airflow. This Standard does not require that every clinical unit has laminar airflow availability, but high-efficiency particulate-free air (HEPA) filtration with positive pressure outflow from the room is recommended for high-risk patients. If non-HEPA filtered rooms are used for lower-risk patients or if there is a shortage of HEPA filtered rooms, the SOP(s) on infection control, biosafety, chemical, and radiological safety should indicate how allocation of rooms is prioritized. Furthermore, auditing of airborne microbial infections in non-HEPA rooms should be performed as part of the QM Program.

Evidence:

The inspector will tour the inpatient unit during the on-site inspection. Because different patients have different infection control needs, the Clinical Program must have policies and SOPs that include the following:

- Infection control requirements based upon differing patient conditions and room configurations.
- Types of air handling documented from a facilities management office.
- Alternative plan in case there is a shortage of isolation rooms; steps for preventing and controlling specific nosocomial infections, such as methicillin-resistant staphylococcus aureus (MRSA), C. Difficile, legionella, and community respiratory virus infections.

Procedures for monitoring airborne infections will provide evidence of compliance. Compliance can also be demonstrated by signs posted around the clinical unit and staff behavior consistent with expectations for the type of infection control described in the policies and procedures. If there are renovation or construction projects underway, the appropriate environmental controls must be present. The risk of spread of communicable disease agents must be minimized in any setting where patients could reasonably be expected to be, including dialysis or intensive care units (ICUs). Care

should be taken that the ventilation from other isolation rooms (where infected patients may reside) does not pass through the rooms used for cellular therapy recipients. Evidence of compliance with this Standard will require pre-inspection documentation of infection control policies, specifications of air handling, and floor plans.

When an accredited Clinical Program is to be relocated, qualification and validation must be performed to confirm the new space meets the Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the [Maintaining Accreditation Policy](#). The Clinical Program is expected to submit a description and floor plans of the new facility, QM documents, and an expected relocation date. If a JACIE-accredited facility intends to relocate, the program should submit plans and descriptions of the relocation to the JACIE office. Most relocations will be assessed during regularly scheduled inspections or annual reports; however, if there are any concerns with the information submitted by the facility, a relocation inspection may be necessary.

Example(s):

If HEPA filtration with positive pressure is not available, single patient rooms should be located on a patient care unit where infection control policies can be implemented. Infection control policies should include an appropriate response if HEPA filtration is not available.

Visitors should receive information concerning communicable infections. Signs posted to inform the public about visitation restrictions could also include information about incubation periods and risks of live vaccines.

STANDARD:

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, blood products, or cellular therapy products.

Evidence:

The inspector will tour the outpatient care area during the on-site inspection and will verify the elements mentioned in the Standard.

Example(s):

Patients at high risk for infection or transmitting an infectious disease should be managed in a single occupancy room.

Consideration should be given to airflow. This Standard does not require that every clinical unit has laminar airflow availability, but HEPA filtration with positive pressure outflow from the room is recommended for high-risk patients. If non-HEPA filtered rooms are used for lower-risk patients or if there is a shortage of HEPA filtered rooms, the SOP(s) on infection control, biosafety, and chemical, and radiological safety should indicate how allocation of rooms is prioritized. Furthermore, auditing

of airborne microbial infections in non-HEPA rooms should be performed as part of the QM Program.

In ambulatory settings, patients may be accommodated in a hostel, hotel, or home-based setting for periods of the transplant, with frequent or daily review and potential rapid inpatient admission. Clinical Programs should share criteria with these facilities regarding practices to prevent the spread of communicable infections.

STANDARD:

B2.3 When the preparative regimen, cellular therapy product administration, or initial post-transplant and cellular therapy care is provided in an ambulatory setting, there shall be a designated area in an appropriate location and adequate space and design to minimize the risk of microbial contamination.

Explanation:

These Standards apply to the space where outpatients can be evaluated and treated. Given the interchange between inpatient and outpatient units, close organizational relationships should exist, particularly with respect to infection control. The Clinical Program must define appropriate measures of control to minimize the risk of airborne microbial contamination. Auditing of airborne microbial infections in outpatient and ambulatory areas should be performed as part of the QM Program to determine if facilities reasonably protect recipients, particularly the most high-risk patients, from infection. The organizational relationship should also provide 24-hour coverage should recipients become ill in the outpatient area or at home.

Evidence:

The inspector will tour the outpatient areas during the on-site inspection. Relationships between outpatient and inpatient facilities, including steps taken to minimize transmission of infection, must be documented in policies, SOPs, and the organizational chart. An SOP should also describe patient selection criteria for transplantation in an ambulatory setting and the admission process.

Example(s):

It is acceptable to use a portion of an inpatient unit for outpatient visits. An ambulatory unit that provides space for outpatient visits, cellular therapy product administration, and transfusions may also comply with these Standards.

STANDARD:

B2.4 There shall be provisions for prompt evaluation and treatment by an attending physician available on a 24-hour basis.

Explanation:

An attending physician must be available at all times to manage cellular therapy recipients. The attending physician does not necessarily need to be the only health care provider on call nor be the first to see any patient requiring attention.

Evidence:

An on-call schedule that includes an attending physician who meets the requirements in [B3.3](#) should be available for inspector review. Inspectors may choose to test attending physician availability by activating the on-call schedule during the period of the on-site inspection. Patients and caregivers may also be provided with contact information to access providers in the event of an emergency.

Example(s):

Numerous post-transplant complications may require prompt attention, such as central venous line-associated bacterial sepsis. If needed, because of distance to the inpatient facility or for other reasons, a protocol should exist for outpatient facilities to contact emergency medical services if needed for prompt care (e.g., 911 in the U.S. or 112 in the EU).

STANDARD:

B2.5 The Clinical Program shall document facility cleaning and sanitation and shall maintain order sufficient to achieve adequate conditions for operations.

Evidence:

The inspector will observe the clinical unit and look for signs of cleanliness, sanitary practices, and orderly arrangement. If documentation of cleaning and sanitation is performed directly by the Clinical Program's institutional environmental services department, then the program should have knowledge of this documentation and the ability to show that it is complete.

STANDARD:

B2.6 The Clinical Program shall be operated in a manner designed to minimize risks to the health and safety of employees, recipients, donors, visitors, and volunteers.

B2.7 The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure to liquid nitrogen; communicable disease; and chemical, biological, radiological, electrical, or fire hazards.

Explanation:

The Clinical Program's policies and SOPs, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to applicable safety regulations. It is critical that the program has a safety manual and that staff members have ready access to instructions for prompt response. In case of exposure to a hazardous material (e.g., liquid nitrogen; communicable disease; chemical, biological, or

radiological hazards), the response and action taken might be time-sensitive and thus could affect the outcome of the exposure. If an institution-wide manual is used, safety, infection risks, and biohazard waste disposal procedures that are unique to the program must be covered in the program's safety manual.

Safety training, including universal precautions for handling blood, is a requirement of the occupational safety and health administrations in many countries. Other specific safety training for chemical handling (e.g., liquid nitrogen, chemotherapy) is required in accordance with the institutional requirements and Applicable Law. The use of electronic training programs that cover safety and infection control is acceptable, but there must be evidence that the staff has completed all relevant training satisfactorily.

Facilities should post warning signs wherever radioactive materials are in use. All persons who may be exposed to blood or body fluids must utilize appropriate personal protective equipment (PPE). This includes those exposed to cellular therapy products. The type of exposure that may be encountered will determine the appropriate protection. If aerosol exposure is likely, a mask, goggles, and gowns or aprons should be worn. Gloves must be worn whenever potential infectious exposure exists.

An adequate means of egress in areas where liquid nitrogen is stored, moved (e.g., elevators), or transported is required for the safety of personnel and potentially the public. Shippers received which utilize nitrogen may pose a risk, especially if stored in a small space. The Clinical Program is responsible for performing a risk assessment of the space used to temporarily store dry shippers which can encompass a risk to the safety of personnel.

If genetically modified cellular therapy products are administered by the Clinical Program, the Institutional Biosafety Committee (IBC), and potentially third-party manufacturers, will have specific procedures for waste disposal that must be followed. Investigator and staff training must include these procedures.

Evidence:

Inspectors should observe personnel during clinical procedures, whether scheduled events or mock demonstrations, for use of protective clothing and other biosafety precautions. Employee files for training in universal precautions and liquid nitrogen, biological, chemical, and radiation safety (when appropriate) must exist. The inspector should also be alert during the tour for the presence of unused or inappropriately stored supplies or equipment that may contribute to an unsafe environment.

The inspector should examine selected employee files for appropriately documented safety training.

Example(s):

The safety manual may be an institution-wide document available by hard copy or electronically. Access to the institutional safety manual solely by computer is not acceptable without a written

policy describing how to access the information in the event of a computer failure or down time. An SOP that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice.

A condensed or summarized hard copy of the institutional safety manual should be kept in the facility. In this case, there must be written documentation of how the condensed version is kept updated with institutional safety manual revisions. Such a document should focus on those hazards that are most likely to occur in the facility, such as needle sticks or handling patients with a known communicable disease.

STANDARD:

B2.8 All waste generated by the Clinical Program's activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with Applicable Law.

Explanation:

Poor management of medical waste exposes personnel, waste holders, and the community to injuries, infections, and toxic effects. Hazardous waste generated by the Clinical Program's activities includes a broad range of materials, such as used supplies, sharps, chemicals, radioactive material, viral vectors, genetically modified cells, and the cellular therapy products themselves. All medical waste must be discarded in a safe manner according to written protocols for the disposal of biohazard waste and in accordance with Applicable Law.

Contaminated materials shall be placed in appropriate bags and containers marked with the international infectious substance symbol. Radioactive and chemical waste must be discarded using methods approved by appropriate governmental agencies.

If genetically modified cellular therapy products are administered by the Clinical Program, the IBC, and potentially third-party manufacturers, will have specific procedures for waste disposal that must be followed. Investigator and staff training must include these procedures.

Evidence:

The inspector should examine how medical waste and chemicals are handled and discarded (e.g., incinerator, waste field) and compare their observations with the written protocols.

Example(s):

Contaminated materials may typically be discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, using a sanitary landfill. Sharps (e.g., needles, blades) should be considered highly hazardous healthcare waste and placed for disposal in puncture proof containers. Chemicals such as cytostatic drugs used in purging procedures shall be discarded in accordance with Applicable Law.

STANDARD:

B2.9 There shall be a written policy for personal hygiene and the use of personal protective equipment and attire.

B2.9.1 The policy shall define the protective clothing to be worn upon entering the work area and while working within it.

B2.9.2 The policy shall define personal protective equipment appropriate for the activities and classification of the environment to be worn while handling biological specimens.

B2.9.3 Such personal protective equipment shall not be worn outside the designated work area.

Explanation:

Personal protective equipment (PPE) is equipment worn to reduce exposure to hazards that could cause injury or illness in the workplace, and to protect the cellular therapy product from exposure to hazards that could cause injury or illness to the recipient. Personal hygiene, at a minimum, includes hand hygiene that is undertaken to reduce disease transmission.

Clinical Programs must follow their institutional policies regarding appropriate PPE (e.g., gowns, goggles, plastic aprons, gloves) that must be worn when handling potentially hazardous substances. To prevent the spread of hazardous substances, PPE must be removed before leaving the workspace.

Evidence:

One way to demonstrate compliance with hygiene is for the program to have a policy on handwashing.

STANDARD:

B2.10 There shall be adequate equipment and materials for the procedures performed.

Explanation:

The amount of relevant equipment in the Clinical Program should be proportionate to the volume of work done and should be conveniently located. The program should have policies and SOPs that address interruption in administration due to equipment failure, such as for the handling and storage of cellular therapy products.

Evidence:

The inspector will evaluate whether there is adequate equipment available in the Clinical Program, if the equipment is being used appropriately, and if there is a back-up plan in the event of equipment failure.

Example(s):

Examples of equipment include intravenous pumps, water baths, and heart monitors. Each institution should identify equipment that the Clinical Program uses related to cellular therapy.

STANDARD:

B2.11 There shall be access to an intensive care unit or emergency services.

Explanation:

The Clinical Program must have documentation that there is ready access to an ICU or equivalent coverage in an immediate fashion for its patients when appropriate. This requires the ability to provide multisystem support, including assisted respiration. Ordinarily, this would be within the institution; however, contractual arrangements with another institution may be considered if transfer SOPs are in place to ensure prompt service and patient safety.

Outpatient facilities must document a plan for immediate transfer to an ICU, emergency department (ED), or inpatient unit if clinically warranted. The outpatient plan for providing inpatient care, if needed, should be discussed with the patient regardless of the type of outpatient setting (e.g., home, day unit, hotel). The outpatient plan should address the specific needs of recipients, such as the need for isolation protocols for immunocompromised patients, transfer to transplant-designated units related to clinical indications, and transplant-specific discharge plans.

Clinical Programs administering IECs should communicate with their ICUs, EDs, or equivalents regarding the transfer and care of patients with immune effector cell-associated neurotoxicity syndrome (ICANS) so that they are prepared to provide the appropriate care.

Example(s):

This requirement may be achieved through an ICU within the institution, multisystem support capabilities within the inpatient program's unit, or through a well-documented arrangement with a neighboring institution's ICU that meets the Standards and with which the inpatient program has a good working relationship.

For example, a combined adult and pediatric Clinical Program may have an ICU within its institution; however, it may not have personnel trained in pediatrics. It may be more beneficial for a pediatric patient to be transferred to a pediatric hospital's ICU. This is acceptable if the transfer is timely and there is a written agreement defining the responsibilities of each party.

The ED may be acceptable when other outpatient facilities are unavailable, if the physical space and physician coverage are adequate to ensure that the cellular therapy recipient is evaluated promptly and not exposed to risk of infectious disease transmission, including respiratory pathogens. For example, a busy trauma center may be inadequate to provide these safeguards.

STANDARD:

B2.11.1 There shall be written guidelines for communication, patient monitoring, and prompt triage or transfer of patients to an intensive care unit, emergency department, or equivalent when appropriate.

Explanation:

Clinical Programs must have written guidelines for the transfer of patients to an ICU or equivalent coverage. The purpose of this Standard is to facilitate clear communication between the program and any other departments and health care professionals, and the prompt transfer and ongoing monitoring of appropriate patients. It is not the intent to dictate which patients require transfer, to set criteria for patient transfer, nor to define the amount of intensive care that can or should be provided on a transplant unit. Facility guidelines may allow flexibility depending on recipient characteristics. There should be quality parameters regarding the transfer, such as how quickly the recipient is transferred.

Evidence:

The ICU should be part of the tour if it is on the same site(s) as the clinical unit(s). The SOP for transfer of patients to the ICU must be available. An interview may be requested with a representative from the ICU team, to include discussion about specific needs of hematopoietic stem cell transplant patients and how these needs are met in the unit. Similar actions should be taken for the ER when appropriate.

Example(s):

Depending on the recipient's status, acute needs may arise while on an inpatient unit, at an outpatient clinic, or after discharge. The ICU and emergency teams need to be aware of the types of patients served at the Clinical Program and how to adequately care for them. Examples include protecting immunocompromised patients from infection and quickly treating central nervous system disease or cytokine release syndrome (CRS).

STANDARD:

B2.12 There shall be a pharmacy providing 24-hour availability of medications needed for the care of cellular therapy patients.

B2.12.1 The pharmacy shall have prompt access to medications adequate to treat expected complications of cellular therapy, including cytokine release syndrome (CRS), for each recipient of a cellular therapy product.

Explanation:

Cellular therapy recipients often require a highly specialized set of medications that may require special authorization or may not be routinely available. In addition to having medications available, there must always be a pharmacist, trained to care for cellular therapy patients as described in [B3.7](#), available on-site or on-call. The pharmacy must have mechanisms to prevent dosing errors.

The intent of this Standard is to have appropriate medications, including those required by regulatory agencies, for the specific product. The Standard does not exclusively apply to tocilizumab, nor is it about the storage of the cellular therapy product. The FACT-JACIE Standards do not cover pharmacy's storage, receipt, and distribution of cellular therapy products.

Example(s):

Institutional limitations on select medications, such as expensive drugs, may need consideration. Some medications may need to be dispensed immediately. Tocilizumab is commonly needed to treat CRS. Clinical Programs may need to consult with their pharmacies to develop a plan for accessing this drug on a 24-hour basis and ultimately having on-site, immediate access. One method is to keep a minimum number of doses on the clinical unit.

STANDARD:

B2.13 There shall be access to renal support, such as dialysis, under the direction of nephrologists and trained personnel.

Evidence:

The Clinical Program must provide documentation that renal support services such as dialysis are readily available to recipients.

Example(s):

The need for dialysis may be fulfilled by provision of dialysis under the direction of nephrologists and trained staff on the transplant unit, in an ICU, or in an outpatient setting as appropriate. Services including hemodialysis and Continuous Renal Replacement Therapy (CRRT) may be provided through a dialysis unit within the institution or through a written agreement with an outside vendor.

The Standard requires access to consulting specialists or support services, which entails not only having an established relationship with a provider or service but also utilizing them when appropriate. For additional information regarding consulting specialists and support services that must be accessible to the Clinical Program, please see [B3.8](#) and [B3.11](#).

STANDARD:

B2.14 There shall be 24-hour availability of Cytomegalovirus (CMV)-appropriate and irradiated blood products or equivalent needed for the care of cellular therapy recipients.

Explanation:

This Standard is applicable to autologous and allogeneic recipients and requires availability of CMV-appropriate and irradiated blood products but does not dictate clinical practice. Clinical Programs are responsible for defining the type of blood products required for each recipient.

Those blood components appropriate for CMV-negative recipients must be defined by the Clinical Program in one or more SOPs. There must be a procedure in place for procurement of irradiated blood products or equivalent as needed.

It is acknowledged that there may be technologies believed to be equivalent to irradiation (e.g., pathogen reduction), but there are limitations as these technologies may not be available for red blood cells (RBCs). In this case, RBCs must still be irradiated.

Example(s):

If leukocyte-reduction is used to meet this Standard and is performed at a transfusion service (e.g., blood bank), there must be a validated method in place to adequately and consistently reduce the leukocytes in the blood components. Most transfusion services procure pre-stored leukocyte-reduced blood products from their blood supplier(s).

STANDARD:

B2.15 There shall be attending physician oversight if general medical physicians, physicians-in-training, or advanced practice providers/professionals (APPs) provide care to cellular therapy patients. The scope of responsibility of general medical physicians, physicians-in-training, or APPs shall be defined.

Explanation:

There must always be an attending physician available to evaluate and treat cellular therapy recipients, whether available on site or on call. This Standard applies to hematologists, oncologists, hospitalists, general internists, physicians in other specialties, physician assistants, nurse practitioners, or other advanced practice providers (APPs). It is acceptable to allow general practitioners to provide patient care during specified hours; however, the attending physician is ultimately responsible for oversight of recipients' care. There must be criteria for distinguishing when evaluation and treatment by an attending physician is required. There are patient care issues unique to cellular therapy that must be addressed by a physician with specific training for these events. Clinicians providing coverage must have a clear understanding of when the attending physician must be notified and how to reach that physician.

The amount and type of oversight are dependent on the experience and level of training of the physicians-in-training. The level of care provided by physicians-in-training should be within their competence.

Medical students require oversight, and this responsibility falls on their medical education program. If medical students are involved in the delivery of care, this should be defined and overseen by a licensed physician.

Evidence:

There must be guidelines that describe inpatient, outpatient and after-hours care, including when and under what conditions the attending physician must be contacted by general medicine physicians. The scope of responsibilities of general medicine physicians, physicians in training, and APPs to the cellular therapy program must be defined in policies and SOPs, position descriptions, or similar documents.

STANDARD:

B2.16 Clinical Programs administering cellular therapies shall use laboratories that are accredited, registered, certified, or licensed in accordance with Applicable Law.

Explanation:

This Standard is intentionally broad because these are international Standards. The labs utilized by the Clinical Program must be accredited, registered, certified, or licensed in accordance with Applicable Law for its jurisdiction.

STANDARD:

B2.17 Clinical Programs performing allogeneic transplantation or cellular therapy shall use human leukocyte antigen (HLA) testing laboratories that are appropriately accredited by the American Society for Histocompatibility and Immunogenetics, European Federation for Immunogenetics, College of American Pathologists, or other accrediting organizations providing histocompatibility services appropriate for hematopoietic cellular therapy transplant patients.

B2.17.1 HLA testing labs shall be capable of carrying out DNA-based intermediate and high-resolution HLA typing and screening for anti-HLA antibodies.

Explanation:

If applicable to the scope of service, Clinical Programs need to use labs accredited by ASHI, EFI, College of American Pathologists (CAP), or other accrediting organizations that provide histocompatibility services appropriate for the types of cellular therapy patients treated. If a Clinical Program wishes to use a histocompatibility laboratory with accreditation other than ASHI, EFI, or CAP, that Clinical Program must ensure the alternative accreditation has been determined to be acceptable.

Evidence:

A copy of the current (in-date) certificate of ASHI, EFI, CAP, or other accrediting organization must be submitted, including at least the competencies listed above.

Example(s):

If the HLA testing laboratory is ASHI accredited for the appropriate technologies and methods, the Clinical Program must have sufficient expertise to select the best matched donor for the recipient.

STANDARD:

B2.18 Testing to monitor chimerism shall be performed in laboratories accredited for the techniques used.

B2.18.1 Lineage-specific chimerism should be performed.

Explanation:

Monitoring of chimerism after allogeneic transplant is valuable in terms of determining the quality of engraftment of donor cells and the risk of relapse and GVHD. Results of chimerism testing are an important consideration in clinical decision-making regarding withdrawal of immunosuppression, administration of post-transplant donor lymphocyte therapies, or the option of additional therapy.

There are a variety of methodologies available for monitoring chimerism after allogeneic transplant; however, increasingly most centers monitor use of short tandem repeat polymorphisms. Other DNA polymorphisms, including single nucleotide, a variable number of tandem repeats, or insertion/deletion polymorphisms, may also be used. Older techniques such as sex mismatch fluorescence in situ hybridization (FISH) or blood group markers are used infrequently and lack sensitivity and generalizability. Sensitivity of peripheral blood assays is improved if lineage specific chimerism is evaluated, most frequently with T-cell chimerism along with whole blood or myeloid chimerism. B-cell or natural killer (NK) cell chimerism monitoring is less common.

Clinical teams should define a protocol that includes the schedule of monitoring, sample type (peripheral blood or bone marrow), and lineages to be monitored. Expertise is expected within the Clinical Program to understand the tests, test limitations, and interpretation of test results. The focus of the Standard is on laboratory qualifications, not the patient or test itself. These need to be defined by the program. The Standard does not prohibit sending specimens to outside laboratories nor specify a prescribed turnaround time.

Evidence:

Laboratories doing tests for chimerism will have documentation of their accreditation for the tests performed. A copy of the current (in-date) external accreditation for high-complexity testing should be available at the on-site inspection. Inspectors should also review policies or SOPs that guide clinical interpretations of engraftment monitoring test data.

Example(s):

ASHI, EFI, CAP, and other organizations provide external laboratory accreditation and quality assurance proficiency testing in recipient/donor chimerism specifically. Laboratories are not required to be specifically accredited for chimerism testing, but they must be accredited for the

techniques they use to determine chimerism and must participate in an external proficiency testing program for the technique.

B3: PERSONNEL

STANDARD:

B3.1 CLINICAL PROGRAM DIRECTOR

B3.1.1 The Clinical Program Director shall be a physician appropriately licensed to practice medicine in the jurisdiction in which the Clinical Program is located and shall have achieved certification in one (1) or more of the following specialties: Hematology, Medical Oncology, Immunology, Pediatric Hematology/Oncology. For immune effector cell (IEC) programs, specialty certification is required in the applicable disease area. A physician trained prior to requirements for specialty training may serve as the Clinical Program Director if they have documented experience in the field of hematopoietic progenitor cell (HPC) transplantation extending over ten (10) years.

Explanation:

The Clinical Program Director must be licensed or registered according to Applicable Law to practice medicine in the state, province, or country in which the Clinical Program is located.

The Clinical Program Director must have been specialist-certified in one or more of the specialties listed. Where physicians have received training outside the EU or North America, the FACT or JACIE Accreditation Committee or Board of Directors will assess their documentation of training to determine equivalency. Specialty certification may have been obtained from jurisdictions other than where the Clinical Program Director practices.

Maintenance of specialty and sub-specialty certification requires time, effort, and financial resources, and the value of maintaining certification has become controversial. Two articles published by the *New England Journal of Medicine*, [Maintenance of Certification 2.0 — Strong Start, Continued Evolution](#) (Irons, Nora. 2015;372(2):104-106) and [Boarded to Death — Why Maintenance of Certification Is Bad for Doctors and Patients](#) (Teirstein. 2015;372(2):106-108), offer commentary on this issue. It is recognized that board certification exam questions in hematology/oncology may not extensively cover or be relevant to cellular therapy and HPC transplantation. Maintenance of specialty certification is recommended; however, it is not required for the Program Director or for attending physicians. There may be circumstances under which expiration of board certification or specialist registration can be allowed, if permitted by Applicable Law. For example, if a significant portion of a Clinical Program Director's duties include the direct care of cellular therapy patients,

they will have the experience to maintain and continuously update the knowledge and skills required.

Those physicians who completed their medical training prior to the availability of specific training in transplantation may qualify as Clinical Program Directors if they have at least ten years of documented experience in transplantation. This includes immunologists who were involved in the advent of HPC transplantation or had specific training in transplantation.

Only one Clinical Program Director is required by this Standard. The Clinical Program may have additional directors operationally, but one Program Director must be designated to serve as the point of contact for communication with FACT or JACIE as needed.

Evidence:

FACT no longer requires clinical programs to submit medical licenses for staff (physicians, APPs, pharmacists, nurses) if the program is accredited by a recognized U.S. accrediting body. The Joint Commission, HFAP, DNV Healthcare, and CMS ensure appropriate licensure in their accreditation processes. U.S.-based hospital transplant programs accredited by any of these entities are not required to submit clinical personnel medical licenses.

Required documentation for specialty certification is a photocopy of the certificate from the relevant certifying authority or board, or equivalent documentation from countries outside of the U.S. and EU.

Individuals who believe that they have equivalent training and experience, but who have specialty certification or registration in other subspecialty areas not listed in this Standard, must submit their qualifications for consideration by the appropriate Accreditation Committee or Board of Directors.

A physician who completed training prior to the availability of specific training in transplantation must document a minimum of 10 years of HPC transplant experience, including the size and complexity of the program(s) in which they have worked (e.g., autologous transplant only, autologous and allogeneic, unrelated donors, allogeneic transplant using T-cell depletion) and the approximate number of transplant patients the individual has managed. Documentation must include one or more letters from the supervisor or professional colleague of the applicant and may also include representative publications from the transplant literature demonstrating the applicant's contributions to the field. These contributions should extend over the entire 10-year timeframe. Both a curriculum vitae (CV) and photocopies of representative publications must be submitted.

Example(s):

Specialty certification in the U.S. means sub-specialty certification by the American Board of Medical Specialties. The equivalent EU requirements include specialist registration or completion of the higher specialist training (Certificate of Completion of Training [CCT] or Certificate of Completion of Specialist Training [CCST]) in one of the specialties listed in B3.1.1. The [General Medical Council](#) provides information on specialist training in the UK.

For programs seeking FACT accreditation, physicians who received all or part of their medical or specialty training outside of the U.S. must submit documentation of their training, experience, and a photocopy of any registration or certification in a relevant specialty. The FACT Accreditation Committee or the Board of Directors will assess this documentation to determine if it is “equivalent” to U.S. board certification.

STANDARD:

B3.1.1.1 The Clinical Program Director shall have a minimum of two (2) years of experience as an attending physician responsible for the direct clinical management of HPC transplant and cellular therapy patients throughout the continuum of care.

Explanation:

In addition to having achieved specialty certification, the Clinical Program Director must have two (2) years of experience providing direct patient care in HPC transplantation or cellular therapy. Clinical fellowship training often includes a significant portion of time in laboratory or basic research. Only the specific amount of time dedicated to direct management of transplant recipients can be counted towards the required two (2) years of clinical experience.

Evidence:

Written confirmation of experience in patient management can be a letter from the directors of the programs, departments, or institutions where this experience was obtained. The letter must include at least the following information: an estimate of the actual number of weeks committed to this experience; an estimate of the number of patients the applicant has managed; whether patient management included both inpatient and outpatient care; whether the experience was exclusively in autologous or allogeneic transplantation, cellular therapy, or both; and if both, an estimate of the proportion of patients in each category. If it is not possible to obtain letters from the directors where initial experience was gained, letters from directors at subsequent places of experience are acceptable.

STANDARD:

B3.1.2 The Clinical Program Director shall be responsible for administrative and clinical operations, including compliance with these Standards and Applicable Law.

B3.1.3 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 recipients and donors, and cell collection and processing, whether internal or contracted services.

Explanation:

The Clinical Program Director may delegate some of the duties associated with the operation of the Clinical Program to other qualified individuals. Individual physicians may accept recipients or donors for entry into the Clinical Program according to institutional policies or SOPs. It is the responsibility of the Clinical Program Director to ensure such policies exist and are followed.

“Design” in this Standard refers to the current structure of the Clinical Program. The Clinical Program Director is responsible for ensuring the program is designed in a manner that meets all FACT-JACIE Standards.

When a director works remotely, the Clinical Program must clearly outline how the responsibilities of the position are performed. Responsibilities for remote directors do not differ from the responsibilities of an in-person director; however, there may be more challenges in the completion and documentation of these responsibilities. The following are requirements for remote directors:

- A director must be fluent in the language of the program and must meet the minimum credentials, training, experience, competency, and continuing education requirements as defined in the current edition of Standards.
- A director is responsible for leading the program and for providing oversight of its services, personnel, cellular therapy products, and procedures.
- A director is expected to be actively engaged in the decision-making process, policy and procedure development, and QM activities, including management of adverse events. This involvement must be documented.
- When a director is physically not present at the facility site, there must be a qualified designee named and documented to manage those responsibilities that require immediate or in-person attention. Further, all critical director functions must be covered.
- A qualified designee must meet minimum director qualifications for the delegated function and have a defined scope of authority and activity.
- Specific responsibilities of each director and medical director type are defined in the Standards. Documentation of director involvement in these responsibilities must be available on-site for review.

Evidence:

Documented evidence of a director’s specific involvement in leadership, oversight of the Clinical Program (whether on-site or remote), and performance of designated responsibilities must be available on-site for review by the inspector. Examples of documentation include, but are not limited to:

- Meeting minutes.
- Record review.
- Personnel review.
- SOP review and approval.

- Donor or recipient management.
- Investigative report review.
- Qualification/validation studies: plan and final report review and approval.
- Planned deviation pre-approval.

Example(s):

A Clinical Program Director who oversees clinical, collection, and cell processing functions may assume some of these duties. Similarly, a Quality Manager may facilitate the execution of a process improvement program. Because cell collection and processing services play a major role in patient outcomes, the Clinical Program Director must monitor whether these services meet the Standards and contractual requirements (see [B4](#)). The final responsibility for all delegated duties remains with the Clinical Program Director.

STANDARD:

B3.1.4 The Clinical Program Director shall have oversight of the medical care provided by all members of the Clinical Program.

B3.1.4.1 The Clinical Program Director shall be responsible for verifying competency of members of the Clinical Program annually.

Explanation:

This Standard is not meant to imply that the Clinical Program Director is directly responsible for the medical activity of another physician, APP, or other member of the program. The Clinical Program Director is responsible for reviewing their knowledge and skills by verifying competency. Provisions should be made for verification of knowledge and skills of new staff within the first year of employment, including a plan to evaluate competence.

Staff training may occur through the appropriate specialty pathway, but the Clinical Program Director shall have verified through documented review of records that every member who is part of the Clinical Program is trained and competent. The level of verification may differ depending on the staff member's role in the program (e.g., a physician versus a pharmacist or nurse).

Evidence:

Program Directors may utilize direct clinical observation, physician's evaluations, presentations at interdisciplinary patient care meetings, observation of formal lectures delivered, and chart reviews to document competency.

The inspector should review the organizational chart to determine which positions are included as part of the Clinical Program and how appropriate training and competency are documented.

Example(s):

The annual verification of competency does not need to include all knowledge and skills required for members of the Clinical Program. A rotational schedule could be used. For example, a program could create a competency verification schedule that results in all knowledge and skills being verified within an accreditation cycle.

STANDARD:

B3.1.5 The Clinical Program Director shall participate in a minimum of ten (10) hours of educational activities related to HPC transplantation and other cellular therapies annually.

Explanation:

The field of cellular therapy continues to evolve rapidly. Clinical Program Directors must participate regularly in educational activities related to cellular therapy, including areas of service routinely provided and other areas to broaden the scope of knowledge and keep up with current advancements in the field. This may include topics specific to cellular therapy or diseases in which cellular therapy is a therapeutic option.

Treatment for toxicities related to cellular therapy continues to evolve as experience is gained and new cellular therapy products are introduced. Professional societies and product manufacturers are resources for continuing education regarding toxicities.

Evidence:

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not a Clinical Program Director meets this Standard. Recognized educational activities include both certified continuing medical education (CME) credits (preferable) and non-credit educational hours, including internal presentations and conferences.

To assess the appropriateness of the amount and type of continuing education, Clinical Programs must submit the following information for each of the completed continuing education activities within each accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, grand rounds).
- Topic of activity demonstrating relevance to cell therapy (e.g., hematology, cell transplantation).
- Date of activity.
- Approximate number of hours of activity.

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Use of a formalized continuing professional development (CPD) record such as the FACT [Educational Activities Form](#) or equivalent is recommended. Use of this form is not required, but it can be used to document compliance with continuing education requirements.

Example(s):

Evidence of compliance may include either formal or informal study. Educational activities do not necessarily require large financial resources. The Clinical Program may choose to establish its own guidelines for the number of hours from each type of activity that can be counted toward the minimum requirement in this Standard.

Examples of appropriate continuing education activities include:

- The annual meetings of several professional societies include information directly related to the field.
- Grand Rounds, if specifically related to cellular therapy or diseases for which cellular therapy is a therapeutic option. The continuing education log must include the title, subject, and date of the presentation.
- Presentation of CME/CPD lectures.
- Presentation of a paper at a scientific meeting, such as abstracts and oral presentations.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or online tutorial.
- Review of articles in the medical literature related to cellular therapy, including those where the journal offers CME credits.
- Local or regional journal club, potentially including the preparation time.
- Morbidity and Mortality conferences.

American Society for Transplantation and Cellular Therapy (ASTCT) also offers an online [Learning Center](#) that hosts recordings from its many educational events. Additional educational opportunities are provided by the European School of Haematology (ESH) and the European Society for Blood and Marrow Transplantation (EBMT) through their respective e-learning programs ([ESH](#) and [EBMT](#)).

STANDARD:**B3.2 ATTENDING PHYSICIANS**

- B3.2.1 Attending physicians shall be appropriately licensed to practice medicine in the jurisdiction of the Clinical Program.*
 - B3.2.1.1 Attending physicians for transplantation shall be certified or trained in one (1) of the following specialties: Hematology, Medical Oncology, Immunology, or Pediatric Hematology/Oncology.*
 - B3.2.1.2 Attending physicians for non-transplant cellular therapies shall be certified or trained in the therapeutic disease area and experienced in cellular therapy.*
- B3.2.2 Clinical Programs performing adult transplantation shall have at least one (1) attending physician who has achieved specialty certification in Hematology, Medical Oncology, or Immunology.*
- B3.2.3 Clinical Programs performing pediatric transplantation shall have at least one (1) attending physician who has achieved specialty certification in Pediatric Hematology/Oncology or Pediatric Immunology.*

Explanation:

This Standard is applicable to clinical attending physicians other than the Program Director and is parallel to the requirements for the Clinical Program Director. However, it requires just one attending physician per patient population (adult and pediatric) to be specialty-trained, rather than requiring specialty certification for all attending physicians. Specialty-trained implies that the attending physician has completed the formal training and all other requirements to be eligible to take examinations required for certification.

Evidence:

FACT no longer requires clinical programs to submit medical licenses for staff (physicians, APPs, pharmacists) if the program is accredited by a recognized U.S. accrediting body. The Joint Commission, HFAP, DNV Healthcare, and CMS ensure appropriate licensure in their accreditation processes. U.S.-based hospital transplant programs accredited by any of these entities are not required to submit clinical personnel medical licenses.

For sub-specialty board certification, eligibility, or equivalent, a copy of the current certificate or documentation of completion of the requisite fellowship and primary board certification in Internal Medicine or Pediatrics is required.

Example(s):

Specialty certification in the U.S. means sub-specialty certification by the American Board of Medical Specialties. The equivalent EU requirements include specialist registration or completion of the higher specialist training (CCT or CCST) in one of the specialties listed in [B3.2.1.1](#). The [General Medical Council](#) provides information on specialist training in the UK.

In the U.S., specialist-trained includes physicians who are eligible to complete specialist board examinations. In the EU, this includes consultant or senior physicians who have completed higher specialist training but are not on the higher specialist register. Specialty certification can be obtained in a jurisdiction other than where the physicians practice.

For FACT accreditation purposes, physicians will be considered to be specialist-trained if they have completed 1) all of the formal training required by the particular board; and 2) all other necessary requirements to be permitted to take the certification examination of that board the next time it is offered.

Physicians who completed their medical training prior to the availability of specific training in transplantation may be qualified if they have at least ten years of documented experience in transplantation.

STANDARD:

B3.2.4 Clinical Programs performing pediatric transplantation shall have a transplant team trained in the management of pediatric recipients.

Explanation:

Teams treating children must include at least one attending physician who has achieved specialty certification in Pediatric Hematology/Oncology or Pediatric Immunology. Pediatric expertise and experience are also required among the nursing, pharmacy, and social services staff.

Example(s):

Evidence of compliance with these Standards may include age-specific competencies and proficiencies, attendance at age-specific continuing educational activities, or age-specific preceptorships.

STANDARD:

B3.2.5 Attending physicians shall participate in a minimum of ten (10) hours of educational activities related to HPC transplantation and other cellular therapies annually.

Explanation:

The field of cellular therapy continues to evolve rapidly. Clinical attending physicians must participate regularly in educational activities related to cellular therapy, including areas of service routinely provided and other areas to broaden their scope of knowledge and keep up with current advancements in the field. This may include topics specific to cellular therapy or diseases in which cellular therapy is a therapeutic option. The Clinical Program Director should evaluate the continuing education obtained by attending physicians periodically, for example, as part of the annual performance review required in [B4](#).

Treatment for toxicities related to cellular therapy continues to evolve as experience is gained and new cellular therapy products are introduced. Professional societies and product manufacturers are resources for continuing education regarding toxicities.

Examples of acceptable forms of education are referenced in this Accreditation Manual.

Evidence:

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not each attending physician meets this Standard. Recognized educational activities include both certified CME credits (preferable) and non-credit educational hours, including internal presentations and conferences.

For additional Evidence and Examples related to continuing education, see the guidance following [B3.1.5](#).

STANDARD:

B3.3 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

B3.3.1 Each attending physician shall have had a minimum of one (1) year of supervised training in the management of HPC transplant and IEC therapy patients throughout the continuum of care.

B3.3.2 Clinical training and competence shall include the management of autologous and allogeneic HPC transplant recipients and patients receiving IEC or other cellular therapies, as applicable to their scope of practice.

Explanation:

Clinical Program Directors and attending physicians must have written confirmation of their training or experience and documentation of competency. The minimum of one year of supervised training is a cumulative requirement; the Standard does not require a year of continuous training. Training and experience must be in the area of care provided.

Evidence:

Specialty certification is fulfillment of the training requirement. Other documentation could include a letter from each of the directors of the programs, departments, or institutions where this training or experience was obtained. The letter must include at least the following information: an estimate of the number of patients the physician has managed, whether patient management included both inpatient and outpatient care, whether the training or experience was exclusively in an autologous or allogeneic setting or both, and an estimate of the actual number of weeks committed to this training or experience. If appropriate, the letter could also document initial competency or knowledge (as required) in each of the subjects and procedural skills listed in [B3.3.4](#) and, as applicable, [B3.3.5](#).

STANDARD:

B3.3.3 Clinical Program Directors and attending physicians shall each be assessed for competency on an annual basis.

Explanation:

Competency in each of the areas must be documented for each attending physician (in the U.S.) or for each consultant or senior physician (in Europe) by the Clinical Program Director. It is the responsibility of the Clinical Program to define how competency will be assessed. Some competency evaluations must be documented annually. Clinical Programs do not have to assess competencies for all items listed in [B3.3.4](#) and, as applicable, [B3.3.5](#) each year; however, each area should be addressed at least once during each accreditation cycle.

Evidence:

Clinical Program Directors and attending physicians will have documented specific training and competency evaluations submitted as part of the accreditation application. Documentation of competency can be in the form of a letter, checklist, description of the number of times the physician has handled a particular situation, self-assessment, preparation of SOPs, teaching sessions, presentations, number of cases, or discussion(s) with the Clinical Program Director. If the physician has published any articles relating to an area of competency, a copy of the publication will serve as documentation.

Evidence of competency may be verified prior to the inspection by review of documents and will also be assessed on site by process review, interviews, and observation.

Example(s):

Clinical Programs may divide the required competencies into thirds (or fourths) and perform competency evaluations on a portion each year of the accreditation cycle. This would allow some competency assessment each year and assessment for all Standards within each accreditation cycle.

STANDARD:

B3.3.4 Clinical Program Directors and attending physicians shall have received specific training in each of the following areas as applicable to the Clinical Program's services:

Explanation:

The following list of specific training areas is meant to go above and beyond basic medical competencies. Complications that can occur in a variety of clinical situations are not included.

Example(s):

The British Society of Blood and Marrow Transplantation and Cellular Therapy has training guidelines and curriculum available at <https://bsbmtct.org/e-learning/>. Additional educational opportunities are provided by ESH and EBMT through their respective e-learning programs ([ESH](#) and [EBMT](#)).

STANDARD:

B3.3.4.1 Indications for allogeneic and autologous HPC transplantation.

Explanation:

Clinical Program Directors and attending physicians who perform only autologous transplants must be competent to recognize when an allogeneic transplant is indicated.

STANDARD:

B3.3.4.2 Indications for IEC therapies.

B3.3.4.3 Selection of suitable recipients and appropriate preparative regimens, including lymphodepletion regimens.

Example(s):

An example of a preparative regimen can include lymphodepletion regimens.

STANDARD:

B3.3.4.4 Donor selection, evaluation, and management.

Explanation:

Donor selection, evaluation, and management may be the responsibility of one or more than one clinical team. If responsibilities are divided, documented communication between teams is required. Donor evaluation and management also includes autologous donors.

STANDARD:

B3.3.4.5 Donor and recipient informed consent.

B3.3.4.6 Selection and administration of preparative regimens.

B3.3.4.7 Selection and administration of growth factors or other agents for HPC mobilization and for post-transplant hematopoietic cell reconstitution.

Explanation:

Appropriate mobilization agents should be chosen for the disease being treated and for the donor being collected.

Example(s):

Filgrastim should not be used for mobilizing patients with sickle cell disease.

STANDARD:

B3.3.4.8 Administration of cellular therapy products, including HPC, IEC, genetically modified cells, and other cellular therapies.

B3.3.4.9 Management of complications related to the administration of cellular therapy products.

Explanation:

Management includes the initial and ongoing diagnostic efforts, therapeutic interventions, and appropriate monitoring.

It is difficult to anticipate adverse events caused by novel cellular therapies, but Clinical Programs must make an effort to learn about theoretical risks and experiences of providers. Programs should encourage ongoing training related to novel and existing therapies.

Example(s):

Examples include the recognition and management of adverse events including, but not limited to, CRS, neurological toxicities, immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS), and the appropriate medications.

STANDARD:

B3.3.4.10 Administration and management of immunomodulatory agents.

Explanation:

The management of immunomodulatory agents is unique from managing patients using immunosuppressive drugs.

STANDARD:

B3.3.4.11 Management of neutropenic fever.

B3.3.4.12 Management of pulmonary complications.

B3.3.4.13 Management of sinusoidal obstruction syndrome and other causes of hepatic dysfunction.

B3.3.4.14 Management of thrombocytopenia and bleeding.

Explanation:

Management of thrombocytopenia and bleeding would include the recognition of disseminated intravascular coagulation (DIC).

Example(s):

Diagnosis of thrombocytopenia should include thrombocytopenia associated with chemotherapy, disseminated intravascular coagulation, thrombotic microangiopathy and other causes.

STANDARD:

B3.3.4.15 Management of hemorrhagic cystitis.

B3.3.4.16 Management of blood transfusion, including the use of CMV-appropriate and irradiated (or equivalent) blood products.

Explanation:

Attending physicians must be trained on the Clinical Program's institutional policies for blood transfusion. They also need to understand when blood transfusion is indicated and how to manage patients with transfusion-related acute lung injury and transfusion-associated circulatory overload.

Donors may require a blood transfusion during the apheresis collection procedure. Cellular therapy programs, especially their apheresis collection facilities, need to be prepared to provide appropriate blood products. Autologous units may be collected prior to apheresis, or allogeneic CMV-appropriate and irradiated units may be used. Many places have difficulty collecting autologous blood from donors <40 kg. The decision to use autologous or allogeneic blood depends on the benefits and risks to the donors, especially in the case of pediatric donors.

A special concern for allogeneic donors is the fact that transfused allogeneic blood contains lymphocytes that can become part of the collected cellular therapy product. Since under most circumstances the need for blood products occurs during collection, these transfusions must undergo irradiation (or equivalent technology such as pathogen reduction) to prevent engraftment of third-party lymphocytes in the transplant recipient. Because of the occasional need for a second cellular therapy product collection, it is advisable to continue irradiating blood transfused to the donor in the immediate post-collection period (Cancelas, Bandarenko, eds. [*Cellular Therapy: A Handbook*. 2nd ed.](#) AABB. 2023).

It is expected that normal-sized, adult marrow donors would donate autologous blood and therefore not require allogeneic blood. However, in the situation of small-sized marrow donors and large-sized recipients, transfusion is expected. An example of this would be a 25 kg donor and an adult-sized recipient (common in sibling transplants). In this case, transfusion is expected, frequently occurs during the collection, and the blood products must be irradiated or equivalent. Additional information can be found in Chapter 14 “Transfusion Therapy in Hematopoietic Stem Cell Transplantation” (Marques, Schwartz, Wu, eds. [*Transfusion Therapy: Clinical Principles and Practice*. 5th ed.](#) AABB. 2025).

STANDARD:

B3.3.4.17 Management of mucositis.

B3.3.4.18 Management of gastrointestinal complications.

Explanation:

Nausea and vomiting are among the gastrointestinal complications that must be addressed in policies and SOPs.

STANDARD:

B3.3.4.19 Management of pain.

B3.3.4.20 Management of CRS.

Explanation:

CRS, although commonly associated with IEC administration, may also be seen in allogeneic transplantation such as haploidentical donors or after Anti Thymocyte Globulin (ATG) therapy.

STANDARD:

B3.3.4.21 Management of neurologic toxicity syndromes, including immune effector cell- associated neurotoxicity syndrome (ICANS).

Explanation:

With the evolution of cellular therapy products and increasing data, more neurologic toxicity syndromes are being identified. In addition to ICANS, these toxicities include complication of initial cytopenia, Parkinsonian symptoms, and other neurological symptoms (e.g., cerebellar dysfunction).

STANDARD:

B3.3.4.22 Management of immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS).

B3.3.4.23 Management of macrophage activation syndrome/hemophagocytic lymphohistiocytosis.

B3.3.4.24 Management of cardiac dysfunction.

B3.3.4.25 Management of renal dysfunction.

B3.3.4.26 Diagnosis, monitoring, and management of infectious complications.

Explanation:

Attending physicians must be trained in the management of infectious disease complications, including those from bacterial, fungal, parasitic, and viral sources.

In addition to opportunistic infections, chronic immunodeficiencies caused by other medications prescribed to the cellular therapy recipient can cause infections.

STANDARD:

B3.3.4.27 Management of HPC graft failure and prolonged cytopenia.

B3.3.4.28 Management of dermatologic complications.

B3.3.4.29 Evaluation of post-transplant and other cellular therapy outcomes.

Evidence:

It is recognized that outcomes may not be completely understood for investigational cellular therapy studies. In these cases, investigative approaches and endpoints must be defined by the investigator.

STANDARD:

B3.3.4.30 Management of tumor lysis syndrome.

B3.3.4.31 Evaluation and management of late effects of cellular therapy.

Explanation:

Late effects can be caused by the disease being treated or by the treatment itself. Different cellular therapies, such as standard of care transplantation and genetically modified cellular therapy, may have different considerations.

Example(s):

Prolonged cytopenia and secondary malignancies after receipt of genetically modified products.

STANDARD:

B3.3.4.32 Documentation and reporting for patients on investigational protocols.

B3.3.4.33 Reporting responsibilities for adverse events according to Applicable Law.

B3.3.4.34 Palliative and end of life care.

B3.3.4.35 Age-specific donor and recipient care.

Explanation:

Age-specific competencies are not limited to young people. As cellular therapy increasingly becomes an option for elderly recipients, Clinical Programs must recognize and document needed adjustments in their care.

STANDARD:

B3.3.5 Additional specific clinical training and competence required for physicians in Clinical Programs requesting accreditation for allogeneic HPC transplantation shall include:

B3.3.5.1 Identification, evaluation, and selection of HPC source, including use of donor registries.

Explanation:

Depending on patient characteristics, cells from bone marrow, peripheral blood, or umbilical cord blood may be advantageous over other options. The Clinical Program should determine general guidelines for product choices for specific recipients and potential donor sources, including registries and cord blood banks.

Example(s):

HPCs collected from marrow may be preferred for treating recipients with nonmalignant disorders.

STANDARD:

B3.3.5.2 Donor eligibility determination.

B3.3.5.3 Methodology and implications of HLA typing.

Explanation:

Knowledge regarding HLA typing is specific to allogeneic transplants.

STANDARD:

B3.3.5.4 Methodology and implications of testing for chimerism.

Explanation:

Clinical decisions regarding the pace of withdrawal of post-transplant immunosuppression or subsequent administration of donor lymphocytes based on chimerism results may have potentially life-threatening consequences with respect to GVHD, relapse risk, or graft failure. Clinicians should have an understanding of the methodologies, interpretation, and limitations of various types of chimerism testing and utilize SOPs or clinical protocols to guide clinical decisions.

Recipient and donor chimerism testing may be performed by a variety of techniques, including cellular phenotype and molecular methods. Molecular methods commonly identify and quantify genetic differences between recipient and donor by analysis of short tandem repeats or single nucleotide polymorphisms. Molecular techniques may include polymerase chain reaction, in situ hybridization, or next generation sequencing. Methods may vary in terms of accuracy and sensitivity.

Clinical teams typically define a protocol that includes the schedule of monitoring and the sample type (peripheral blood or marrow). Expertise is expected within the Clinical Program to understand the tests, the test limitations, and interpretation of test results.

STANDARD:

- B3.3.5.5 Management of patients receiving ABO-incompatible cellular therapy products.*
- B3.3.5.6 Diagnosis and management of acute and chronic Graft versus Host Disease (GVHD).*

Explanation:

Clinical Program Directors and attending physicians must have current training and documentation of competency that reflect evolution in the current understanding, classification, and management of acute and chronic GVHD. A key reference on this topic is [*NIH Chronic Graft-Versus-Host Disease Consensus Conference 2025 Update*](#) published in *Transplantation and Cellular Therapy* (Lee, Williams, Sarantopoulos, et al. 2025).

Institutional or Clinical Program protocols combined with physician education and experience will determine the program's approach to managing acute and chronic GVHD. Competency in GVHD includes competency in immunodeficiency and opportunistic infections, including CMV, BK virus, adenovirus, fungal infections, and others.

STANDARD:

- B3.3.6 The attending physicians shall be knowledgeable in the following procedures:*
 - B3.3.6.1 Cellular therapy product collection, including apheresis and bone marrow harvest.*
 - B3.3.6.2 Cellular therapy product processing, including washing and diluting.*
 - B3.3.6.3 Genetic modification of cells and impact on patient care.*
 - B3.3.6.4 Cellular therapy product cryopreservation.*
 - B3.3.6.5 Extracorporeal photopheresis (ECP) for GVHD.*

Explanation:

Every physician must be knowledgeable about the collection procedure and its risks and benefits in order to counsel recipients and donors regarding the alternative sources of stem cells, the advantages and disadvantages of each, and to make a recommendation for a specific patient.

Cell collection by apheresis and by marrow harvest and cellular therapy product processing and cryopreservation are procedures that must be familiar to every attending physician; however, it is not necessary for every physician to be specifically trained or competent to collect or process the cellular therapy product. Each physician should know, for example, the indications for and limitations of some common cell processing procedures (e.g., RBC reduction, T-cell reduction, volume reduction), reasons to cryopreserve or not to cryopreserve a cellular therapy product, some consequences of cryopreservation, and the basic principles of apheresis (although not necessarily how to prime or run the machine).

The increase in use of peripheral blood as a source of HPC has been associated with a proportional decrease in the number of marrow harvests performed. Some Clinical Programs use peripheral blood exclusively as a source of HPC. Due to the small number of marrow harvests performed in some programs, it is not necessary or practical for every physician to be specifically trained and competent to collect marrow.

ECP is a leukapheresis-based immunomodulatory therapy used in the treatment of acute and chronic GVHD (and for other non-transplant indications), involving the separation of leukocytes by apheresis followed by addition of a psoralen, usually 8-methoxypsoralen, and exposure to ultraviolet A light. For programs that have ECP programs within their institution or that have access to this therapy through agreements with another institution, it is required that the attending physicians be knowledgeable in the use of ECP.

Similarly, clinical attending physicians must be knowledgeable in cellular therapy product cryopreservation and preparation for administration to ensure they are competent to provide appropriate orders for freezing, washing, dilution, RBC reduction, and volume reduction for different types of cellular therapy products (e.g., peripheral blood stem cells [PBSCs], marrow, cord blood) in different clinical situations. Physicians should be knowledgeable in the indications for product manipulations and in the unavoidable consequences of these manipulations, including loss of nucleated cells.

To protect the safety and rights of donors, cryopreservation should not be used as a method to collect and store cellular therapy products well in advance of when they are needed or “just in case” a recipient may need them. There should be relative certainty that the product will be needed prior to ordering cryopreservation. Donor registries may forbid cryopreservation, allowing it only in extenuating circumstances such as the COVID-19 pandemic.

Example(s):

Examples of required knowledge in processing include volume reduction versus washing, or dilution. Examples of genetic modification of cells include risk of secondary malignancy, persisting presence of vectors, biosafety, and disposal.

The following publications may be used as references when establishing processes for ECP:

- Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, et al. [Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease](#). *Biol Blood Marrow Transplant*. 2011;17(1):1–17.
- Pierelli L, Perseghin P, Marchetti M, Messina C, Perotti C, Mazzoni A, et al. [Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation \(SIdEM\) and Italian Group for Bone Marrow Transplantation \(GITMO\) consensus process](#). *Transfusion*. 2013;53(10):2340–2352.
- Das-Gupta E, Dignan F, Shaw B, Raj K, Malladi R, Gennery A, et al. [Extracorporeal photopheresis for treatment of adults and children with acute GVHD: UK consensus statement and review of published literature](#). *Bone Marrow Transplant*. 2014;49:1251–1258.
- Dignan FL, Amrolia P, Clark A, Cornish J, Jackson G, Mahendra P, et al. [Diagnosis and management of chronic graft-versus-host disease](#). *Br J Haematol*. 2012;158(1):46–61.
- Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, et al. [Diagnosis and management of acute graft-versus-host disease](#). *Br J Haematol*. 2012;158(1):30–45.
- Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, et al. [Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the ninth special issue](#). *J Clin Apher*. 2023;38(2):77–278.

STANDARD:

B3.3.6.6 *Therapeutic apheresis.*

Example(s):

Examples include plasma exchange for reduction of antibodies and HLA antibodies.

STANDARD:**B3.4 PHYSICIANS-IN-TRAINING**

B3.4.1 Physicians-in-training shall be licensed to practice medicine in the jurisdiction of the Clinical Program, shall be limited to a scope of practice within the parameters of their training and license, and shall be appropriately supervised.

Explanation:

This Standard applies to Clinical Programs in which physicians-in-training, including residents, fellows, and registrars, play a role in the direct clinical care of recipients or donors.

Evidence:

Where there are national post-graduate medical education programs, recognized or accredited training programs, or training regulated by national regulations, compliance with those programs can be taken as compliance with this Standard.

In the U.S., documentation that the physician-in-training is a resident or fellow in an Accreditation Council for Graduate Medical Education (ACGME)-accredited training program will be accepted by FACT as evidence of medical licensure, appropriate attending medical staff supervision, and an appropriate curriculum. If all physicians-in-training in a Clinical Program are part of the Accreditation Council for Graduate Medical Education-accredited training program, it is sufficient for the program to submit one (1) certification of accreditation to cover all trainees. Documentation will be required for bone marrow transplant or cellular therapy training programs that are accredited by a state or other agency. Individuals with less formal training arrangements may be required to submit individual credentials. FACT may audit a training program if needed.

Example(s):

There are approved fellowships available in the U.S. for training in Oncology, Hematology, Pediatric Hematology/Oncology, and various other specialties. Fellows in these programs may be involved in the care of transplant and cellular therapy recipients; documentation of their credentials may be achieved through the submission of Accreditation Council for Graduate Medical Education certificate. Programs would be expected to provide documentation for these persons that include licensure and appropriate supervision.

STANDARD:

B3.4.2 Physicians-in-training shall receive specific training and develop competence in transplant and cellular therapy-related skills, including but not limited to those listed in [B3.3.4](#) and [B3.3.5](#).

Explanation:

Physician training programs may differ depending on the goals of the physician-in-training and the purposes of the program. Training duration (e.g., a year or month of training) and type (e.g., training

as a medical or pediatric resident, an oncology fellow versus a transplant fellow) will determine the level of cellular therapy-related knowledge and competence a physician-in-training is expected to achieve. Training should include both allogeneic and autologous transplantation and cellular therapy for all fellows.

Treatment for toxicities related to cellular therapy continues to evolve as experience is gained and new cellular therapy products are introduced. Professional societies and product manufacturers are resources for continuing education regarding toxicities.

Evidence:

Physicians-in-training should be routinely evaluated as part of their training. Each of the areas described in [B3.3.4](#) and [B3.3.5](#) should be covered in any program training HPC or cellular therapy physicians. The Clinical Program Director should review the curriculum content and the results of training evaluations periodically. Pediatric physicians-in-training must also have training in pediatrics. Documentation should reflect the progress in the course of training that the physician has reached at any given time and may be reviewed by the inspector at the on-site inspection.

Use of a formalized CPD record such as the FACT [Educational Activities Form](#) or equivalent is recommended. Use of this form is not required, but it can be used to document compliance with continuing education requirements.

Example(s):

Clinical Programs (and trainees) are encouraged to document the curriculum presented. Documentation could include:

- Duration of contact (e.g., a three-month clinic, a half day per week).
- Goal of activity (e.g., "The purpose of consult clinic is to educate the trainee as to what types of patients should be considered for cellular therapy, the timing of procedures, risks and benefits, and alternative therapies.").
- Type of patient contact (e.g., pre-therapy consult, inpatient management, post-therapy outpatient management).
- Type of treatment (e.g., autologous, allogeneic, matched related, unrelated, mismatched transplants, cord blood transplants).
- Participation in cellular therapy grand rounds, journal clubs, morbidity and mortality conferences, and orientation lectures.
- Participation in cell collections.

[The evolution of HCT self-paced learning course](#) was developed by NMDP with content approval by physicians from the ASTCT. This free, five-part self-paced learning course aims to help providers better understand the current state of the science for HCT and cell therapy by following the evolution of HCT and addressing common misconceptions. ASTCT also offers an online [Learning](#)

[Center](#) that hosts recordings from its many educational events. Additional educational opportunities are provided by ESH and EBMT through their respective e-learning programs ([ESH](#) and [EBMT](#)).

STANDARD:

B3.5 *ADVANCED PRACTICE PROVIDERS/PROFESSIONALS (APPs)*

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 license.

Evidence:

Evidence of current licensure to practice in the jurisdiction of the Clinical Program will be submitted with the accreditation application. If the APPs are a part of the cellular therapy team, a written description of the clinical responsibilities of the APP and the expected physician oversight should be available within the program. The program is not required to have APPs participate in the direct care of cellular therapy recipients.

STANDARD:

B3.5.2 APPs shall have received specific training and maintain competence in the transplant and cellular therapy-related skills that they practice, including those listed in [B3.3.4](#) and [B3.3.5](#).

Evidence:

Competency in each of the areas described in [B3.3.4](#) and [B3.3.5](#), as applicable to the procedural skills they routinely practice in their facility, must be documented for APPs by the Clinical Program Director. Pediatric APPs must have training in pediatrics as specified by [B3.3.4.35](#).

Documentation of training and competency may be provided to FACT or JACIE in a variety of formats, including a copy of reports or listings submitted to professional organizations to obtain related credentials. Competencies must be evaluated and documented according to a defined process.

Example(s):

Documentation of training and competency can be in the form of a letter, checklist, or competency evaluation. When conferences or courses attended cover the subjects required or other relevant aspects of cellular therapy, documentation of such continuing education could be used to support training and competency.

The ASTCT Advanced Practice Provider Special Interest Group has developed a website with additional resources for APPs, including a guideline for training in hematopoietic cell transplantation, available at <https://www.astct.org/Membership/Special-Interest-Groups>.

The British Society of Blood and Marrow Transplantation and Cellular Therapy has training guidelines and curriculum available at <https://bsbmtct.org/e-learning/>. Additional educational opportunities are provided by ESH and EBMT through their respective e-learning programs ([ESH](#) and [EBMT](#)).

STANDARD:

B3.5.3 APPs shall participate in a minimum of ten (10) hours of educational activities related to HPC transplantation and other cellular therapies annually.

Explanation:

The field of cellular therapy continues to evolve rapidly. APPs must participate regularly in educational activities related to cellular therapy, including areas of service routinely provided and other areas to broaden the scope of knowledge and keep up with current advancements in the field. The Clinical Program Director should evaluate the continuing education obtained by APPs. Examples of acceptable forms of education are referenced in this Accreditation Manual and may include topics specific to cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Treatment for toxicities related to cellular therapy continues to evolve as experience is gained and new cellular therapy products are introduced. Professional societies and product manufacturers are resources for continuing education regarding toxicities.

Evidence:

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not each APP meets this Standard. Recognized educational activities include both certified continuing education credits (preferable) and non-credit educational hours, including internal presentations and conferences.

For additional Evidence and Examples related to continuing education, see the guidance following [B3.1.5](#).

STANDARD:

B3.6 NURSES

B3.6.1 Nurses shall be formally trained and experienced in the management of patients receiving cellular therapy.

Explanation:

Nurses shall be trained and competent in the areas that they routinely practice. Nurses who occasionally treat transplant recipients, such as nurses in an ICU or nurses who rotate onto the inpatient unit, may not have the degree of training and experience in all aspects required for the

management of cellular therapy patients, but they must have sufficient expertise and adequate supervision to safely care for these patients. How these issues are addressed when the recipient must be treated on a unit other than the transplant or cellular therapy unit must be defined.

Example(s):

Nurses who work with cellular therapy patients have varying areas of focus. For example, ICU nurses may not be competent in infusing cells or the management of late effects. Nurses who provide inpatient care may have extensive knowledge in cellular therapy infusion but not have competency in late effects.

The Oncology Nursing Certification Corporation (ONCC) offers a certification program in blood and marrow transplantation nursing. ONCC initiated this certification in 2014 after identifying the tasks involved in blood and marrow transplantation nursing and the knowledge needed to perform those tasks competently. Certification requires passing a written examination that covers autologous and allogeneic transplant in adult and pediatric recipients. Nurses who meet eligibility requirements, including a minimum of 1,000 hours of nursing practice experience, may apply to take the examination.

Blood & Marrow Transplant Certified Nurse (BMTCN®) certification provides evidence of competency in this specialty. Additional information, eligibility, reference lists, and practice exams are available at <https://www.oncc.org/blood-marrow-transplant-certified-nurse-bmtcn>.

STANDARD:

B3.6.1.1 Nurses shall be trained in age-specific management of patients receiving cellular therapy.

B3.6.1.2 Clinical Programs treating pediatric recipients shall have nurses formally trained and experienced in the management of pediatric patients receiving cellular therapy.

B3.6.2 Nurses shall have received specific training and maintain competence in the transplant and cellular therapy-related skills that they practice, including:

Explanation:

Age-specific training is not limited to young people. Specific considerations are necessary for older patients. Specific training is required for each nurse who is involved in the care of transplant recipients and patients receiving cellular therapies. Training may be a part of the formal job orientation and/or may be provided in increments over a specified period of employment. Specific training may also be obtained through agreements with another established transplant institution. Competencies must be evaluated and documented according to a defined process. Nursing personnel must be able to recognize when rapid notification of another cellular therapy team

member is required. The Clinical Program is responsible for identifying what situations would constitute a need for rapid notification.

Treatment for toxicities related to cellular therapy continues to evolve as experience is gained and new cellular therapy products are introduced. Professional societies and product manufacturers are resources for continuing education regarding toxicities.

Example(s):

Older patients may require dosage modification and precautions to avoid the risk of falling.

STANDARD:

B3.6.2.1 Hematology/oncology patient care, including an overview of the cellular therapy process.

B3.6.2.2 Administration of preparative and lymphodepletion regimens.

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

B3.6.2.4 Administration of blood products, growth factors, cytokines, and other supportive therapies.

Explanation:

Some cellular therapy products, such as tumor infiltrating lymphocytes (TILs), require administration of cytokines (e.g., interleukin 2). These can cause toxicities, and the Clinical Program and its staff must be prepared to manage them.

STANDARD:

B3.6.2.5 Recognition of cellular therapy complications and emergencies requiring rapid notification of the cellular therapy team.

B3.6.2.6 Care interventions to manage cellular therapy complications.

B3.6.2.7 Palliative and end of life care.

Explanation:

Care interventions for cellular therapy patients include but are not limited to CRS, ICANS, IEC-HS, tumor lysis syndrome, cardiac dysfunction, respiratory distress, neurologic toxicity, macrophage activation syndrome, renal and hepatic dysfunction, disseminated intravascular coagulation, anaphylaxis, neutropenic fever, infectious and noninfectious processes, mucositis, nausea and vomiting, and pain management.

Because CRS requires rapid care and attention, nurse training on this condition should include institutional policies on accessing and administering pertinent medications (such as tocilizumab).

EBMT offers training and resources for nurses at <https://www.ebmt.org/ebmt-jacie-books/ebmt-textbook-nurses>.

STANDARD:

- B3.6.3 There shall be an adequate number of nurses experienced in the care of cellular therapy recipients.*
- B3.6.4 There shall be a nurse/recipient ratio satisfactory to manage the severity of the recipients' clinical status.*

Explanation:

The intent of this Standard is to acknowledge that nursing needs of recipients vary based upon the severity or acuity of recipients' clinical status. The clinical unit should be staffed so that if several recipients require periods of >1 nurse/patient, there will be an adequate number of trained nursing staff available. Similarly, if no recipient requires this intensity of care, fewer staff should be able to care for the recipients. Thus, there is no specific number or ratio sought, unless required in accordance with Applicable Law (e.g., California state statute). Sufficient flexibility shall exist within the pool of trained staff to meet intensive recipient needs when they occur.

Evidence:

The inspector may ask to meet with senior nursing staff or the Clinical Program Director to assess how the nurse staffing issues are handled. To determine that the nurse staffing is adequate, inspectors may interview nursing staff, review documentation of flexible staffing, or review overtime records that may indicate a shortage of trained staff.

Example(s):

Nurse staffing laws enacted in the U.S. are referenced by the American Nurses Association at <https://www.nursingworld.org/practice-policy/nurse-staffing>.

The National Database of Nursing Quality Indicators (NDNQI), maintained by Press Ganey, is a comprehensive, nationwide repository of nursing-sensitive quality measures. It provides hospitals and healthcare organizations with standardized data to evaluate and improve nursing care and patient outcomes. More information about this benchmarking tool is available on [Press Ganey's website](#).

STANDARD:**B3.7 PHARMACISTS**

- B3.7.1 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.*
- B3.7.2 Training and knowledge of designated pharmacists shall include:*
- B3.7.2.1 Hematology/oncology patient care, including the process of cellular therapy.*
 - B3.7.2.2 Recognition and management of adverse events, including but not limited to CRS, neurological toxicities, IEC-HS, and the appropriate medications.*
 - B3.7.2.3 Therapeutic drug monitoring, including but not limited to anti-infective agents, immunosuppressive and preparative regimen agents, anti-seizure medications, and anticoagulants.*
 - B3.7.2.4 Monitoring for and recognition of drug/drug and drug/food interactions and necessary dose modifications.*
 - B3.7.2.5 Recognition of medications that require dose adjustment for organ dysfunction, age, weight, and other medical conditions.*

Explanation:

Functions may be performed by individuals with different titles trained in clinical pharmaceutical science. In the U.S., a pharmacist is a licensed pharmacist, but in other countries this role may be filled by other individuals with the required training and knowledge.

Training of designated pharmacists would ideally include one year of supervised training (or in accordance with Applicable Law) in the management of hematology/oncology patients, including hematopoietic stem cell transplant recipients. There may be different amounts of training for different individuals in a designated pharmacy. Documentation of training should include a list of pharmaceutical related cellular therapy topics, such as:

- Prevention and treatment of viral, bacterial, and fungal infections.
- Febrile neutropenia.
- Nausea, vomiting, and mucositis.
- Treatment of acute and chronic GVHD.
- Stem cell mobilization regimens.
- High-dose chemotherapy preparative therapy.

- Management and responsibility for IEC products when received from the manufacturer for administration.
- Long-term follow-up medication, including vaccinations.
- Prevention and treatment of other complications associated with cellular therapy, including, but not limited to, sinusoidal obstruction syndrome, bronchiolitis obliterans syndrome, bronchiolitis obliterans organizing pneumonia, hemorrhagic cystitis, iron overload, and management of CRS resulting from CAR (chimeric antigen receptor) T-cell therapy, management of neurologic toxicities, including dosing and timing of the administration of the appropriate medications.
- Pain and palliative care.
- Different types of conditioning regimens.

Recommendations for the roles, responsibilities, and competencies of the pharmacists are defined by the ASTCT and EBMT Pharmacists in the following publications:

- Bubalo J, Carpenter PA, Majhail N, Perales M-A, Marks DI, Shaughnessy P, et al. [Conditioning Chemotherapy Dose Adjustment in Obese Patients: A Review and Position Statement by the American Society for Blood and Marrow Transplantation Practice Guideline Committee](#). *Biol Blood Marrow Transplant*. 2014;20(5):600–616.
- Clemmons AB, Alexander M, DeGregory K, Kennedy L. [The Hematopoietic Cell Transplant Pharmacist: Roles, Responsibilities, and Recommendations from the ASBMT Pharmacy Special Interest Group](#). *Biol Blood Marrow Transplant*. 2018;24(5):914-922.
- Langebrake C, Admiraal R, van Maarseveen E, Bonnin A, Bauters T, EBMT Working Group. [Consensus recommendations for the role and competencies of the EBMT clinical pharmacist and clinical pharmacologist involved in hematopoietic stem cell transplantation](#). *Bone Marrow Transplant*. 2020;55(1):62-69.

STANDARD:

- B3.7.3 Designated pharmacists shall be involved in the development and implementation of controlled documents related to the pharmaceutical management of cellular therapy recipients.*

Explanation:

Designated pharmacists must be knowledgeable of relevant guidelines or SOPs and facilitate their creation, revision, and approval when a pharmacist's expertise is needed. They are not expected to develop these documents on their own but may have their own internal SOP manual if they wish.

Evidence:

The inspector shall request documentation of the designated pharmacist(s) responsibilities. In addition, provisions of minutes from protocol development meetings that include identified pharmacist(s) could be shown to the inspector.

STANDARD:

B3.7.4 Designated pharmacists shall participate in a minimum of ten (10) hours of educational activities related to HPC transplantation and other cellular therapies annually.

Explanation:

The field of cellular therapy continues to evolve rapidly. Pharmacists must participate regularly in educational activities related to cellular therapy, including areas of service routinely provided and other areas to broaden their scope of knowledge and keep up with current advancements in the field.

Examples of acceptable forms of education are referenced in this Accreditation Manual and may include topics specific to cellular therapy or diseases in which cellular therapy is a therapeutic option.

Evidence:

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not each designated transplant or cellular therapy pharmacist meets this Standard. Recognized educational activities include both certified continuing education credits (preferable) and non-credit educational hours, including internal presentations and conferences.

For additional Evidence and Examples related to continuing education, see the guidance following [B3.1.5](#).

Example(s):

Additional resources are available through the [ASTCT Special Interest Groups](#) (Pharmacy SIG) and through the [EBMT Pharmacist Committee](#). The ASTCT Pharmacy SIG and EBMT Pharmacist Committee exist to provide a forum for pharmacists to network and share ideas and move the field of hematopoietic stem cell transplantation forward.

The [UK BMT Pharmacists Group](#), a specialist-interest group affiliated with the British Oncology Pharmacy Association, has developed a generic training passport for BMT pharmacists and has produced a set of e-learning modules covering various aspects of the care of the bone marrow transplant (BMT) patient.

STANDARD:**B3.8** *CONSULTING SPECIALISTS*

B3.8.1 The Clinical Program shall have access to certified or trained consulting specialist services from key disciplines capable of assisting in the management of recipients and donors requiring medical care, including but not limited to:

Explanation:

The Standard requires access to consulting specialist services, which can include physicians, physician assistants, nurse practitioners, and others; establishing a relationship; and utilizing them when appropriate. In addition to the specialties specifically listed in these standards, Clinical Programs should also have access to other specialists directly related to the diseases being treated, such as metabolic diseases or immunodeficiencies.

STANDARD:

B3.8.1.1 Cardiology.

B3.8.1.2 Dermatology.

B3.8.1.3 Fertility.

B3.8.1.4 Gastroenterology.

B3.8.1.5 Infectious disease.

B3.8.1.6 Intensive care.

Explanation:

Complications from cellular therapy can be unique, and intensive care specialists should be prepared for the cardiopulmonary and neurologic needs of these patients.

STANDARD:

B3.8.1.7 Nephrology.

B3.8.1.8 Neurology.

B3.8.1.9 Obstetrics/Gynecology.

Explanation:

The Clinical Program must have guidelines for the use of obstetric and gynecologic services in pediatric donors and recipients. Guidelines may be defined by the program, institution, or in accordance with Applicable Law (e.g., a 3-year-old versus a 17-year-old pediatric donor or recipient).

STANDARD:

B3.8.1.10 Ophthalmology.

B3.8.1.11 Palliative and end of life care.

Explanation:

There may be a variety of professionals who have training in palliative and end of life care.

STANDARD:

B3.8.1.12 Pathology.

B3.8.1.13 Psychiatry.

Explanation:

While having access to a psychiatrist is required, it is acknowledged that other specialists (e.g., psychologists) may have a role in the care of recipients and donors.

STANDARD:

B3.8.1.14 Pulmonary medicine.

B3.8.1.15 Radiation oncology with experience in large-field (i.e., total body, total lymphoid) irradiation treatment protocols, if radiation therapy is administered.

B3.8.1.16 Radiology.

B3.8.1.17 Surgery.

B3.8.1.18 Transfusion medicine.

B3.8.1.19 Primary disease specialty, when applicable.

Explanation:

Transplantation and cellular therapy products are being utilized for an increasing number of indications, including some outside of the hematology/oncology field. These recipients may have

medical needs unrelated to the cellular therapy being administered. For these cases, the Clinical Program must have access to specialists in the primary disease for which a patient is being treated if the expertise is not already within the program. The purpose of this Standard is to meet the needs of the patient when their needs surpass the expertise of an attending physician who is trained in the primary disease-specialty area. In this case, further appropriate specialization may be required.

Evidence:

The inspector will use their professional judgement to determine whether the Clinical Program has identified the appropriate sub-specialists determined by the type of patients being managed.

Example(s):

Physicians trained in adrenoleukodystrophy or polysaccharide storage myopathy.

STANDARD:

B3.8.2 A Clinical Program treating pediatric donors and recipients shall have consultants, as defined in [B3.8.1](#), qualified to manage pediatric patients.

Evidence:

Not all specialty certifications have a certificate specifically for pediatrics. In these cases, Clinical Programs must provide documentation that the consultants are qualified to treat the pediatric patient population. Policies on patients that are defined as pediatric can be determined by hospital internal credentialing requirements.

STANDARD:

B3.9 QUALITY MANAGER

B3.9.1 There shall be a Clinical Program Quality Manager to establish and maintain systems to review, modify, and approve all policies and Standard Operating Procedures intended to monitor compliance with these Standards or the performance of the Clinical Program.

B3.9.2 The Clinical Program Quality Manager should have a reporting structure that is independent of clinical program operations.

Explanation:

The Clinical Program must identify at least one person responsible for QM. The title held by this individual is not mandated by the Standards and may differ among facilities. This is acceptable as long as duties include those described in the Standards. The Quality Manager should be an individual with at least an undergraduate degree or equivalent in the field of health sciences or biological sciences with training, education, or experience in either QM or cellular therapy. The

Quality Manager should have knowledge in the areas of document control, auditing, validation, qualification, risk assessment, and foundational knowledge in cellular therapies.

This person could be a member of another department, such as an institutional Quality Assurance Department, who devotes some time to the QM activities of the Clinical Program. If it is a member of the clinical team, this requirement does mandate a full-time position, and this person might have additional responsibilities. In their capacity as the QM Manager, it should be under a separate reporting structure that can facilitate unbiased oversight and provide freedom from undue influence.

Formal training and certification in one or more aspects of QM is encouraged but not required. Formal training may include practical work experience in a facility, fellowship, or certification program. Additional information related to certification in quality is available from the [American Society for Quality \(ASQ\)](#) and the [National Association for Healthcare Quality \(NAHQ\)](#). Finally, resources are available on both the FACT and JACIE websites to assist Quality Managers in advancing their knowledge and skill sets.

The Clinical Program Quality Manager must have an active role in preparing, reviewing, approving, or implementing QM policies and SOPs and must confirm that SOPs are in compliance with the FACT-JACIE Standards and Applicable Law before implementation. A key role of the Quality Manager is to develop systems for auditing Clinical Program activities to confirm compliance with the written policies and SOPs.

The Quality Manager should have a degree of autonomy from operational departments within an organization, allowing them to objectively assess and report on quality issues without being influenced by pressures to prioritize production or other factors that could compromise quality standards; essentially, they should be able to function independently to ensure the highest quality is maintained.

Evidence:

The inspector should look for documentation (e.g., audit reports) that a Quality Manager is in place and performs or oversees the functions covered in the QM section of the Standards. During inspection, the inspector may want to inquire about SOPs in place to avoid bias when Quality Managers must review their own work.

Example(s):

Formal training may include practical work experience in a Clinical Program, fellowship, or a certification program. Additionally, the Quality Manager's CV, job description, organizational chart, audit reports, or proficiency test reports (if applicable) are all examples of documentation that may demonstrate compliance.

The [FACT Quality Handbook](#) and the [FACT Quality Management Series webinars](#) are resources available through the FACT website. Additionally, JACIE offers [Quality Management and Certification in Hematopoietic Stem Cell Transplantation and Cellular Therapy: The JACIE Guide](#). These are all excellent resources for Quality Managers.

STANDARD:

B3.9.3 The Clinical Program Quality Manager shall participate in a minimum of ten (10) hours of continuing education related to cellular therapy and quality management annually.

Explanation:

The amount of activity required to meet this Standard depends on the type and frequency of the educational activities.

The field of cellular therapy continues to evolve rapidly. Quality Managers must participate regularly in educational activities related to cellular therapy and QM, including areas of service routinely provided and other areas to broaden their scope of knowledge and keep up with current advancements in the fields. While continuing education in cellular therapy (including HPC transplantation and IEC therapies) is important, it is also vital that the Quality Manager continue to improve knowledge in the field of quality, including the knowledge and skills necessary for auditing; occurrence reporting; deviation management, including complaints, adverse events and reactions; corrective and preventive action (CAPA); and process improvement. A total of ten hours in combination of these topics is required. Each topic does not need to be covered in ten hours individually.

Recognized educational activities include both certified CME credits (preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are referenced in this Accreditation Manual and may include topics specific to cellular therapy and diseases in which cellular therapy is a therapeutic option.

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not the Quality Manager meets this Standard. Recognized educational activities include both certified continuing education credits (preferable) and non-credit educational hours, including internal presentations and conferences.

For additional Evidence and Examples related to continuing education, see the guidance following [B3.1.5](#).

STANDARD:**B3.10 DATA MANAGEMENT STAFF**

B3.10.1 There shall be data management staff sufficient to comply with [B9](#).

Explanation:

Sufficient data management staff is important for accurate and timely data submission to comply with data registry requirements, these Standards, and Applicable Law. Adequate staffing reduces the risk of high error rates discovered as part of data audits performed by FACT, JACIE, and Center for International Blood and Marrow Transplant Research (CIBMTR) or EBMT.

Evidence:

Adequacy of data management personnel could be assessed based on accuracy and timeliness of registry reporting and the existence or absence of significant backlogs.

STANDARD:

B3.10.2 Defined data management staff shall participate in a minimum of five (5) hours of continuing education related to cellular therapy and data management annually.

Explanation:

Data management staff includes personnel responsible for data entry, performing statistical analysis, and submitting data to registries.

Example(s):

Continuing education for data management staff may include FACT and CIBMTR educational activities and training, which can be found on the FACT website [Data Management Resource Center](#), or those offered by the [EBMT Registry](#).

FACT also offers an [Educational Activities Form](#) which can be used to document compliance with continuing education requirements.

STANDARD:**B3.11 SUPPORT SERVICES**

B3.11.1 The Clinical Program shall have access to support services with appropriate training and education to assist in the provision of pre-cellular therapy recipient evaluation, treatment, and post-therapy follow-up. Support services shall include:

Explanation:

The Standards require that other services, as listed above, are available to support the Clinical Program. These services do not need to be completely dedicated to the cellular therapy program

but must be available to meet the recipient's needs through the delivery of care along the continuum of the cellular therapy process. Both inpatient and outpatient facilities need access to support service staff that are sufficiently trained to meet the specific needs of transplant patients.

STANDARD:

B3.11.1.1 Social services.

B3.11.1.2 Psychosocial services.

Explanation:

There are a wide range of possible psychological support professionals and patients undergoing treatments using cellular therapies, and their families should have access to these services. These service professionals can assist in the provision of recipient evaluation and treatment and post-therapy treatment. The publication *Guidelines for the role of psychological specialists in the assessment of adults undergoing Haematopoietic Stem Cell Transplantation* is available through the [Anthony Nolan's Latest clinical guidelines webpage](#) and provides relevant information to address the complexity of factors which may impact a patient's experience of and ability to cope with the cellular therapy treatment process. The inclusion of psychological services can help inform the wider multidisciplinary team. See also [Psychological Consequences of Hematopoietic Stem Cell Transplant](#) (Cooke, Gemmill, Kravits, et al. *Semin Oncol Nurs.* 2009;25(2):139-150).

STANDARD:

B3.11.1.3 Physical therapy services.

B3.11.1.4 Dietetic services.

Explanation:

Dietetic services must be 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 and to optimize the nutritional status of the patient.

B4: QUALITY MANAGEMENT

STANDARD:

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

B4.1.1 The Clinical Program Director shall have authority over and responsibility for ensuring that the overall QM Program is effectively established and maintained.

Explanation:

The QM Program includes quality assurance, control assessment, and improvement activities. The strategy (QM Plan) and associated policies and SOPs drive the operation of the QM Program.

The Clinical Program must define what key performance data it will analyze. Minimally, this should include data necessary to complete the QM activities required by these Standards.

Evidence:

Records to demonstrate an active QM Program with oversight of the Clinical Program should be available to the inspector.

Example(s):

The Clinical Program may choose to participate in an existing QM Program in its affiliated hospital, have a stand-alone QM Program, or use portions of the affiliated hospital's program in its own QM Program.

In the case of shared manufacturing arrangements, such as multi-center trials and centralized processing, the Clinical Program must have arrangements to report and share QM data among all participating entities. A working group that includes representation from commercial manufacturing entities, clinical trial sites, and others involved in cellular therapy product manufacturing and administration may be useful for defining key performance metrics and disseminating data.

STANDARD:

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

Explanation:

The QM Plan is a written document that outlines how the QM Program is implemented. The QM Plan must detail all key elements that affect the quality of recipient and donor care and cellular therapy products. The specific controlled documents for each of these elements do not have to be

fully described in the QM Plan, but they must be referenced within the plan and linked to the appropriate document(s) where the details are described.

The QM Plan does not necessarily need to be stand-alone, serving only the Clinical Program. If a QM Plan is shared, it must include all elements required by the Standards and clarify the nature and extent of participation by other areas or institutions.

An integrated cellular therapy program may, but is not required to, have one QM Plan that addresses all aspects of the Clinical, Collection, and Processing Facilities. If managed across organizational boundaries, there must be clear evidence of relationships, including organizational charts, among the QM Programs. Relationships and interactions among Quality Managers and representatives in the different organizations should be explicit to underpin cohesion within the overall cellular therapy program. There must also be mechanisms for communication of information and sharing of quality data among key elements of the program, including vendors and collaborators.

Evidence:

The written QM Plan for the Clinical Program will be provided to the inspector prior to the on-site inspection. If policies and SOPs are referenced in the QM Plan, they may be requested in advance to enable the inspector to review the details of the QM Program. The inspector is expected to evaluate implementation of the QM Plan at the facility and assess the understanding of QM by the staff.

STANDARD:

B4.2.1 The Clinical Program Director shall be responsible for the overall QM Plan as it pertains to the Clinical Program.

Explanation:

The Clinical Program Director is in charge of the elements of the QM Plan that are directly related to the program. A designee must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. Delegation to a qualified designee must be documented, either in the QM Plan or in controlled documents related to it.

Evidence:

QM Plan review and approval should provide evidence of the Clinical Program Director's involvement.

Example(s):

A designee can be a member of another department, such as an institutional Quality Assessment and Improvement or Compliance Department, who devotes some time to the QM activities of the Clinical Program, or they could be a member of the clinical team. The same person may be responsible for QM of all components of the cellular therapy program or each individual area

(clinical, collection, processing) and may have a distinct individual responsible for QM, as long as there is a mechanism for sharing information to all participating entities.

STANDARD:

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

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

Explanation:

The organizational chart must include the titles of key positions and the reporting structure of the Clinical Program and the QM Program. The chart should also depict the reporting relationship among the participating sections of the cellular therapy program (clinical, collection, and processing at a minimum), even if supporting functions are performed by contract with another facility or by individuals within the program. Lines of responsibility and communication must be clearly defined in a way that is understood by all involved.

Evidence:

The organizational chart for the Clinical Program, and the charts for collection and processing, will be provided to the inspector prior to the on-site inspection. The inspector will verify that the organization and daily function are as described in the chart and QM Plan (e.g., meetings, participants, schedules, reporting, documentation).

Example(s):

Organizational charts for matrix programs, where an individual may report to different people for different duties (i.e., to the facility supervisor for technical duties and to the Quality Manager for quality duties), should reflect the sphere of influence of individuals rather than only the lines of legal authority.

STANDARD:

B4.4 The QM 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:

Explanation:

The QM Plan, as approved by the Clinical Program Director, identifies the key personnel for whom documentation of training, competency, and continuing education is expected. This must include all individuals responsible for critical elements of the Clinical Program. Documentation of training for each individual must include all procedural skills routinely practiced. These requirements are

detailed in [B3](#). These requirements apply to all personnel in these positions, including those not directly employed by the Clinical Program but who perform clinical services.

Evidence:

The inspector should review training records to verify compliance with these Standards. Organization-specific issues and safety training are generally covered by orientation programs and continuing education programs, but inclusion of this content should be confirmed by the inspector. The inspector should review policies or SOPs describing the elements of staff training and continued competency.

The inspector should review the records of one or more personnel to confirm that all of the required elements have been documented.

Example(s):

Although only one job description is needed for each key position, documentation for each staff member is on an individual basis. For example, a staff nurse position will have one job description for that position, but each individual nurse needs their own information on file that includes documentation of qualifications, new employee orientation, training, assessment of continued competency, and continuing education as outlined in Standards [B4.4.2.1](#)–[B4.4.2.6](#).

EU regulations contain some specific requirements for personnel training that are not specifically stated in the Standards that include:

- Information sufficient for an understanding of the scientific and technical processes and principles relevant to their designated tasks.
- Information on the organizational framework, quality system, and health and safety rules of the establishment in which they work.
- Information concerning the broader ethical, legal, and regulatory context of their work.

The following resources from the Human Tissue Authority (HTA) provide further guidance for programs in the UK:

- [Code G: Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation.](#)
- [HTA Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment.](#)

STANDARD:

B4.4.1 A current job description for each position.

STANDARD:

B4.4.2 A system to document the following:

B4.4.2.1 Initial qualifications.

Explanation:

Initial qualifications generally include minimal educational requirements, formal training that is either required or preferred, and licensing or certification (e.g., registered nurse, bachelor's degree).

STANDARD:

B4.4.2.2 New employee orientation.

Explanation:

New employee orientation refers to training employees on general organizational issues upon hire, such as safety, training, or benefits.

Evidence:

Organizational specific issues are generally covered by institutional orientation programs, but this should be confirmed by the inspector.

STANDARD:

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

Explanation:

Initial training documentation must include all specific procedures that an individual staff member will perform (as defined in the job description) and should clearly indicate when that staff member has been approved to perform each procedure or function. Initial training should also include:

- Relevant scientific and technical material specific to individual duties.
- Organizational structure, quality systems, and health and safety rules specific to the organization.
- Ethical, legal, and regulatory issues specific to the organization.

Example(s):

Training and its documentation may be accomplished in a variety of formats. Training may be facilitated through formal or informal presentations, self-learning by reading suggested materials on a topic, or reviewing previously presented audio or visual presentations. Documentation may include attendance rosters, attestation statements of attendance, certificates of attendance, or competency assessments following the training.

STANDARD:

B4.4.2.4 Continued competency for each critical function performed, assessed annually at a minimum.

Explanation:

Competency is the ability to adequately perform a specific procedure or task according to direction. Clinical Programs must have a system for documenting competency and retraining, when appropriate, for each critical function performed by a staff member (see [Part A](#) for the definition of "critical").

Evidence:

The inspector should review records of employees' initial and annual competencies. The inspector should review policies or SOPs describing the elements of staff training and continued competency assessment and the records of one or more employees to determine whether all of the required elements are documented.

Example(s):

Competency may be assessed by direct observation, the use of written tests, successful completion of proficiency surveys, review of outcomes, or self-assessment and discussion with the Clinical Program Director or appropriate supervisor.

STANDARD:

B4.4.2.5 Annual training in applicable good practice (GxP).

Explanation:

GxP is an abbreviation that stands for "good practice" following various quality standards (such as [ISO 9001:2015](#)) and regulations (such as U.S. [21 CFR 211](#)). The "x" is variable, with further definition of good practices defined by different countries, fields, and laboratories. The type of work that is being performed will define which GxPs should be followed.

Training topics will depend on the type of work performed in accordance with Applicable Law. There will be local variations depending on Applicable Law for a particular jurisdiction. Comprehensive training on every aspect of GxPs each year is not expected; rather, there must be some training based on a GxP topic annually.

The extent and level of GMPs implemented is dependent on the type of manufacturing that is performed (e.g., manufacturing of minimally manipulated HPC cellular therapy products versus investigational and licensed cellular therapy products). GTPs are rooted in GMPs; in other words, the relevant GMPs are included in GTP regulations.

Evidence:

Many of the procedures performed by personnel already require training in GxPs to perform the work; therefore, GxP training is not required to be separate. However, documentation must provide evidence that the GxPs were included. For example, training in environmental control could include an overview of GTPs or GMPs, the relevant requirements based on the work to be performed, and the specific tasks performed by personnel.

Example(s):

These Standards require training in GxP as they are required by Applicable Law. Third parties such as commercial manufacturers may have different expectations. This responsibility should be defined in the written agreement with the manufacturers.

Collection and Processing Facilities in the U.S. follow a variety of GxPs:

- Good Tissue Practice (GTP) according to [21 CFR Part 1271 Subpart D](#).
- Current Good Manufacturing Practice (GMP or cGMP) as it pertains to the activities performed.
- Good Documentation Practice (GDP) and data integrity practices.

The [Guide to the Quality and Safety of Tissues and Cells for Human Application](#) (5th Edition, 2022), published by the European Directorate for the Quality of Medicines & Health Care (EDQM), provides guidance on Good Practice Guidelines based on current scientific knowledge, expert opinion, and the results of many international projects. The use of this guide is becoming more commonplace throughout Europe, including both EU member states and non-EU states who are members of the council (47 countries with approximately 820 million inhabitants). Many competent authorities use it as part of their inspections. The information provided may be applied to HPC transplantation, IEC therapy, and other novel cellular therapies.

STANDARD:

B4.4.2.6 Continuing education.

Explanation:

Staff should adhere to local and governmental continuing education requirements.

Evidence:

The inspector should find evidence of educational opportunities for staff related to their duties, such as quality-related meetings, webinars, or FACT or JACIE training sessions, if applicable.

STANDARD:

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

Explanation:

Document control is the Clinical Program's method of establishing and maintaining critical documents required by the Standards or deemed necessary for the effectiveness of the QM Program. The hierarchy and number of documents or extent of documentation is dependent on the processes, size, and complexity of the Clinical Program and will differ from one program to another.

Controlled documents serve multiple purposes for the QM Program and can consist of different document types, such as policies, SOPs, worksheets, or forms. Controlled documents provide the structure needed for quality assurance through applicable policies and SOPs. Controlled documents also ensure consistent quality control when using forms, worksheets, audit reports, outcomes analyses, training records, etc. The QM Program must identify which documents are critical and describe how they are controlled.

STANDARD:

B4.5.1 There shall be identification of the types of documents that are considered critical, and these shall comply with the document control system requirements. Controlled documents shall include at a minimum:

B4.5.1.1 Policies, Protocols, Standard Operating Procedures, Manuals, and Guidelines.

B4.5.1.2 Worksheets.

B4.5.1.3 Forms.

B4.5.1.4 Labels.

Explanation:

The QM Program must maintain a controlled document hierarchy which provides identification of the types of documents considered critical. A critical document refers to an internal document that is directly related to and could impact patient care or cellular therapy product safety, purity, potency, identity, or integrity. For example, all manuals, SOPs, forms, worksheets, and labels required by these Standards must be considered to be critical documents within the program and must be controlled. Clinical Programs may call documents by different names (such as patient guidelines instead of protocols) and may identify additional types of documents as critical within the scope of the document control system.

It is up to each program to define which documents are controlled under the QM Program. Documents and manuals that are the property of other institutions (e.g., a commercial CAR-T apheresis manual) should not necessarily be controlled by the program. However, programs must ensure that they are referring to the current version of such documents and manuals.

Evidence:

The inspector should review a listing of which documents fall under the document control system. For example, quality manuals, safety manuals, procedural SOPs, and technical guidance are all controlled documents authored by the program which must be available at the inspection.

Example(s):

Examples of such documents include the quality manual, SOPs, forms, practice guides and work sheets.

STANDARD:

B4.5.2 There shall be policies or Standard Operating Procedures for the development, approval, implementation, distribution, review, revision, and archival of all controlled documents.

Evidence:

The inspector should review active controlled documents to ensure they have been written correctly, approved by the appropriate staff before being implemented, and comply with the document control system and the Standards. The inspector will observe how the Clinical Program controls modifications of documents and maintains accurate archival systems.

STANDARD:

B4.5.3 The document control system shall include:

B4.5.3.1 A standardized format for controlled documents.

Explanation:

The Clinical Program should be consistent in the format or design of controlled documents, including a standardized date format. The facility should define acceptable date formats for documents where no specific date format is mandated by the form.

The Clinical Program must have an SOP outlining the method by which the Clinical Program creates, approves, implements, reviews, and revises its SOPs (the "SOP for SOPs"). Documents authored by the Clinical Program should follow the document control system; however, departmental and institutional documents may differ.

Evidence:

The inspector must verify that all elements of a controlled document are present as defined in the document control system and that there is consistency in format from one controlled document to another.

STANDARD:

B4.5.3.2 Assignment of a numeric or alphanumeric identifier, version, and title to each controlled document.

Explanation:

The document control system must include a system for numbering and titling that allows for unambiguous identification of documents. The numbering system must allow for identification of revisions of a document with the same title by creating a new unique identifier (e.g., numerical, alpha numerical). Worksheets and forms must also be controlled documents and contain a title, unique identifier, and version identifier.

Evidence:

The inspector must verify that controlled documents are consistently identified, titled, and versioned as defined in the document control system.

STANDARD:

B4.5.3.3 A system for document approval, including the approval date, signature of approving individual(s), and effective date.

Explanation:

The individual approving documents must have appropriate qualifications and responsibility for the document being approved.

The effective date of a controlled document is the day the new version of a document has been implemented and the previous version has been recalled or archived.

Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate individual entered the signature.

Evidence:

The inspector must verify that records indicate consistent approval of controlled documents.

STANDARD:

B4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.

Explanation:

The methods of document distribution and storage should control or prevent unwanted or unauthorized document modification or duplication. The intention of this Standard is to make sure that only the currently approved document is available for use.

Evidence:

The inspector should review the storage and accessibility of currently approved documents and archived documents to verify strict access control.

Example(s):

Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software (to lock specific areas or a specific document to prevent printing) or having copies clearly printed with an expiration date, watermarked as copies, or printed with a clear statement that printed copies may not be the current version, which can only be reviewed by going to source library.

STANDARD:

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

Explanation:

Review does not require an amendment of the version identifiers if the document is still current, but there must be clear evidence that the review has taken place. However, if changes to a controlled document are planned or have occurred since the last review, the document should be changed immediately and should not wait for the two-year review.

Evidence:

The inspector should look for documentation of the biennial review. There shall be documentation of review by an authorized person even in the absence of changes.

Example(s):

When an SOP is reviewed, associated documents (e.g., forms, worksheets) must be reviewed concurrently to ensure alignment.

STANDARD:

B4.5.3.6 A system for document change control that includes a description of the change, version, signature of approving individual(s), approval date(s), communication or training on the change as applicable, effective date, and archival date.

Explanation:

A change control system must include at least the following elements: change proposal, review of the proposed change, analysis of change for compliance with the Standards and Applicable Law, risk and impact assessment on existing processes and controlled documents, approval of change and revision of documents, communication or training on the change as applicable, and implementation of the change. Changes in practice should not occur before change in the appropriate controlled document has been made and approved. If immediate implementation of a change is required prior to official document edits, then the department should issue a planned deviation documenting this deviation from routine practice. A copy of the new document reflecting the changes could suffice for a description of the change.

The effective date of a controlled document is the day the new version of a document has been implemented and the previous version has been recalled or archived.

A staff member may not perform a new or modified procedure until they have been notified of the change, reviewed the SOP, and, if applicable, completed required training and competency assessment. The amount and format of training and competency assessment may differ based on complexity of the changes. Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate person entered the signature.

Evidence:

The change control process should be reviewed to assess if it is effective to prevent unintended changes to processes or controlled documents.

STANDARD:

B4.5.3.7 A system for archival of controlled documents for a minimum of ten (10) years from archival or according to governmental requirements or institutional policy, whichever is longer. The system shall include the inclusive dates of use and their historical sequence.

Explanation:

Archival of controlled documents is essential to enable facilities to go back to previous versions to confirm historic practices and review operational changes and rationale for the change.

Evidence:

The inspector will examine how the Clinical Program archives controlled documents, whether retrospective review is possible, and whether previous documents can be identified (e.g., unique identifier, version, title).

Example(s):

The archival system must include items such as date removed, version number, reason(s) for archival, and identification of the individual who performed the archive.

STANDARD:

B4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

Explanation:

When controlled documents are updated, there needs to be a secure process in place to ensure that any electronic and hard copies of obsolete or inactive versions are not accessible for use.

Example(s):

There should be a system in place to rescind obsolete or inactive documents to prevent unintended use. For example, on paper copies, a visible watermark could indicate that the document may not be the current version and direct staff to the source library for the most current version. If paper copies are distributed, there must be a process to rescind obsolete or inactive controlled documents.

STANDARD:

B4.6 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the establishment and maintenance of written agreements.

Explanation:

The Clinical Program must have policies and SOPs describing the requirement, development, and maintenance of written agreements or contracts with external organizations or individuals providing a critical service for the program (e.g., donor or recipient work up prior to treatment, collection, processing, testing, storage or administration of cellular therapy products, donor or recipient follow-up post-treatment). This Standard does not apply to entities within the Clinical Program's own facility or institution.

When an agreement is required, the parties involved must define responsibilities as to who is required to initiate, maintain, and review the agreement. The content, terms, and conditions within the agreement must be defined and accepted by all parties prior to signing and execution of the agreement.

Evidence:

Written agreements that match current practices must be available for the inspector to review on-site.

Example(s):

A cellular therapy program within a single institution is not required to have written agreements with the Collection and Processing Facilities. Examples of written agreements include:

- Agreement with a local blood center for infectious disease markers testing.
- Agreement with manufacturers of CAR-T products.
- An agreement for contingency planning.

STANDARD:

B4.6.1 Agreements shall be established with external parties providing critical services that could affect the quality and safety of the cellular therapy product or the health and safety of the donor or recipient.

Explanation:

It is the Clinical Program's Medical Director's responsibility to determine which internal or external entities provide critical services that require an agreement.

Documented agreements must clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements must be dated and approved by both parties and legal counsel, if necessary. Agreements must also describe the maintenance or transfer of records and cellular therapy products following termination of the agreement.

Evidence:

Written agreements with external parties must be available for the inspector to review on-site.

Example(s):

External facilities may be defined as those that are a different legal entity or those whose activities are not under the control of the Clinical Program Director.

One form of written agreement that may be acceptable for closely related but separately operated units is a shared SOP that describes the collaborative arrangements.

STANDARD:

B4.6.2 Agreements shall include the responsibility of the external party performing any step in collection, processing, testing, storage, distribution, or administration to provide clinically relevant information, to maintain required accreditations, and to comply with these Standards and Applicable Law.

Explanation:

The Standard requires that agreements include defined responsibilities for critical tasks between the program and the external party. The Standard does not require Clinical Programs to monitor a third party's compliance with Applicable Law when they are operating under regulatory oversight, such as INDs or BLAs. It does, however, require that programs specify in written agreements that those third parties are responsible for complying with accreditation standards and Applicable Law.

Example(s):

The Clinical Program is responsible for verifying that an external party has maintained required accreditations (e.g., ASHI or EFI accreditation). Agreements should include language requiring notification if accreditation is lost.

When formulating written agreements either for clinical trials or licensed cellular therapy products, the Clinical Program should consider adding language to require that it be notified of clinically relevant information such as:

- If initial incoming material did not meet the appropriate cell (e.g., mononuclear cell [MNC]) dose. Receiving this information as feedback allows the program to investigate the collection failure.
- Notification of product manufacturing failures such as purity (positive sterilities, mycoplasma endotoxin), cell dose, characterization, or vector copy number.
- Potential scheduling or production issues that impact availability.

For agreements that provide critical services that may impact patient care, language can be added to address communication pathways and notification timeframes. For example, if contracting out administration of products for infusion, the following are questions related to how relevant information will be communicated if the patient has a reaction or adverse event during the procedure:

- What type of reaction or adverse event requires urgent notification?
- What is the timeframe to notify the medical team?
- Which medications were administered after the adverse event?

Similar information should be found in agreements for other critical services which may include collection, processing, testing laboratories, or other contracted services.

STANDARD:

B4.6.3 Agreements shall be dated and reviewed on a regular basis, at a minimum every two (2) years.

Explanation:

Written agreements should be reviewed internally at least every two years, similar to SOPs, although greater or lesser time intervals may be appropriate under some conditions. The Clinical Program can define whether a formal review and approval is appropriate to complete with the external organization. The effective dates of an agreement could be specified within the agreement itself. It is helpful to have a list of written agreements to ensure each is reviewed appropriately.

Evidence:

The inspector should be able to view documentation that clinical agreements have been reviewed or revised, and, if appropriate, approved every two years. There shall be documentation of review by an authorized person even in the absence of changes.

Clinical Programs should have an awareness of, and a review plan for, all written agreements. This includes those that the program does not control (i.e., does not develop or provide authorized signatures), but which are relevant to the clinical care of the recipient or donor or impact the cellular therapy product.

Example(s):

A master list of written agreements and a checklist could assist with appropriate review and ensure that important elements are included and that a designee in the program is notified when changes are made.

STANDARD:

B4.7 The QM Plan shall include, or summarize and reference, policies and Standard Operating 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.

Explanation:

Outcome analysis is a process by which the results of a therapeutic procedure are formally assessed. Outcome analysis is focused on patient-related issues. Efficacy assessment focuses on the cellular therapy products and determines if the cellular therapy products can be demonstrated to produce a desired or intended result.

Evidence:

The inspector should confirm documentation of all activities, from definition of expected outcome to process improvement, when indicated. There must be evidence of ongoing analysis of data in addition to mere data collection.

The inspector should ask to see the data analysis, formal statistical review and peer reviewed publications, meeting minutes, and Clinical Program review of the data, including the personnel in attendance and where data are presented.

Example(s):

Examples of policies can include those related to adverse events and microbial contamination.

STANDARD:

B4.7.1 Criteria for cellular therapy product safety, efficacy, and the clinical outcome as appropriate shall be determined and shall be reviewed at regular time intervals.

Explanation:

It is expected that criteria for which reasonable data can be obtained (cellular therapy product safety, product efficacy, and the clinical outcome) will be determined and reviewed. Where product efficacy cannot be established, it is expected that product safety will still be assessed. Data should include products from both commercial and clinical trial sources, when applicable.

When the Clinical Program is only receiving cellular therapy products manufactured by an external facility and preparing them for administration (such as commercially available products manufactured by industry or clinical trial sponsors), the program must still perform some outcome analysis, although the outcome criteria may be less rigorous (such as focusing only on safety of the administration rather than potency). In these cases, the program must still be able to request or have access to other outcome data from the manufacturer when needed to perform investigations of adverse events, reactions, errors, or accidents.

Example(s):

Different committees may review outcome analyses for cellular therapy products under research (e.g., INDs) or commercially available products (e.g., those licensed by the applicable governmental authority). Examples of such committees include QM committees, investigational data review committees, or research committees. Provided that the data and results are reviewed by a designated group of qualified individuals and are reported back to the Clinical Program's QM Program, these are all acceptable.

STANDARD:

B4.7.2 Both individual cellular therapy product data and aggregate data shall be evaluated for each type of cellular therapy product, recipient diagnosis, and donor type.

Explanation:

Outcome analysis should include each individual product or recipient to assess efficacy or safety as appropriate; however, that assessment alone is insufficient to meet this Standard. The intent of the

Standard is that similar recipients (e.g., diagnosis, donor type) of a similar product be assessed together for efficacy, safety, trends, and opportunities for improvement. Individual Clinical Programs will choose how to aggregate data based upon the size and complexity of the program.

Outcome analysis should not only be performed on individual cellular therapy products, but on aggregate data as a whole to identify overall trends. A detailed statistical analysis should be performed, including descriptive statistics for the various cellular therapy products and procedures performed by the cellular therapy program. Product characteristics, especially cell dose, should also be considered in such analysis. This data can be used to identify changes that might require further investigation.

Clinical Programs are required to collect data included in CIBMTR or EBMT forms as appropriate (see [B9.1](#)) and should use these data when analyzing outcomes. The program is encouraged to define internal benchmarks and compare them to national or international data. A plan for improvement should be developed when a specific benchmark falls below the program-defined threshold.

The Clinical Program should develop and prioritize performance measures. The specific parameters to be monitored or reviewed regularly should be prospectively identified in the QM Plan and should address all key elements of the Clinical Program.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported prospectively or at the time of occurrence, while others may be retrospectively analyzed and reported at defined intervals. The data should be analyzed and assessed for improvement opportunities on a regular basis, such as at each QM meeting. Strategies (prospective and retrospective) to determine causes of issues and make improvement should be identified and implemented. The results of the implemented strategies should be measured and the improvement strategies either continued or new alternatives developed depending on the results. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated.

Example(s):

Outcome analysis may be performed by grouping data based on graft source (e.g., marrow, peripheral blood, cord blood) or IEC therapies and by relationship of donor to recipient (i.e., allogeneic donor [related, unrelated] or autologous donor). Disease-specific analysis is also recommended. Some programs may find the numbers of recipients limit the number of groups that can be assessed.

STANDARD:

B4.7.3 Review of outcome analysis and product efficacy shall include at a minimum:

B4.7.3.1 For HPC products intended for hematopoietic reconstitution, time to neutrophil and platelet engraftment following cellular therapy product administration.

Explanation:

Ordinarily, engraftment is assessed by time to recovery of neutrophils and platelets in the peripheral blood. The facility should use a standardized definition of engraftment per CIBMTR or EBMT, as the use of these definitions will help the Clinical Program compare its own data to published data. Each Clinical Program shall define acceptable engraftment criteria for its patients, comparing criteria to any existing national and international data. Recipients who do not meet expected engraftment parameters should be individually investigated to determine the factors that may have contributed to delayed or failed engraftment.

Evidence:

The Clinical Program should be prepared to provide the engraftment data, the methods used to evaluate consistency in engraftment, and the documentation of review of the analyses to the on-site inspector. Graft failure may be reviewed as an adverse event.

STANDARD:

B4.7.3.2 For IEC products, including donor lymphocyte infusions, an endpoint of clinical function as approved by the Clinical Program Director.

Explanation:

The indication (therapeutic, pre-emptive, prophylactic) for donor lymphocyte infusion (DLI) should be considered when determining a meaningful endpoint of clinical function. Chimerism studies may be used to analyze the outcome of DLIs. This Standard is intended for standard of care and investigational cellular therapy products.

Example(s):

In addition to overall and treatment-related morbidity and mortality at required time points, examples of clinical function endpoints include:

- Time to white cell and platelet recovery.
- Incidence of CRS and neurotoxicity.
- Karnofsky Performance Status.
- Target disease response.
- Disease-free survival.

STANDARD:

B4.7.3.3 For genetically modified HPC products, an endpoint of clinical function as approved by the Clinical Program Director.

Explanation:

In addition to overall and treatment-related morbidity and mortality at required time points, clinical function endpoints should be determined based upon the disease being treated. This Standard is intended for standard of care and investigational cellular therapy products.

Example(s):

Examples of clinical function endpoints include transfusion independence for transfusion-dependent thalassemia and induction of fetal hemoglobin for sickle cell disease.

STANDARD:

B4.7.3.4 Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration.

Explanation:

Performance measures may include survival, treatment-related mortality, specific complication rates, adherence to selected policies or SOPs, and other clinical outcomes, in addition to overall and treatment-related morbidity and mortality at 30 days, 100 days, and one year after transplantation. Morbidity may include re-hospitalization, prolonged hospitalization, or other measures as defined by the Clinical Program. The measures may include overall outcomes in certain groups of recipients, which may be compared to existing internal or published data, for example, by the WMDA or the EBMT.

STANDARD:

B4.7.3.5 Acute GVHD grade within one hundred (100) days after allogeneic transplantation.

B4.7.3.6 Chronic GVHD grade within one (1) year after allogeneic transplantation.

B4.7.3.7 Monitoring of infections, including central venous catheter and nosocomial infections.

Explanation:

A central venous catheter (CVC) infection is an outcome that has long-term implications on patient management, quality of life, and survival. Review of such infections is defined by the Clinical Program (with or without input from the institutional infection control department) but should at a minimum include central line-associated bloodstream infections (CLABSI). Programs are

encouraged to assess all catheter, catheter site, and blood stream infections as part of adverse event monitoring.

STANDARD:

B4.7.4 Data on outcome analysis and cellular therapy product efficacy, including adverse events related to the recipient, donor, or product, shall be provided in a timely manner to entities involved in the collection, processing, and distribution of the cellular therapy product.

Explanation:

Because patient outcome data is critical to the evaluation of cellular therapy product collection and processing, the Clinical Program must provide this information to entities involved in these processes. Collection facilities, processing facilities, registries, and third-party manufacturers, such as cord blood banks, are dependent on these data to adequately assess their practices. Data should be shared quarterly at a minimum.

NMDP does provide engraftment data to the Collection Facilities for products provided through this program.

Example(s):

The Clinical Program should inform the Collection and Processing Facilities of the results of the cellular therapy product administration so that the facilities can track product engraftment or effectiveness. If collection involves an unrelated donor through an external donor registry, programs must provide the data to the registry, and the registry to the facilities.

Clinical Programs must provide all requested data to cord blood banks in a timely manner, including at least information related to the shipment of the cord blood unit, the condition of the unit on arrival, the techniques used for thawing or thawing and washing, cell recovery and viability after thawing, adverse events related to administration, and suspected microbial contamination. These data must be provided immediately when available. When a recipient receives two or more cord blood units for a single transplant, the Clinical Program should inform the respective cord blood banks of engraftment time and the identity of the unit that engrafted. It is suggested that a mechanism to report directly to the bank be used in addition to any requirements for reporting to a registry for unrelated units. Many cord blood banks provide a form with the cord blood unit shipment to provide initial information.

STANDARD:

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 implement a Corrective Action Plan that meets FACT or JACIE requirements.

Explanation:

With the introduction of published comparative national and international data, Clinical Programs have additional resources to evaluate their one-year survival rates and improve upon them when they fall below expected ranges. Emphasis on program-defined, longer-term benchmarking against national and international data is expected to receive more scrutiny in the development of future transplant quality review across the health care enterprise. Because improving one-year survival when the outcome within the expected range is not met requires a detailed and often lengthy process of root cause analysis and performance improvement, Clinical Programs must continuously study their outcome data and take the appropriate steps.

In the U.S., it is expected that Clinical Programs performing allogeneic transplant will utilize the CIBMTR [Stem Cell Therapeutic Outcomes Database \(SCTOD\)](#) reports to demonstrate patient outcomes within the expected range at a minimum. Center-specific outcomes for autologous transplant patients should be compared to CIBMTR data. Reporting center-specific survival rates is a requirement of the Stem Cell Therapeutic and Research Act of 2005 (reauthorized in 2010, 2015, and 2021). CIBMTR has the contract to report these data.

Because transplant centers vary considerably in the risk level of recipients treated, a statistical model was developed to adjust for several risk factors known or suspected to influence outcome. Although these data are only available for one-year overall survival for recipients of allogeneic HPC transplants in the U.S., programs are encouraged to use these data for quality improvement initiatives. Programs should also define benchmarks for other significant outcomes.

The [EBMT Benchmarking](#) project is intended to give hospitals that are EBMT members insight into how their performance compares with other centers that report data to the EBMT. The reports cover a five-year period and are sent annually for eligible centers.

Some regions of the world may not have comparison data readily available. Clinical Programs in those areas should use published literature to establish a benchmark for use in evaluating their one-year survival.

Evidence:

Outcome data will be reported to the FACT or JACIE office prior to on-site inspections and also at interim reporting. If expected outcomes are not met, the Clinical Program must submit a corrective action plan prior to being awarded accreditation.

The following guidelines have been developed to help Clinical Programs write corrective action plans that convey the thought process they employed to identify root causes and implement remedial measures. Corrective action plans must:

- Identify specific causes of death.
- State current 100-day and one-year overall and treatment-related mortality based on internal outcome analyses.
- Provide quantitative data.
- Identify reasonable causes of the low one-year survival rate.
- Address the identified causes.

Example(s):

In the U.S., Clinical Programs will provide their outcomes as published in the CIBMTR Transplant Center Survival Report. European programs will use similar European or national schemes such as the EBMT Benchmarking project, British Society of Blood and Marrow Transplantation and Cellular Therapy, and Swiss Blood Stem Cell Transplant and Cellular Therapies Group.

STANDARD:

B4.7.6 The Clinical Program should set benchmarks for non-relapse mortality at one hundred (100) days after cellular therapy product administration and describe the rationale and process for review in the QM Plan.

Explanation:

This Standard requires Clinical Programs to set benchmarks for non-relapse mortality at 100 days. The QM Plan must describe the rationale for the determined benchmark, how the program analyzes non-relapse mortality at 100 days and how frequently, and actions to take when the benchmark is not met. The benchmark(s) that the Clinical Program sets should allow the program to assess non-relapse mortality at 100 days and identify specific corrective actions to take when the benchmark is not met.

The benchmark(s) should be specific to the Clinical Program and based on a number of factors, including program size, the number of allogeneic and autologous transplants performed, and the population being treated. A program may want to set different benchmarks for each type of disease based on the disease characteristics and available data. No matter how a program sets its benchmark(s), it must be based on data, from sources such as literature and registry publications.

Small programs may not have a substantial amount of data in just one year, and statistically significant analysis is not required. Programs may use cumulative data over multiple years (i.e., the accreditation cycle) to conduct the analysis and trend results.

STANDARD:

B4.8 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for, and a schedule of, audits of the Clinical Program's activities to verify compliance with the QM Program, policies and Standard Operating Procedures, these Standards, and Applicable Law.

Explanation:

The purpose of a Clinical Program audit is to gather objective evidence to verify whether clinical activities comply with applicable standards, guidelines, and SOPs. In addition, a clinical audit may provide information on potential improvements that the process owner may want to consider.

The audit process should occur throughout the year in accordance with the Clinical Program's QM Plan and schedule, with reporting of audit results, corrective action, and follow-up on a regular schedule (at least once a year). There must be regular auditing of critical clinical activities; frequency will depend on the importance of these activities, and to some extent on the results. Where there are published studies, these should be used to help assess audit results. Additionally, responsibilities of the audit for external parties who provide critical services must be detailed in a written agreement as described in [B4.6](#).

A schedule of prospective audits is expected. Required audits for the Clinical Program are listed in [B4.8.5](#), but there may be other audits required in response to specific occurrences. Review by the Clinical Program Director is to be documented. There should be evidence that audit reports are shared with the clinical staff, the Collection Facility Director, and the Processing Facility Director as appropriate and that any open audits are assessed.

Further information is available in the [FACT Quality Handbook](#) and [The JACIE Guide](#).

Evidence:

The Clinical Program should facilitate the on-site inspection with a concise presentation of recent audits, supported by policies and SOPs, and include documentation of CAPA and follow-up. Examples of how results are trended and presented to relevant directors and staff are also helpful. The inspector should review with whom report data has been shared. The inspector should review internal audit results and the schedule of planned audits, but it is not the intent to use a facility's audits to identify deficiencies during an inspection; the inspector shall maintain the confidentiality of the information.

The inspector should expect to find, at a minimum, a written audit plan, assessment and audit results, actions taken, and follow-up assessments and audits.

Example(s):

Required audits in the Clinical Program are included in [B4.8.5](#) and [B4.8.6](#).

STANDARD:

B4.8.1 Clinical Program audits shall be conducted by an individual with sufficient knowledge in the process and competence in auditing to identify problems but who is not solely responsible for the process being audited.

Explanation:

The individual performing an audit does not need to be external to the Clinical Program, but they should not have performed the actions being audited.

The Clinical Program auditor must be knowledgeable in the process and competent in auditing techniques. Sufficient knowledge must include auditing and the subject matter. The organization must demonstrate how they assess auditor competency.

Example(s):

Clinical Programs may have a designated position for an individual who performs such audits. Some programs share auditors with other clinical services within the institution. It is also possible to use a team member with other responsibilities who also has sufficient expertise. For example:

- If donor eligibility determination is normally performed by outpatient clinic staff, the audit could be performed by an inpatient nurse or by an apheresis nurse.
- In a joint adult and pediatric Clinical Program, pediatric staff could audit functions performed by the adult team and vice versa.
- Cell processing laboratory staff, particularly those with audit experience, could also audit clinical processes.
- Data management staff can audit forms completed by other data management staff. This encourages discussion among staff and facilitates learning.

STANDARD:

B4.8.2 An audit plan for each audit shall include:

B4.8.2.1 Title.

B4.8.2.2 Name of individual(s) to complete the audit.

B4.8.2.3 Audit purpose.

B4.8.2.4 Audit scope.

B4.8.2.5 Documentation of review and approval by the Clinical Program Director and the Quality Manager.

STANDARD:

B4.8.3 An audit report shall include:

B4.8.3.1 Approved audit plan.

B4.8.3.2 Identification of auditor.

B4.8.3.3 Date started and completed.

B4.8.3.4 Records or processes audited.

B4.8.3.5 Summary of results to include findings, assessment of the underlying cause of errors, recommendations, and conclusions.

B4.8.3.6 Plan for follow-up, if appropriate, including a timeline.

B4.8.3.7 Documentation of review and approval by the Clinical Program Director and Quality Manager.

Explanation:

Audit reports are an important tool to provide inspectors evidence of adherence to the Standards and effectiveness of implemented CAPA plans; to provide management guidance on future actions and decisions; and to document the evaluation process plans and decisions made in response to issues detected.

An acceptable Clinical Program audit report contains the elements described in Standards [B4.8.2–B4.8.3.7](#), and may also include the following elements:

- Audit type (e.g., Yearly Key Element, 2-Year Key Element, Focused, Follow-up).
- Audit location: Clinical site or unit (e.g., pediatric, adult).
- Date audit is assigned, including name and title of staff who assigned the audit.
- Title of staff assigned to complete the audit.
- Audit period (date range).
- If errors were found but not included in the final analysis, an explanation must be provided.
- Development of an appropriate CAPA, which should be included in the audit report to demonstrate that an appropriate corrective action plan was implemented.
- Auditor signature and date.
- BMT quality committee chair signature, date, and comments.
- Documented staff review and date of review.
- Quality meeting results presentation date, if required.

Initially, the audit report is completed by the auditor (e.g., quality coordinator) and reviewed and approved by the appropriate personnel (e.g., Quality Manager and Facility Director). At this stage in the audit process, the report does not contain evaluation of the results (determination of the root cause) or the corrective actions, but it may contain recommendations from the auditors. The approved audit report is distributed to the manager of the audited area. It is the responsibility of the manager of the audited area to evaluate the findings and recommendations to determine the appropriate CAPA, including a timeline, and sign the audit. The audit report is considered complete when the CAPA is complete and re-evaluated after implementation.

STANDARD:

B4.8.4 The results of Clinical Program audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions (CAPAs) when necessary, and follow up on the effectiveness of these actions in a timely manner.

Evidence:

The Clinical Program audit process and example audits must demonstrate that this is an ongoing process and that the QM and clinical records demonstrate CAPAs that are based on audit findings. Additionally, when audit results identify corrective action or process improvement, there should be a date designated as the expected date of completion of the corrective action and a planned time to re-audit the process to verify that the corrective actions were effective.

Example(s):

For example, central line infection rates may be expected to remain within a certain range based on national or international data. Although the yields continue to fall within that range, a trend upward towards the higher end of the expected range will indicate a need to investigate the cause (e.g., training of new staff, central line care policy, a new central venous access device supply from a different supplier).

STANDARD:

B4.8.5 Clinical Program audits shall be performed annually at a minimum and shall include at least the following:

Explanation:

The Clinical Program must have an audit calendar that shows at least these required audits annually. Other processes should be chosen for audits at the discretion of each individual program or identified by risk assessment. Audits that continuously fail to identify potential problems or opportunities for improvement should be replaced on the schedule by a new audit topic.

STANDARD:

B4.8.5.1 Audit of the accuracy of the clinical data, including the data contained in the Transplant Essential Data forms and the Cellular Therapy Essential Data forms of the Center for International Blood and Marrow Transplant Research (CIBMTR) or the Data Collection Forms of the European Society for Blood and Marrow Transplantation (EBMT).

Explanation:

The purpose of this Standard is to define the data set, not the entity to whom data is submitted. [CIBMTR's data collection forms](#) (both the Transplant Essential Data forms and the Cellular Therapy Essential Data forms) and [EBMT's data collection forms](#) are easily accessible online.

STANDARD:

B4.8.5.2 Donor screening and testing.

B4.8.5.3 Management of cellular therapy products with positive microbial culture results.

B4.8.5.4 IEC therapy safety endpoints and toxicity management.

B4.8.5.5 Documentation that each external facility performing critical contracted services has met the requirements of the written agreements.

Explanation:

It is essential that audits include a review of external facilities performing critical contracted services to confirm that the requirements of the agreements have been met. Such reviews should be performed on a regular basis and should also be performed after there has been a change in the agreement or in Applicable Law that pertain to the agreement.

The Clinical Program shall determine specific quality indicators that need to be monitored for each critical contracted service. For example, out of spec products, aberrant test results, turnaround times, maintenance of license or accreditation, staff training and competency.

Critical contracted services (such as commercial CAR-T manufacturers) should be qualified by the Clinical Program. It may not be possible to physically inspect or obtain desk audit information; however, the Clinical Program should have a process to assess the quality and performance of those third-party companies. For example, ensuring appropriate government licensure, distributor approval, and commercial business approvals. Ultimately, the terms of the product agreement or quality agreement should be validated by the Clinical Program.

Example(s):

Audits of external facilities may be accomplished by reviewing the facilities' internal and external audit reports, performing on-site inspections for compliance, receiving periodic performance reports from the facility, or the Clinical Program can audit its experience with the contracted facility using data that it defines and collects. There may be other alternatives, but the contracting facility must establish that their contracted services are meeting requirements.

Clinical Programs completing audits of external facilities can include the following:

- Verification of accurate donor identity.
- Timely receipt of complete collection prescription and medical information to ensure donor safety.
- Critical supplies inventory control.
- Equipment maintenance.
- Environmental monitoring to include temperature, humidity, facility cleaning, and prevention of contamination and cross-contamination.
- Marrow and Other Tissue collection process.
- Staff training and competency.

STANDARD:

B4.8.5.6 Verification of the chemotherapy drug administered against the written order.

B4.8.6 Additional audits shall be performed as part of a risk-based approach to the follow-up of occurrences.

Explanation:

This Standard ensures that programs implement a proactive and systematic method to monitor and improve quality and patient safety in response to occurrences. The decision to perform additional audits is guided by an evaluation of the potential severity, frequency, and impact of the occurrence. Additional audits are not routine inspections but are focused and issue-specific evaluations designed to identify root causes and contributing factors, assess whether the existing quality system controls were adequate, evaluate the effectiveness of any CAPAs, and prevent recurrence by addressing systemic issues.

By tailoring audit activities to the level of risk, the Clinical Program can allocate resources effectively, maintain quality assurance, and protect outcomes.

STANDARD:

- B4.9 The QM Plan shall include, or summarize and reference, policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency.*
- B4.10 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results that address at a minimum:*
- B4.10.1 Criteria for the administration of cellular therapy products with positive microbial culture results.*
 - B4.10.2 Notification of the recipient, collection facility staff, processing facility staff, and any other facility in receipt of the cellular therapy product and, if relevant, the donor and the sponsor.*
 - B4.10.3 Recipient follow-up and outcome analysis.*
 - B4.10.4 Donor follow-up, if relevant.*
 - B4.10.5 Documentation and investigation of cause.*
 - B4.10.6 Reporting to regulatory agencies as required by Applicable Law.*

Explanation:

The cellular therapy program (i.e., Clinical Program and Collection and Processing Facilities) must develop an integrated approach to the management of cellular therapy products with positive microbial culture results that are identified before or after the products have been administered. Policies and SOPs are required across areas of an integrated cellular therapy program to manage the aspects for which each particular area of the program is responsible. This requirement may be satisfied with a single policy or SOP, or there may be separate documents. The Policies and SOPs should cover investigation of the cause of the positive microbial culture, detail what action is to be taken, including reporting to regulatory authorities if applicable, identify who is responsible for taking the action, and state the expected timeframe of the actions. In many cases, the actual responsibilities for these activities may be in the Processing or Collection Facility. For this reason, different approaches to management may be acceptable as long as they are consistently followed and meet regulatory requirements.

The Processing Facility is usually the first facility to be notified of a positive culture result. There should be timely (without clinically relevant delay) notification to the Clinical Program and Collection Facility. This notification should in turn initiate investigation of all records related to that collection to determine if anything prior to or during the collection process could have contributed to the positive culture result.

In some cases, a positive microbial culture result will be known prior to administration. In other cases, a positive microbial result may only become known after the product has been administered. The Clinical Program must have criteria for use of a cellular therapy product with a positive microbial culture result, and, if administered, guidelines for recipient management, such as prophylactic antibiotics, increased monitoring, or other precautions.

The Clinical Program is typically responsible for recipient notification and consent and must assist with urgent medical need documentation. It is important to note that the extent of the investigation may vary depending on the type of organism or source of the graft.

Evidence:

An example of administration of a cellular therapy product with a positive microbial culture result should be prepared in advance by the Clinical Program. The example should include the donor collection record, the laboratory results, the recipient medical record, documentation of all notifications with the date and time of notification, the result of the administration (including evidence of recipient blood cultures following the administration and engraftment details), and evidence of appropriate reporting to regulatory agencies. There must be evidence of integration and collaboration with the Collection and Processing Facilities.

Example(s):

Each area in a cellular therapy program may have responsibilities that do not apply to another area. In this case, an overarching document for the management of cellular therapy products with positive cultures is recommended.

Examples of evidence of compliance with this requirement may include:

- Policies or SOPs on management of products with positive microbial culture results.
- QM meeting minutes containing a report on products with positive microbial results.
- Non-conformance reports for products with positive microbial results.

Examples of investigation and follow-up into a positive culture result may include:

- Review of collection and processing records for any indication of breach in sterile technique or other adverse event, particularly if any deviations noted in collection or extensive processing were required.
- Documentation of proper equipment cleaning.
- Review of environmental conditions for sources of possible contamination.
- Review of staff competency for possible trends.
- Follow-up and review of findings from collections or processing for possible breach in aseptic technique, donor sepsis, or other issues.
- Follow-up of the recipient for adverse reaction to administration, infection by contaminating organism, or other adverse events.

Evidence of investigation of cause, outcome analysis, and any preventive or corrective action taken as a result of the investigation should be communicated to all areas of the program (clinical, collection and processing) and be evident in QM meeting minutes.

The autologous donor, particularly when a CVC may have become colonized, represents the most common case of positive microbial culture results and requires specific monitoring. It is advisable, however, to also verify the well-being of an allogeneic donor, particularly if a positive culture result is noted within hours of the end of collection. The Clinical Program is responsible for notifying the donor of the positive microbial result and providing recommendations for care; however, a donor center or collection center may have a role in follow-up of the donor, especially for unrelated donors. In the case of a minor donor, the Clinical Program is responsible for follow-up with the minor's parent or legal guardian.

In the U.S., reporting regulations are detailed in [21 CFR Part 1271](#). A cellular therapy product with a positive microbial result must be reported to the FDA only if the product is administered, regardless of whether the result was known prior to or after administration. Marrow-derived products with positive microbial results do not need to be reported.

STANDARD:

B4.11 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for occurrences (errors, accidents, deviations, adverse events, adverse reactions, and complaints). The following activities shall be included at a minimum:

Explanation:

One of a QM Program's goals is to continuously improve processes. Monitoring occurrences and trends facilitates recognition of improvement opportunities and reduces the negative impact of an occurrence on the program. There must be policies, processes, and procedures to detect, evaluate, take corrective action, document, and report a summary of the factual details of the occurrence report in a timely fashion to key individuals, including the Clinical Program Director, Quality Manager, and governmental agencies and other entities as appropriate. The Clinical Program should define errors, accidents, deviations, adverse events, adverse reactions, and complaints in SOPs and describe when, how, by whom, and to whom each is reported. Programs may use the definitions stated by applicable regulatory agencies; however, the definition should meet the intent of these Standards. See [A4: Definitions](#). Management of each of these types of occurrences is slightly different; however, the same steps (detection, evaluation/investigation, documentation, determination of CAPA, and reporting) apply to all types.

Evidence:

The inspector should expect to find a process for documenting occurrences including detection, investigation, documentation, corrective action, preventive action, and follow-up. This should be reviewed by the Clinical Program Director and the Quality Manager. The process shall include, as

appropriate, reporting to the Collection Facility, the Processing Facility, appropriate governmental agencies, and other third parties involved in the manufacture of the cellular therapy product.

STANDARD:

B4.11.1 Detection.

Explanation:

Detection involves the means by which an occurrence is discovered. For example, occurrences may be discovered by audits, analysis of process improvement data, patient surveys, and complaints. Corrective action must be taken and documented to mitigate further risks to product quality or patient safety.

STANDARD:

B4.11.2 Investigation.

B4.11.2.1 A thorough and timely 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.

B4.11.2.2 Investigations shall identify the root cause and a plan for short- and long-term CAPAs as warranted.

B4.11.2.3 Occurrences shall be tracked and trended.

Explanation:

Investigation may also identify clinical outcomes that are not necessarily related to cellular therapy products. Examples include:

- Determining if appropriate and timely antibiotic administration has been undertaken.
- Appropriate dose adjustment of cyclosporine, tacrolimus, or sirolimus levels.
- Appropriate administration of methotrexate or GvHD prophylaxis.
- Drug adjustment for neutropenia post engraftment.
- Administration of antibiotic prophylaxis.

It is critical to identify the cause(s) of events that pose significant risk or severity and to establish and determine what CAPA will most likely be effective. Clinical Programs should be encouraged to stratify occurrences according to risk or severity and invest more time and energy into management of the more critical issues. Often “systems” play a role in causation. Only an understanding of root

cause allows creation and implementation of new or revised systems and controlled documents that will correct the issue and may prevent recurrence.

STANDARD:

B4.11.3 Documentation.

B4.11.3.1 Documentation shall include a description of the occurrence, the date and time of the occurrence, the involved individuals and cellular therapy product(s) including the unique identifier for the product involved as applicable, when and to whom the occurrence was reported, and the immediate actions taken.

Explanation:

As in the investigation, documentation of the involved individuals in any adverse event or other deviation should not be punitive. This information should be used for investigation and trending purposes to identify potential corrective and preventive measures, such as the need for additional training and staff resources.

STANDARD:

B4.11.3.2 All investigative reports shall be reviewed in a timely manner by the Clinical Program Director and Quality Manager.

Explanation:

Timing of investigative reports may vary based upon the nature of the investigation, program or institutional policy, or regulatory requirements. Programs must define the schedule of investigative reports.

STANDARD:

B4.11.3.3 Cumulative files of occurrences shall be maintained and include written investigative reports containing conclusions, root cause analysis, follow-up, CAPAs, and a link to the records of the involved cellular therapy products, donors, and recipients, if applicable.

Explanation:

Documentation should be done as close as possible to the time of detection and concurrently to ensure all critical information including description, personnel involved, date and time, and actions are captured. Sufficient information, such as unique identifiers, should be provided to link the investigative report to the records of the involved cellular therapy products, donors, and recipients, if applicable.

Complaints of cellular therapy product performance, delivery of service, or transmission of disease must be investigated and resolved. In this context, a complaint should be considered as information that implies the product or service did not meet quality specifications, failed to function as expected, or resulted in an adverse event or reactions for the recipient.

The FDA definition of a complaint is more restrictive and deals primarily with the transmission of a communicable disease, likely due to the cellular therapy product or to a failure to comply with practices that might increase the risk of transmission of a communicable disease. Corrective action or process improvement must be implemented to prevent recurrence as defined by an SOP.

Evidence:

The Clinical Program should be prepared to show examples of the cumulative files of occurrences and how they have been managed according to this process. If any occurrences have been reported to a governmental agency or other entity, the report(s) should be available for inspector review.

A tracking and filing system must be evident to show that all occurrences are logged, tracked and maintained to facilitate review and trending. Trending data should be presented at the quality meeting to ensure the effectiveness of the system is meeting requirements.

The inspector should review the complaint file and determine if corrective, preventive, or process improvement actions have been identified, implemented, and are adequate to prevent future occurrences and that regulatory agencies have been notified where that is required.

Example(s):

Communication of occurrences, investigations, and conclusions may occur in many formats, such as reporting during a regularly scheduled QM meeting with inclusion in the meeting minutes. Alternatively, a separate report may be generated, distributed, and signed by the appropriate individuals, including the Clinical Program Director. As appropriate, some documentation should be included in specific donor/patient records related to specific incidents, reactions, or products.

STANDARD:

B4.11.4 Reporting.

B4.11.4.1 When it is determined that a cellular therapy product has resulted in an adverse event or reaction, the Occurrence Report and results of the investigation shall be reported to the donor's and recipient's physician(s), as applicable, to other facilities participating in the manufacturing of the cellular therapy product, registries, grant agencies, sponsors, Institutional Biosafety Committees (IBCs), Institutional Review Boards (IRBs), Ethics Committees, accrediting bodies, and governmental agencies as required by Applicable Law.

STANDARD:

B4.11.4.2 Occurrences shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product.

Explanation:

The FDA defines an adverse reaction as an adverse event involving the transmission of communicable disease, cellular therapy product contamination, or failure of the product's function and integrity if the reaction a) is fatal, b) is life-threatening, c) results in permanent impairment of a body function or permanent damage to body structure, or d) necessitates medical or surgical intervention.

Adverse reactions may also include unexpected reactions to the graft that are designated as possibly, probably, or definitely related. For suspected adverse reactions to administration of cellular therapy products, the results of investigation and any follow-up activities must be documented.

Adverse reactions meeting the FDA definition of products regulated under GTP or GMP (products produced under IND or IDE) must be reported to FDA within their specified guidelines. Reporting to other oversight organizations may also be necessary (e.g., accrediting agencies, registries, grant agencies, Institutional Review Boards (IRBs) or Ethics Committees).

The EU [Directive 2004/23/EC](#) distinguishes between serious adverse events, which are incidents, errors, etc. that have potential consequences, and serious adverse reactions, which are actual reactions in a donor or recipient. Both must be documented and reported.

- "Serious adverse event" is defined as any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells that might lead to the transmission of a communicable disease; to death or life threatening, disabling, or incapacitating conditions for patients; or which might result in or prolong hospitalization or morbidity.
- "Serious adverse reaction" means an unintended response, including a communicable disease in the donor or in the recipient associated with the procurement or application of tissues and cells that is fatal, life threatening, disabling, incapacitating, or which results in or prolongs hospitalization or morbidity.

EU Commission Directives [2006/17/EC](#) and [2006/86/EC](#) include equivalent requirements for non-conforming products.

If an unexpected or serious adverse reaction occurs due to cellular therapy product collection or administration for which there is a reasonable possibility that the response may have been caused by the product, the report of the adverse reaction and its outcome and investigation should be communicated to all facilities associated with collection, processing, and/or administration of the product. This includes graft failure. Usually, the Clinical Program is responsible for making the initial

report; however, each involved facility must participate in the investigation and evaluation of the potential cause, particularly related to its own procedures that were involved.

Example(s):

The following are examples of adverse events that may need to be reported based on the requirements of the relevant competent authority:

- Adverse events involving the transmission of communicable disease.
- Product contamination.
- Adverse reactions that are fatal, life threatening, result in permanent impairment of a body function or permanent damage to body structure, or necessitate medical or surgical intervention.

Reoccurring clinical events (e.g., issues with conditioning regimens, immunosuppressive protocols, engraftment, variations in the status of the disease or of the patient involving a specific planned deviation) are examples of adverse events that may not require reporting to governmental agencies, but should be assessed in aggregate and trended as part of the program's quality improvement to determine if a policy, SOP, or other change may be appropriate.

For clinical trials, it may be appropriate to report adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) criteria. In the U.S., reporting to MedWatch may also be acceptable. After a cellular therapy product has been licensed by the applicable regulatory authority and is available for commercial use, the manufacturer will specify the reporting mechanism. Some may have a pharmacovigilance plan. The U.S. FDA provides guidance for such plans in [E2E Pharmacovigilance Planning](#) and [Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment](#) (both issued in 2005).

STANDARD:

B4.11.5 Corrective and preventive action.

B4.11.5.1 Appropriate 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.

Explanation:

All events may not require immediate corrective action. Follow-up after implementation of CAPA plans is critical to ensure effectiveness. Lack of effectiveness would indicate the need to continue further investigation of cause or other contributing circumstances and additional actions. Clinical Programs should define in their policies or SOPs when events warrant preventive plans, along with their plan to audit the effectiveness of the changes.

Immediate actions are those actions taken for each non-conformity detected in order to minimize and mitigate the impact of the non-conformity. Preventive actions are actions taken to eliminate the cause(s) of the nonconformity in order to reduce the likelihood of recurrence or occurrence elsewhere.

Investigations and corrective actions should, at a minimum, address:

- Identification of the involved individuals or cellular therapy product affected and a description of its disposition, where relevant.
- The date and time of the event.
- The nature of the problem requiring CAPA.
- To whom the event was reported.
- A description of the immediate corrective action taken.
- The date(s) of implementation of the corrective action.
- Follow-up of the effectiveness of the corrective action, where relevant.

STANDARD:

B4.11.5.2 Follow-up audits of the effectiveness of CAPAs shall be performed in a timeframe as indicated in the investigative report.

Explanation:

Short term corrective (immediate) actions are those actions taken immediately upon discovery of the occurrence or shortly thereafter to contain the problem and prevent it from causing further harm. These actions typically address the symptoms of the problem rather than the root causes. Long term corrective (preventive) actions are taken to address the root causes of the problem and are intended to be a permanent solution to the problem, preventing recurrence.

STANDARD:

B4.12 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for cellular therapy product Chain of Identity and Chain of Custody that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

Explanation:

The Clinical Program must have a policy or SOP for Chain of Identity and Chain of Custody to allow tracking and traceability of each cellular therapy product through all steps from collection to administration or final disposition. Documentation in the medical record should include the proper product name, unique product identifier(s), ISBT 128 donation identification number (DIN) and product code, EU Single European Code (SEC) or equivalent, content of the cellular therapy product, identification of the donor including medical record numbers, unrelated donor registry identifiers

including Global Registration Identifier for Donors (GRID), allogeneic donor eligibility status, and the unique identity of the intended recipient including registry identifiers, where appropriate. There must be a process, including the use of the ISBT (Information Standard for Blood and Transplantation) 128 barcode or other barcode or unique numbering system, to track and trace specimens removed from a cellular therapy product for testing at an external facility such as an HLA testing facility, transfusion service, or microbiology laboratory. This process must ensure linkage between the results of testing and the original product. There should also be a means, direct or indirect, that will allow outcome information to be related back to any other facilities involved in collection, processing, and distribution of the product. The final disposition of the product must be documented, whether the product was administered, destroyed, released, or used for research, remains in storage, or other disposition. The tracking and tracing system must comply with the Standards and Applicable Law.

Evidence:

The inspection team will review examples of clinical, collection, and processing records, including worksheets and reports and final cellular therapy product labels, to determine if tracing and tracking from donor selection through final product disposition and recipient identification is possible. All critical steps should identify who performed the procedure and when it was completed. The Clinical Program or Marrow Collection Facility must have a system in place to request information, if not initially provided, to identify manufacturing procedures performed by external facilities (e.g., genetically modified cellular therapy product).

Example(s):

A Clinical Program may assign an ISBT 128 DIN as a unique product identifier upon receipt of a cellular therapy product from an unrelated donor collection facility that does not use ISBT 128 labeling, as long as tracking and tracing from the donor to the recipient is possible (i.e., the unique product number assigned at the collection facility is recorded in the medical record to maintain the linkage).

Full implementation of ISBT 128 labeling ensures tracking and traceability of the cellular therapy product and associated pilot vials and segments in a facility. However, if a Clinical Program or Marrow Collection Facility removes specimens from a cellular therapy product and sends these to an external laboratory such as an HLA testing laboratory or a transfusion service for testing, the laboratory information system at the testing laboratory might not be compatible with ISBT 128 barcodes. If the testing laboratory assigns a new laboratory or barcode number to these specimens, there must be a system to link the reports generated following testing to the original cellular therapy product.

STANDARD:

B4.13 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event that Clinical Program operations are interrupted.

Explanation:

Clinical Programs should be prepared for situations that may interrupt typical operations so that such interruptions do not adversely affect recipients, donors, or cellular therapy products. While a policy or SOP is required that addresses emergencies and disasters (see [B5.1](#)), the program must also have a plan for the management of interruptions that do not rise to the disaster level. It is difficult to anticipate every possible situation that may occur. Therefore, the Standards do not require the program to outline actions for specific events; rather, the program is required to describe actions to take when an interruption presents, including who needs to be contacted, how to prioritize cases, key personnel to be involved in identifying alternative steps to continue functions, and notification of staff.

A contingency plan specific to the Clinical Program would convey evidence that risk has been assessed for program-defined potential events of varying impact, such as a failure of the scheduling system, a water supply interruption, or shortage of a chemotherapy agent. The plan should reflect differences between specific program needs and general hospital needs and complement the hospital plan.

As more and more of the Clinical Program's documents exist on an electronic platform, there is an increasing risk of temporary or permanent document loss. The institutional Information Technology Department generally confirms that software in use is validated for its function and that there is a regular schedule of backups to allow for retrieval of information when necessary. Freestanding facilities, as well as programs utilizing desktop storage, must have a plan to create a similar level of security. In either case, the program also needs a method to produce current versions of critical documents, such as preprinted orders, consent forms, and SOPs, when the electronic format is not available.

Policies, SOPs, and associated worksheets and forms must be available to Clinical Program staff at all times. Arrangements must be made so that these documents are available in the event that the computer system goes down. Staff should have periodic training and review of alternate systems so they will be competent in the use of these systems should the need arise.

Evidence:

The inspector should review policies and forms to be used in case the electronic record system is unavailable.

Example(s):

Examples of interruptions include malfunctioning electronic records systems, drug shortages, power outages, equipment failures, and supply shortages. Particularly important drug shortages would

include chemotherapy agents typically used as part of the preparatory regimen or antibiotic/antifungal agents. A contingency procedure would identify alternative sources of supplies, alternative supplies, or alternative preparative regimens.

STANDARD:

B4.14 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services.

Explanation:

Quality can be maintained only if there is control over critical manufacturers (including CAR-T manufacturers), vendors, equipment, supplies, reagents, facilities, and services. The QM Plan must include a process to qualify these elements to safeguard their consistent function in validated procedures. This process must include the establishment of minimal standards for the acceptance of critical supplies and reagents and must document that those standards are met before they are made available for use.

Where purchasing is beyond the direct control of the Clinical Program, steps should be taken to verify supplier and vendor qualification have been performed by the parent organization.

In the U.S., if the Clinical Program or an intermediary facility receives cellular therapy products directly from a third-party manufacturer, the program must qualify the manufacturer by verification of an IND or BLA for the product. Regulatory compliance is the responsibility of the IND or BLA holder, and further qualification of the manufacturing facility is not required of the Clinical Program. As a vendor of services, the manufacturer should be qualified to ensure it is meeting the needs of the Program for such issues as labeling, level of service, or other issues defined in an agreement.

Evidence:

The inspector should find evidence of qualification of manufacturers, vendors, supplies, equipment, facilities, services, and critical reagents. Qualification procedures should include instructions for requalification and under which circumstances qualification is required. Accredited facilities should participate in external inspections as required by Applicable Law.

Example(s):

It is not the intent of this Standard for the Clinical Program to qualify licensed pharmaceutical products, but rather a risk-based approach should be taken to identify items which require qualification. For example:

- Critical documents include a document that is directly related to and could impact donor welfare, recipient care, or cellular therapy product integrity.

- Updated software versions have the potential to materially affect performance of equipment. For further definitions and examples of qualification, see the [FACT Quality Handbook](#) and [The JACIE Guide](#).

STANDARD:

B4.14.1 Critical equipment, software, supplies, reagents, and facilities used for cellular therapy collection procedures shall be qualified.

B4.14.1.1 Qualification shall be required following any significant changes to these items.

Explanation:

The Clinical Program has the ultimate responsibility for ensuring qualifications have been performed.

Example(s):

If there is a software change or upgrade, the Clinical Program must assess the need to qualify or requalify the software. Requalification would typically be necessary when the software version changes, but smaller upgrades may also critically affect donor safety or cellular therapy product efficacy.

STANDARD:

B4.14.2 Qualification plans shall include minimum acceptance criteria for performance.

Explanation:

The Clinical Program must have a system in place that confirms that vendors provide materials in a timely and consistent manner that meets their acceptance criteria. Supplier qualification must also confirm that vendors have a system in place that is consistent with the Standards, that they can demonstrate process control, and they are compliant with Applicable Law. Suppliers of infectious disease testing must also be qualified.

Supplier qualification provides assurance that the supplier will consistently furnish the materials and components that the program requires in accordance with applicable regulations. When the supplier is a pharmaceutical manufacturing organization, the key elements of vendor qualification (appropriate registrations and certifications, quality management system requirements, notification of changes in critical processes) can be addressed in the BLA and/or the Quality Agreement between the Clinical Program and the Manufacturer.

Example(s):

Suppliers with pre-existing service agreements preceding the implementation of this Standard can be qualified as meeting expectations by a retrospective review of the quality of service provided.

Documentation in the form of a brief written statement that the service provider has met the Clinical Program's requirements, worked with the facility to identify the cause of service failures, and has taken corrective actions in the past may serve as documentation of service provider qualification.

General medical equipment qualification is performed to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. This qualification may be delegated to other institutional departments.

STANDARD:

B4.14.3 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Clinical Program Director.

Explanation:

A plan for qualification must be reviewed and approved prior to performing a qualification.

Qualification of critical items should include:

- Design Qualification (DQ).
- Installation Qualification (IQ).
- Operation Qualification (OQ).
- Performance Qualification (PQ).

The qualification plan should be reviewed after the qualification to determine if all acceptance criteria were met. This process must include the establishment of minimal standards for acceptance and must document that those criteria are met before use.

Example(s):

There are several ways to qualify a vendor of supplies, reagents, and services. The most effective is to perform an audit of the provider. Other, often more practical, methods may include one or more of the following:

- A review of third-party assessments by accrediting organizations such as FACT, JACIE, AABB (Association for the Advancement of Blood & Biotherapies), CAP, or others.
- Remote audits by questionnaire.
- An ongoing dialog of resolution of service complaints or suggested process improvements.

- The sharing of internal audit findings and implemented corrective action plans from the provider back to the facility as evidence that deficiencies have been recognized and corrected.
- A documented review of the supplier's past performance history.

Suppliers with pre-existing service agreements can be qualified as meeting expectations by a retrospective review of the quality of service provided.

Documentation, in the form of a brief written statement, that the service provider has met the Clinical Program's requirements, worked with the facility to identify the cause of service failures, and taken corrective actions in the past may serve as documentation of service provider qualification.

General medical equipment qualification is performed to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. This qualification may be delegated to other institutional departments.

STANDARD:

B4.15 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

Explanation:

Validation is confirmation by examination and the provision of objective evidence that particular requirements can consistently be fulfilled. A process or SOP is validated by establishing objective evidence that the process consistently produces an expected endpoint or result that meets predetermined acceptance criteria. Validations can be performed prospectively, concurrently, or retrospectively.

Verification is the confirmation of the accuracy of something or that specified requirements have been fulfilled. Verification differs from validation in that validation determines that the process performs as expected, whereas one verifies that the products of a process meet the required conditions.

Example(s):

For further definitions and examples of validation, see the [FACT Quality Handbook](#) and [The JACIE Guide](#).

STANDARD:

B4.15.1 Critical procedures to be validated shall include collection procedures, labeling, storage, distribution, preparation for administration, and infusion, as applicable.

Explanation:

In the Clinical Program, the following should be validated:

- Marrow collection procedures. Validation of the HPC, Marrow collection procedure should include all the variables used in the collection of each product, such as donor variables (e.g., white blood cell count or CD34 cell count at initiation of collection, blood volume, weight) and procedural variables (e.g., marrow volume collected, duration of collection). The validation study should demonstrate that the process reproducibly results in a product that is sterile and is of a predetermined volume and nucleated cell content.
- Labeling of cellular therapy products collected from marrow.
- Storage of cellular therapy products prior to distribution.
- Distribution of the product. This may include packaging, temperature, and monitoring for products transported or shipped within or between facilities.
- Electronic records system, if applicable.

If the Clinical Program is responsible for any operations beyond thawing and infusing, this is considered preparation for administration, and the Standard would apply. An example of this would be new products that require dosing at the bedside.

It is not the intent of the Standards to include hospital-based systems and clinical medical records. For further guidance, see Standard [B10.4.2](#).

Evidence:

The inspector should ask to see the SOPs for conducting validation studies and review a sample of validation studies. The inspector should note that studies are properly designed, objectively collect the required data, outcome and intended actions are summarized, and both the finalized plan and report are reviewed and approved by the Clinical Program Director and Quality Manager.

Example(s):

If there is a requirement from a manufacturer outside of what is established in a Clinical Program's SOP, this can be managed by a separate SOP applicable to manufacturer requirements.

STANDARD:

B4.15.2 Each validation or verification shall include at a minimum:

Explanation:

Validation studies must be performed according to a validation procedure, utilizing a consistent format for approval of the validation plan, conducting the studies, collection and documentation of results, data analysis, conclusions, and approval of the studies. A validation study performed because of a proposed change in a process or SOP shall include a documented assessment of the risk involved in the change to donor and recipient health and safety and the quality and safety of cellular therapy products.

The design of the validation study should be adequate to determine if the process reproducibly achieves the purpose for which it is intended. The validation plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. Any change in the planned study that occurs during the study requires explanation. There should be an explanation, follow-up, and repeat of any test that fails to meet the expected outcome.

Example(s):

It is acceptable, but not required, for the Clinical Program to utilize validation plans, formats, and personnel from the Collection Facility or Processing Facility to perform validation studies, or to contract these validation studies to a contract vendor.

STANDARD:

B4.15.2.1 An approved plan, including conditions to be assessed.

B4.15.2.2 Acceptance criteria.

Explanation:

Marrow collection validation should confirm that acceptable endpoints can be achieved while maintaining the purity, potency, and safety of the cellular therapy product. Examples of acceptable endpoints may include, but are not limited to, nucleated cell recovery, viability, sterility, and RBC reduction.

STANDARD:

B4.15.2.3 Data collection.

B4.15.2.4 Evaluation of data.

B4.15.2.5 Summary of results.

STANDARD:

B4.15.2.6 References, if applicable.

B4.15.2.7 Review and approval of the plan, report, and conclusion by the Quality Manager and the Clinical Program Director.

Explanation:

Review and approval need to be completed by a minimum of two individuals. One must be the Quality Manager, and the second must be the Clinical Program Director. A Quality Manager designee may need to be utilized when the Quality Manager is unavailable (e.g., on vacation, in the process of hiring for that position, on parental leave). In this situation, the Quality Manager designee must be a qualified member of the QM team to complete the review and approval process.

STANDARD:

B4.15.3 Significant changes to critical procedures shall be validated and verified as appropriate.

Example(s):

Use of a new system for collection of bone marrow would require validation to confirm the system performed as expected with no compromise of bone marrow product purity, potency, or safety.

STANDARD:

B4.16 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for evaluating the risk of changes to critical procedures to assess the effect(s) elsewhere in the operation.

Explanation:

Evaluation of risk is a process to assess and document the risks involved in a change in a practice, process, SOP, or environment that has the potential to affect a critical procedure; direct patient care; and/or the cellular therapy product integrity, sterility, viability, or recovery. Critical procedures requiring risk assessment should be defined by the program. Examples include donor management, recipient work-up and treatment, and labeling and storage of cellular therapy products, if performed in the Clinical Program.

Evaluation of risk may be documented in the SOP, in a validation plan, or as a separate document. Documentation may include:

- Identification of a risk.
- Context.
- Evaluation.

- Impact.
- Management response.

Evidence:

The inspector should ask to see the SOP for evaluation of risk for changes to a practice, process, SOP, or environment and preferably an example of how it has been applied.

Example(s):

Identification of a risk can be made by providing a description of a potential or known risk. Establishing the context or scope means all the possible risks are identified and the possible ramifications or impact in all areas are analyzed thoroughly. Once the context or scope has been established, the next step is identification and evaluation of potential risks as either source or effect. During source analysis, the source of risks is analyzed, and appropriate mitigation measures are put in place. This risk source could be either internal or external to the system. During problem analysis, the effect rather than the cause of the risk is analyzed.

A general description of the issue and identification of the specific risk(s) should be included. After the risk has been identified, it must be assessed on the potential of criticality or on its likelihood of occurrence and potential impact, including quantitative and qualitative evaluation. Risk prioritization is when the 'likelihood of occurrence × impact' is equal to risk.

There are many different approaches to calculating risk, and there are tools that can help assist in defining the probability of the effect occurring, the root cause, and the effects and magnitude of risk under different scenarios. Examples of tools that a program might use include The Five Whys technique for root cause analysis, FMEA (Failure Mode and Effects Analysis), an Ishikawa or fishbone diagram, or SWOT (strengths, weakness, opportunity, and threats).

Once the risk assessment is established, then a risk management plan can be developed and implemented. Risk Management includes justification and rationale for accepting the risk and how to manage the impact, if applicable. This can often be established in a simple one-page document for change with low impact and risk. An example might be a change in reagent or supply of appropriate grade.

Below is an example of a risk assessment matrix that combines the concept of likelihood and severity.

		Probability (Likelihood of occurrence)			
		Occasional (Possible to occur in time, if not corrected)	Likely (Will probably occur in most circumstances)	Frequent (Expected to occur in most circumstances)	
Risk Matrix	Severity of Incidence	Minor (low risk to the product or patient)	Low (1)	Low (1)	Medium (2)
		Moderate (Probable risk to product or patient)	Medium (2)	Medium (2)	High (3)
		Major (High risk to product or patient)	High (3)	High (3)	High (3)

STANDARD:

B4.17 *The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining and reviewing feedback and taking action when appropriate.*

B4.17.1 *Feedback shall be obtained from associated Collection and Processing Facilities.*

B4.17.2 *Feedback shall be obtained from donors and recipients or legally authorized representatives.*

Explanation:

The QM Plan must describe how the Clinical Program obtains feedback from the Collection and Processing Facilities. This Standard is not intended to be prescriptive. While casual comments may be included, the intent is to have an active process for soliciting feedback.

Feedback (including complaints) must also be obtained from donors, recipients, and legally authorized representatives. It may be obtained directly by the Clinical Program; however, it is also acceptable to use a hospital-wide system, such as patient satisfaction surveys, as long as the cellular therapy program is included and relevant issues can be readily identified.

Evidence:

Evidence to show compliance may be:

- Minutes of QM meetings where issues are discussed.
- Mutual resolutions of non-compliances.
- Records of compliments and complaints.
- A survey of resolution of complaints.

STANDARD:

B4.18 The Clinical Program Director shall review the quality management activities with representatives in key positions in all elements of the cellular therapy program at a minimum quarterly.

B4.18.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

B4.18.2 Performance data and review findings shall be reported to key positions and staff.

Explanation:

QM activities, including the results of audits, shall be reported quarterly at a minimum to review the performance of the QM Program and its objectives. This is to determine whether the elements in the QM Plan are relevant and effective and necessary actions are taken in a timely manner.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported with each audit, while others may be retrospectively analyzed and reported at defined intervals. The data should be analyzed, assessed, and trended over time to identify improvement opportunities on a regular basis, such as at each QM meeting. Strategies for improvement should be identified and implemented. The results of these implemented strategies should be measured and the improvement strategies either continued or new alternatives developed, depending on the results.

Minimally, quarterly meetings are required. The minutes and attendance lists of regularly scheduled QM meetings are effective ways to document QM activities and communication of quality assessments to key individuals within participating facilities in the cellular therapy program. Having multidisciplinary meetings that involve several academic disciplines or key personnel is an acceptable approach to developing recommendations for performance improvement.

Evidence:

The inspector should ask to see evidence that, at a minimum, a summary of key performance data and review findings have been reported to staff (although all findings can be shared) within all participating entities in the cellular therapy program. The inspector should ask to see the minutes of the QM meetings, which should document who was in attendance and what topics were covered. At a renewal inspection, it is particularly important to ask for QM meeting minutes that represent the time since the previous accreditation in order to determine that the QM Program is and has been ongoing. Minutes should summarize activities such as training performed, documents reviewed, audits performed, SOPs introduced or revised, and outcome parameters reviewed.

STANDARD:

B4.18.3 The Clinical Program Director shall not have oversight of their own work if this person also performs other tasks in the Clinical Program.

Explanation:

Any person responsible for overseeing QM activities should not be directly responsible for review of work solely performed by that person. It is important that the final review be unbiased and that there has been sufficient time away from the work for the review to be objective. In small Clinical Programs where one person may bear responsibility for the majority of clinical activity, an appropriately qualified designee should be assigned to review these activities. It may also be acceptable for an individual to review their own work at a time and place removed from the actual performance of the task.

Evidence:

The inspector should assess if the person documented as performing the task is also the person reviewing or approving the work. For example, the Clinical Program Director should not be the sole approver on a planned deviation for the director's patient.

STANDARD:

B4.19 The Clinical Program Director shall review the effectiveness of the QM Program annually.

B4.19.1 The annual report and documentation of the review findings shall be made available to key personnel, the Collection Facility Director, the Processing Facility Director, and staff of the program.

Explanation:

The ultimate responsibility for performance and monitoring of the QM Program, including internal or contracted components, belongs to the Clinical Program Director. This includes reviewing key performance data across clinical, collection, and processing.

The overall effectiveness of the QM Program must be reviewed and reported to staff on an annual basis. The annual report will provide a year-long view of the overall function of the QM Program, its effect on and interactions with the Collection and Processing Facilities, and clues on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated.

The annual report should also contain trending information related to key indicators that are monitored, patient outcomes, patient satisfaction, adverse events, and other important elements utilizing data from prior years and goals for the coming year.

Example(s):

The Clinical Program Director(s) may wish to report on the effectiveness of the QM Program more frequently than once a year. If so, the report should utilize some data from the previous 12 months to provide a longitudinal perspective of how the QM Program is functioning over time.

Examples of sections to include in the report on the performance of the QM Program are:

- Overall programmatic indicators (e.g., accreditation achieved, new faculty, moves, data updates).
- Quality measures (including clinical, collection, and processing):
 - Clinical outcomes.
 - Audits.
 - Validations.
 - Risk assessments.
 - Service-level agreements.
 - Process improvements.
 - Adverse events.
 - Goals for the coming year.

In the case of shared manufacturing arrangements, such as multi-center trials and centralized processing, the Clinical Program must have arrangements to report and share QM data among all participating entities.

B5: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

B5.1 The Clinical Program shall establish and maintain policies or Standard Operating 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:

Explanation:

The following is a comprehensive list of policies and SOPs for all personnel. In some cases, some policies and SOPs may be for a specific role (e.g., pharmacists and nurses). The policies and SOPs required in B5 are operational in nature, whereas those required in [B4](#) pertain to the QM Program. The policies and SOPs must be detailed, unambiguous, and adequately define all operational aspects of the Clinical Program. It is recognized that the practice of medicine requires some flexibility and that the Clinical Program may choose to describe some elements of clinical practice in clinical guidelines, rather than as policies or SOPs. Unlike SOPs, which must be strictly followed,

clinical guidelines provide recommendations for patient care while allowing for variations in practice depending on the clinical situation(s).

When a clinician decides that a variation or alternative intervention from a clinical guideline is warranted, the reasoning behind that decision shall be documented in the recipient's or donor's chart, but pre-approval of the variation or alternative intervention is not necessary.

The Clinical Program is not required to have a controlled document titled for every item on the list, as long as each item is addressed within one (e.g., policy, SOPs, clinical guideline). The Clinical Program can utilize institutional policies and SOP but retain the responsibility for verifying that those policies and SOPs meet the requirement of the Standards. In those circumstances where program or institution standards vary from these minimal requirements, the program will be held to the higher standards.

Evidence:

Documents addressing the elements listed in B5 must be present. A list of all controlled documents shall be provided to inspectors prior to the inspection to determine if an in-depth review of any documents is necessary. When multiple topics are covered by a single document, it will aid the inspection process if the Clinical Program prepares a crosswalk between the list of required SOPs in B5 and the program's own list of controlled documents.

There will not be time to read all policies and SOPs during the on-site inspection. The list of controlled documents should be examined for evidence of documents addressing each item before arriving at the inspection site. Prior confirmation that a specific document has been generated will reserve limited on-site inspection time for activities that can only be verified in person at the inspection site. When necessary, specific documents may be requested and read in their entirety by the inspector.

Example(s):

An example of the use of guidelines rather than SOPs is for the use of antibiotics for fever. The Clinical Program may need to have flexibility if the patient is allergic to the recommended antibiotic or has a past history of infection that would dictate a particular antibiotic combination.

The policies and SOPs can be generated within the Clinical Program or in collaboration with other institutional infrastructures. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and emergency response. In cases where general policies and SOPs are inadequate to meet standards or where there are issues that are specific to the program, the facility must develop its own policies and SOPs. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for review and approval of revisions within the program initially and every two (2) years thereafter.

Some Clinical Programs may use cellular therapy products that are manufactured by a third party. These manufacturers may require processes different than what is outlined in the program's SOPs

for its usual activities. When this occurs, the program may handle different manufacturer requirements via the planned deviation process (appropriate for infrequent situations), additions within existing SOPs, or separate SOPs for those processes. The program is responsible for verifying that the different process achieves the intended results.

Both FACT and JACIE have published Quality Handbooks (the [FACT Quality Handbook](#) and [The JACIE Guide](#)) to provide additional explanation of quality principles. These handbooks can be used as additional resources to develop policies and SOPs in compliance with the Standards.

STANDARD:

B5.1.1 Donor and recipient confidentiality.

Explanation:

Confidentiality is a critical aspect of care management, and it is applicable in every case. How programs manage confidentiality will look different based on the type of program (e.g., autologous, related allogeneic, unrelated allogeneic).

Example(s):

Donor and recipient confidentiality includes confidentiality of records.

STANDARD:

B5.1.2 Recipient evaluation, selection, and treatment across the continuum of cellular therapy care.

B5.1.3 Donor and recipient informed consent related to treatment and cellular therapy product collection, storage, and disposition.

Evidence:

The inspector will look for information in the policy or SOP for consents that detail how the donor or recipient is informed on treatments, collection practices, storage, and what happens to the product including administration, release for research, used for quality assurance activities, or stability testing.

STANDARD:

B5.1.4 Donor search and selection, including screening, testing, eligibility determination, selection, and management.

Explanation:

Depending on patient characteristics, cells from marrow, peripheral blood, or umbilical cord blood may be advantageous over the other options. The Clinical Program should determine general plans

for how a physician may choose the best source of cells for a recipient and how those cells should be sought (e.g., which registries are available for searching for an unrelated donor, which family members will be tested for a related donor).

STANDARD:

- B5.1.5 Management of donors and recipients who require central venous access.*
- B5.1.6 Administration of the preparative regimen.*
- B5.1.7 Administration of cytotoxic and immunosuppressive therapy.*
- B5.1.8 Administration of HPC and other cellular therapy products, including products under exceptional release.*
- B5.1.9 Management of ABO-incompatible cellular therapy products including indications for red blood cell (RBC) or plasma reduction.*
- B5.1.10 Care of immunocompromised recipients.*
- B5.1.11 Administration of blood products.*
- B5.1.12 Management of complications of transplant and other cellular therapies, including CRS, neurologic syndromes, and IEC-HS.*

Explanation:

CRS and other central nervous system toxicities are adverse events common with the administration of IECs. They have also been reported in haploidentical transplants and have been associated with antibodies such as alemtuzumab, anti-thymocyte globulin, and rituximab. The Clinical Program must be aware of these toxicities resulting from cellular therapy products and medications.

STANDARD:

- B5.1.13 Monitoring patients following cellular therapy product administration, including recognition of cellular therapy complications and emergencies requiring rapid notification of the responsible clinical team.*
- B5.1.14 Provision of appropriate long-term follow-up care for recipients.*
- B5.1.15 Duration and conditions of cellular therapy product storage and indications for disposal.*

STANDARD:

B5.1.16 Data management.

B5.1.17 Handling and disposal of medical and biohazard waste.

B5.1.18 Clinical Programs utilizing genetically modified cellular therapy products shall incorporate or reference institutional or regulatory requirements relating to biosafety practices, including handling and disposal.

Example(s):

The article [The Science and Practice of Current Environmental Risk Assessment for Gene Therapy: A Review](#) (Liu. *Cytotherapy*. 2024;26(7):686-699) can aid programs working with gene therapy products in completing a robust environmental risk assessment.

STANDARD:

B5.1.19 Cellular therapy emergency and disaster plan, including the Clinical Program response.

Evidence:

Compliance with most of the Standards in this section can be determined before the on-site inspection by review of the document control system and SOPs submitted in the pre-inspection material. However, additional SOPs should be reviewed during the inspection for compliance.

Example(s):

For the emergency and disaster plan(s), the Clinical Program may use institutional policies for the general responses; however, specific SOPs relating to the chain of command and necessary SOPs to address the safety of stored cellular therapy products are needed to augment the institutional policies (such as the need for a plan for backup storage facilities). Examples of disasters include fires, hurricanes, floods, earthquakes, and nuclear accidents. Specific natural disaster policies may be more pertinent dependent on geographic location. In cases where institutional policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the cellular therapy program, the program must develop additional policies and SOPs.

Examples of the latter include, for instance, contingency plans for major environmental or infectious threats, such as failure of isolation facilities; outbreak of aspergillosis, respiratory syncytial virus (RSV), or (para) influenza; or pandemics, leading to an emergency closure or modifications to the practices of the clinical unit. The article [Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program](#) (Wingard, Leahigh, Confer, et al. *Biol Blood Marrow Transplant*. 2006;12(11):1229-38) provides a framework for disaster plans that can be customized for individual Clinical Programs.

Additionally, the FDA offers information on its webpage [*Impact of Severe Weather Conditions on Biological Products*](#) (2018).

STANDARD:

B5.1.20 Chain of Identity.

Explanation:

Chain of Identity is the permanent and transparent association of a cell or gene therapy's unique identifiers from procurement of tissue or cells throughout the full product(s) lifecycle.

STANDARD:

B5.1.21 Chain of Custody.

Explanation:

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

STANDARD:

B5.2 The Clinical Program shall maintain a detailed list of all controlled documents, including title and identifier.

Explanation:

Controlled documents must be maintained in an organized fashion so that all current documents can be found. Many Clinical Programs have adopted an electronic method of compiling their controlled documents. Also, institutions may build standardized forms and ordering systems within electronic health records, but it is still the Clinical Program's responsibility to have a detailed list of those controlled documents, along with instrumental input in their development and maintenance.

Evidence:

The detailed list should be organized in such a manner that the inspector can ascertain that the controlled documents are comprehensive and define all aspects of the Clinical Program.

Example(s):

A Clinical Program may choose to have one detailed list of controlled documents or divide controlled documents into several manuals by subject. A technical procedure manual in conjunction with quality, policy, and database manuals may serve to better organize information if the program chooses this format.

STANDARD:

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

Explanation:

Policies and SOPs must be detailed, unambiguous, and adequately define all operational aspects of the Processing Facility. Policies in general should identify an intended goal and include the elements required to meet that goal. However, policies may need one or more associated SOPs to actually describe the actions that are taken. The minimal elements must be included in all SOPs; if one of the items is not applicable, this should be indicated with N/A.

Evidence:

Compliance with most of the Standards in this section can be determined before the on-site inspection by review of the document control system and submitted SOPs contained within the pre-inspection material. However, additional SOPs should be reviewed during the inspection for compliance.

Example(s):

In some Clinical Programs, the actual "SOP" may be limited to minimal work instructions, and required elements such as a reference list may be found only in higher level documents. Such variability is acceptable if all elements are documented and readily available to staff. [*The Art of Writing and Implementing Standard Operating Procedures \(SOPs\) for Laboratories in Low-Resource Settings: Review of Guidelines and Best Practices*](#) describes suggested practices for writing SOPs (Barbé, Verdonck, Mukendi, et al. *PLoS Negl Trop Dis.* 2016;10(11):e0005053). Adherence to a uniform format is required to maintain documents.

STANDARD:

B5.3.1 A clearly written description of the objectives.

B5.3.2 A description of equipment and supplies used.

B5.3.3 Acceptable endpoints and the range of expected results.

B5.3.4 A stepwise description of the procedure.

B5.3.5 Reference to other policies or Standard Operating Procedures required to perform the procedure.

STANDARD:

B5.3.6 Issues related to age, sex, height, and weight, as applicable.

Explanation:

Pediatric and geriatric recipients and donors require adjustments that address issues of co-morbidity, age, and size of the donor. Depending on the age range of recipients and donors treated in the program, Clinical Programs should be able to demonstrate the processes by which age-specific issues are addressed. A Clinical Program that collects a cellular therapy product from a minor donor must have appropriate SOPs that address at least issues of informed consent, donor size, and venous access. A program that includes geriatric patients should perform geriatric assessments.

Example(s):

Examples of age-specific issues include total parenteral nutrition guidelines, blood product administration volume for pediatric recipients, delirium management, geriatric evaluation service, and medication management.

For example, a program admitting Adolescent and Young Adult patients should demonstrate processes that accommodate the psychological, educational, family, and social needs of this age group, including routine peer group contact. Information on working with adolescents and young adults with cancer can be found at <https://www.cancer.gov/types/aya>.

Geriatric recipients (greater than 65 years of age) should have appropriate assessment and access to rehabilitation and social support. The article [Integrating Geriatric Assessment into Cancer Care: A Conversation with Dr. Supriya Mohile](#) (National Cancer Institute, 2018) provides information on caring for the geriatric patient.

STANDARD:

B5.3.7 A reference section listing appropriate and current literature.

B5.3.8 Documented approval of each Standard Operating Procedure by the Clinical Program Director or designated physician prior to implementation and every two (2) years thereafter.

Explanation:

The intent is to be reflective of programmatic SOPs. For example, nursing procedures or institutional procedures have to be reviewed by the Program Director. SOPs are to be reviewed and approved at a minimum every two years but may require more frequent assessment based on new developments or organizational needs.

STANDARD:

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.

Explanation:

Although the FACT-JACIE Standards indicate that an individual designated by the Clinical Program Director may review SOPs every two years, the director remains ultimately responsible for this process. The designated individual should be qualified to review SOPs. If a process changes, the SOP must be updated at that time and reviewed before the changes are implemented; unchanged SOPs must be reviewed at a minimum every two years. Approving several SOPs at once with a single signature and date is not sufficient, as it does not demonstrate that individual SOPs were actually reviewed and approved.

Current versions of worksheets, reports, labels, and forms, where applicable, must be identified in or attached to each SOP as paper copies or via electronic links. The Clinical Program may use the format of its choice, as long as all listed elements are present. The purpose of this Standard is to ensure that these documents are easily accessible to a reader of the SOP and that it is clear which documents may be required for the performance of that SOP. Review of SOPs should include review of the applicable worksheets, forms, and attachments.

Evidence:

Review of SOPs can be documented in several ways, including but not limited to:

- Signature and date on each individual SOP.
- Signature and date for each title and version of individual SOPs listed on a master document.
- Electronic approval via an authenticated electronic document management system.

Orders, worksheets, etc. can be referenced rather than included in the actual SOP as long as the forms are under document control and can be easily accessed by personnel and presented to the inspector on request. The Standards do not prescribe that a review date must appear on a document printed from an electronic document management system; however, the document control system must be validated so that printed documents are the current implemented versions. Such a system would archive obsolete versions or have a method to convey the printed version is an archived version (e.g., watermark).

Example(s):

In some Clinical Programs, the actual SOP may be limited to minimal work instructions, and required elements such as a reference list may be found only in higher-level documents. Such variability is acceptable if all elements can be found within the associated controlled documents.

Though not required, the Clinical and Laboratory Standards Institute standard format can be useful in preparing these SOPs (see <https://clsi.org/> for more information). Some Clinical Programs may utilize a format consistent with ISO (International Organization for Standardization) 9000 in which all documents, policies, SOPs, and work instructions exist in a specific hierarchy. In this case, the inspector must be certain to review all relevant documents.

STANDARD:

B5.4 Controlled documents relevant to the processes performed shall be readily available to the facility staff.

Explanation:

The written copy or electronic version (with provision of hard copy as necessary) of the Clinical Program's controlled documents must be immediately available to all relevant employees in their working environment(s). There must be only one source document created from which review occurs. Any copies of policies and SOPs must be identical to the source document and must not be used to alter, modify, extend, delete, or otherwise edit any SOP.

If an electronic manual is used, there must be a mechanism to access the manual at all times, even if the network is not available.

Evidence:

The written copy or electronic version of the SOPs should be readily identifiable to the inspector. The inspector should expect to see the SOP manual or electronic access to SOPs in all performance areas of the Clinical Program. These include all locations of sustained patient care (inpatient and outpatient facilities). The SOPs should be organized in such a manner for the inspector to ascertain that the SOPs are comprehensive, defining all aspects of the Clinical Program.

STANDARD:

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

Explanation:

Before a staff member is allowed to perform new and revised procedures, they must have reviewed or received the applicable training. Clinical Programs are not required to train all staff members before implementing a new policy or SOP, but they must document an individual's review or training before that person uses the revised policy or SOP.

Evidence:

Documentation that approved and implemented policies or SOPs are performed only after the individual staff member has reviewed and been trained on the new or revised procedure should be reviewed by the inspector.

Example(s):

Sometimes a revision to a policy or SOP is minor, such as an update to a referenced regulation or grammatical corrections. In these cases, full training may not be necessary, and review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

It is recommended that every policy and SOP and associated revisions have a specific signoff sheet to document that each staff member required to review the policy or procedural revision has done so prior to performing the task(s) described. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each procedure and to any major revision also facilitate documentation of appropriate training of staff.

STANDARD:

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

Evidence:

The inspector should observe on site that procedures are performed according to the written policies or SOPs.

STANDARD:

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

Explanation:

Planned deviations should be approved by the Clinical Program Director at a minimum. Retrospective review by the Quality Manager must be performed in compliance with processes designed for deviations. Processes set up for review of planned deviations are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately.

Example(s):

Planned deviations may be necessary in the following scenarios:

- Changing the scheduled date and/or time of a scheduled cell infusion.
- Infusing a product outside of SOP-defined time limits.
- Use of alternative thawing procedure(s).

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

STANDARD:

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

Explanation:

The Clinical Program must have in place written SOPs defining all donor-related aspects including:

- Identification.
- Evaluation.
- Selection.
- Criteria for clearance.
- Management, including identification of the personnel responsible for each aspect (when in the control of the program).

This policy should include the number of cellular therapy product donations permitted by a single (related and unrelated) donor. Clinical Programs performing allogeneic transplantation should endeavor to receive only voluntary and unpaid donations of cells. Donors may receive reimbursement such as expenses for travel, housing, and other incidentals related to the donation. This is based on national and international standards for donation. Patient identification and consent processes in the EU must comply with [Directive 2006/86/EC](#) to ensure traceability and biovigilance.

Evidence:

The inspector may ask to verify compliance with the criteria by reviewing a specific donor evaluation.

Example(s):

Examples of written criteria for allogeneic donors include:

- Infectious disease markers obtained within the appropriate time frame before collection from a donor.
- Criteria for an ineligible but acceptable donor (e.g., an international donor may be ineligible but acceptable if all other donor criteria are fulfilled).
- The number of times a sibling donor can donate cells.
- The role of the donor advocate.

STANDARD:

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

Explanation:

The term “older donors” in this Standard is left to the interpretation of the Clinical Program and can be related to the treatment, protocol, or situation.

STANDARD:

B6.1.2 Allogeneic and autologous donors shall be collected at a collection site with the appropriate capabilities to manage the level of acuity and risks from comorbidities.

Explanation:

The Standard does not require that all collection sites be equivalent. Some collection sites may be within an inpatient hospital or in an outpatient clinic; others may be free-standing collection sites. Furthermore, Collection sites may vary in capabilities, capacity, potential for donor isolation, staffing, access to transfusion services, interventional radiology, or support for pediatric patients. Some collection sites may be relatively distant from the main facility and be most appropriate for collections from healthy adult donors without CVCs.

The intent of this Standard is that the Clinical Program must be aware of what type of donors can be safely managed at each collection site and refer donors to an appropriate place for their individual needs. Variables to consider should include, at a minimum, expertise in central venous line management, expertise in pediatrics, availability of blood components if needed for priming an apheresis device, and ready capability to manage comorbidities such as obesity, cardiac dysfunction, or hypertension. It is acceptable to limit certain sites to specific types of donors.

Evidence:

The donor criteria for each collection site should be documented in the facility’s QM plan, specific site description, or elsewhere.

Example(s):

The following are example statements that could indicate criteria for a collection site:

- Capable of managing co-existing comorbidities.
- Capable of managing allogeneic or autologous donors.
- Capable of managing donors with a central line.
- Capable of managing patients receiving a mobilization regimen.

STANDARD:**B6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT FOR COLLECTION**

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

Explanation:

The informed consent content and process are determined by the law in the jurisdiction of the Clinical Program. The SOP for obtaining consent from donors must comply with Applicable Law.

The essential elements of informed consent are that donors are educated in terms they can reasonably be expected to understand and in their native language, via an approved interpreter when indicated. Important aspects to discuss in the informed consent are:

- Reasons for the proposed procedure.
- Risks associated with the treatment or procedure.
- Benefits of the procedure.
- Alternative collection methods.

While the transplant physician selects the preferred product, the donor must be informed that alternative collection methods exist. In addition, the donor should be given the opportunity to ask questions and to have those questions answered to their satisfaction. Informed consent is to be documented according to institutional standards and criteria and should be easily audited.

The information contained in the informed consent must be given by a trained person able to transmit it in an appropriate and clear manner, using terms that are easily understood. The health professional must confirm that donors have done the following:

- Understood the information provided.
- Had an opportunity to ask questions and been provided with satisfactory responses.
- Confirmed that all the information they provided is true to the best of their knowledge and documented in the medical record.

Evidence:

If a standardized consent form delineating all of the required elements is not used, the provider note must detail all required elements of consent.

Example(s):

This process may take place over several visits. A preprinted consent form detailing all of the above elements is an easy method of documentation; however, informed consent does not specifically require such a form.

It is recommended that the consent process be documented in the donor's medical record by the consenting provider. In addition, it is recommended that a copy of the informed consent document be offered to the donor.

Informed consent requirements of the WMDA or NMDP may be more detailed, and Clinical Programs facilitating unrelated transplants should consult those current requirements.

STANDARD:

- B6.2.1.1 The risks and benefits of the procedure.*
- B6.2.1.2 The intent of the collection for treatment or research.*
- B6.2.1.3 Tests and procedures performed on the donor or donor's specimens to protect the health of the donor and the recipient.*
- B6.2.1.4 The rights of the donor or legally authorized representative to review the results of such tests according to Applicable Law.*
- B6.2.1.5 Protection of medical information and confidentiality.*
- B6.2.1.6 Alternative collection methods.*
- B6.2.2 If the Clinical Program is the entity obtaining consent for the collection procedure, the informed consent for the cellular therapy product donation shall be obtained and documented by a licensed health care professional knowledgeable in the collection procedure and the intended use of the product.*

Explanation:

This Standard does not imply a situation where consent is not obtained but rather serves to clarify that if the Clinical Program is the entity that is obtaining consent, such consent must be obtained and documented by a licensed health care professional knowledgeable in the collection procedure and the intended use of the product.

STANDARD:

- B6.2.2.1 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.*

Explanation:

In the allogeneic setting, to prevent conflict of interest that may exist when a physician or other health care provider cares for both the donor and the recipient, the donor's consent must be

received by a member of the team other than the primary health care professional of the intended recipient.

STANDARD:

B6.2.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.

B6.2.2.3 Family members and legally authorized representatives shall not serve as interpreters or translators.

Explanation:

The intent of this Standard is for interpretation and translation related to consent process for relevant medical care. For family member conversations not related to care, institutional policies should be followed.

There may be instances where a translator is unavailable for a rare language or dialect. This occurrence must be documented, and an explanation must be provided in accordance with the requirements in [B4.11](#).

STANDARD:

B6.2.2.4 The donor shall have an opportunity to ask questions.

B6.2.2.5 The donor shall have the right to refuse to donate or withdraw consent.

B6.2.2.6 The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal in the event that consent is withdrawn after the recipient has begun the preparative regimen.

Explanation:

The right to refuse to donate and the right to withdraw consent are two separate concepts. Refusing to donate is prior to ever consenting to the donation, while withdrawing consent occurs after the consent to the donation has already been given. This Standard is not meant to be coercive, but to require full disclosure of the effects a donor's decisions have on a recipient. Donors shall be informed that the consequences of the donor's refusal to donate for the recipient are significantly different depending on the stage of transplant. If the potential donor declines prior to typing versus refusing after selection and the day before the administration, then the degree of risk incurred to the recipient will be very different.

STANDARD:

B6.2.2.7 In the case of a donor who is a minor or who does not have the capacity to consent, informed consent shall be obtained from the donor's legally authorized representative in accordance with Applicable Law and shall be documented.

Explanation:

Donors must be of legal age of consent (in the jurisdiction of the collection), or the informed consent for donation must be signed by their legally authorized representative. Specific consent is required for the use of growth factors in a minor, allogeneic donor. It is appropriate to discuss the donation procedure with the pediatric donor in terms they can understand. Institutional policy should guide providers in how to define and determine the donor's capacity to consent.

In the event that the legally authorized representative is the potential recipient, an alternative donor advocate should be appointed. There may be other Applicable Laws that apply.

Clinical Programs must be compliant with institutional policy and governmental laws when addressing issues of assent of a minor who may be unwilling to donate. The age of assent and consent varies depending on the legal jurisdiction. Conferring with appropriate legal counsel is indicated in complex cases.

Evidence:

Inspectors may review one or more signed consent forms from minor donors. If the informed consent process is performed verbally, the clinic note must detail discussion of the protocol, including the documentation of required elements consistent with institutional policy and Applicable Law.

Example(s):

It is appropriate to discuss the donation procedure with the pediatric donor in terms they can understand. For minor donors, although consent is obtained from legally authorized representatives in accordance with local regulations and Applicable Law, assent should also be obtained in an age-appropriate manner. It may be helpful to include a child life specialist, a social worker, or another qualified individual in the consent process to determine whether the minor donor has age-appropriate understanding.

STANDARD:

B6.2.2.8 There should be a process to obtain appropriate assent from minor donors.

Explanation:

There are jurisdictions where informed consent may be obtained from minor donors; however, this Standard is the minimum expected. The Clinical Program should define the parameters for obtaining assent. Applicable Law may allow additional documentation when attaining assent for a minor.

STANDARD:

B6.2.2.9 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient or the recipient's physician.

Explanation:

The purpose of this Standard is to protect donor confidentiality regarding their health information and appropriateness to donate. Factors that determine whether or not it is appropriate to select a potential donor include HLA matching, eligibility (i.e., lack of a communicable disease risk), suitability (medical fitness to undergo the collection procedure), and desire to donate their cells. Donors do have the option to specifically limit disclosure of certain information upfront. Release of health information to the recipient is only required after donor selection.

The consent procedure for the recipient should inform them of the right to review their own testing results and the relevant testing and screening results of the selected donor only. The recipient does not have the right to review all health information, including the HLA typing of siblings or other potential donors who are not considered for transplant.

Evidence:

Documentation of donor informed consent and recorded authorization to release relevant donor health information may be used as evidence of compliance. The date informed consent was obtained in relation to the date the release of the donor's health information occurred will be compared.

Example(s):

It is acceptable to obtain informed consent and authorization to release this information after donor screening and testing as long as it is obtained prior to sharing the results and prior to the collection. If a potential donor is screened but is deemed not to be suitable for collection, donor health information related to this decision does not need to be released to the potential recipient.

STANDARD:

B6.2.2.10 The donor shall be informed of the policy for cellular therapy product storage, discard, or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product.

Explanation:

Policies may differ between institutions and donor registries as to the outcome of a donated cellular therapy product that is not or is only partially used for a cellular therapy procedure. It is important that the donor be informed of these policies at the time of donation.

Evidence:

The inspector should review the information provided to the donor regarding cellular therapy product storage and discard.

Example(s):

Many facilities consider that the donated cells become the property of the intended recipient since donation was for the recipient's use. Registries that facilitate unrelated transplants may have specific requirements for what information must be provided to the donor regarding cellular therapy product discard.

STANDARD:

B6.2.2.11 Documentation of consent shall be available to the Collection Facility staff prior to the collection procedure.

B6.3 SUITABILITY DETERMINATION FOR ALLOGENEIC AND AUTOLOGOUS DONORS

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

Explanation:

Donor suitability refers to issues related to the general health of the donor and protection of donor safety. The criteria and evaluation SOPs must account for the entire collection process from initial evaluation and mobilization (where applicable) to collection, anesthesia, and post-collection care.

Example(s):

To avoid overlooking important information, especially in larger Clinical Programs, the facility could have a separate document that highlights major concerns and ensure that this document is distributed to the individuals performing the cellular therapy product collection.

Vulnerable donors (e.g., children) and donors at increased medical risk from donation (e.g., those with cardiac disease) are examples for when donor suitability assessment is crucial.

The HCT Comorbidity Index is a useful tool for determining if any comorbidities put donors at unacceptable risk. The resources below provide additional information about the HCT Comorbidity Index, followed by an example of the calculation tool itself:

- Berro M, Bittencourt H, Oliveira MP, Dulley FL, Saboya R, Arrais CA, et al. [Hematopoietic Cell Transplantation–Specific Comorbidity Index predicts morbidity and mortality in autologous stem cell transplantation](#). *Biol Blood Marrow Transplant*. 2017;23(10):1646–1650.

- Thakar MS, Broglie L, Logan B, Artz A, Bunin N, Burroughs LM, et al. [The Hematopoietic Cell Transplant Comorbidity Index predicts survival after allogeneic transplant for nonmalignant diseases](#). *Blood*. 2019;133(7):754–762.
- Sorrow M. [Hematopoietic Cell Transplantation–Specific Comorbidity Index \(HCT-CI\)](#). MDCalc.

STANDARD:

B6.3.1.1 The Clinical Program shall confirm that clinically significant findings are reported to the prospective donor with documentation in the donor's record of recommendations made for follow-up care.

Explanation:

Clinically significant findings in a donor, including, but not limited to testing and physical evaluation results, may have important implications for the donor apart from their role in the collection process. Appropriate care of the donor requires that clinically significant abnormalities be communicated to them and that recommendations be made for follow-up care. These actions should be documented in the individual's medical record.

Evidence:

The inspector may need to specifically request a record of a prospective donor undergoing collection who had abnormal findings, since this may not be a common occurrence in many Clinical Programs. Review of a chart from an ineligible donor will aid in verification of documentation of abnormal results.

Example(s):

For donors with abnormal test results, it is recommended that appropriate follow-up evaluations be completed or that a referral be made to an appropriate physician.

STANDARD:

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.

Explanation:

A physician or health care professional other than the recipient's primary care provider must perform the donor suitability evaluation to minimize potential bias of the recipient's health care professional(s). This individual should have knowledge of the risks of the donation procedures.

Medical literature supports the idea that having the allogeneic donor evaluated by a physician or health care professional who is not the primary health care provider of the recipient decreases the

potential conflict of interest with regard to the health and safety of the recipient and the donor (van Walraven, Nicoloso-de Faveri, Axdorph-Nygell, et al. [Family donor care management: principles and recommendations](#). *Bone Marrow Transplant*. 2010;45(8):1269–1273). Furthermore, the American Academy of Pediatrics (AAP) and the ASTCT recommend this practice for related donations.

Evidence:

The Clinical Program's policy on donor evaluation and medical charts can be used to verify that an individual other than the recipient's primary licensed health care professional evaluates the donor for suitability.

Example(s):

A potential donor could be evaluated by another attending physician of the Clinical Program; however, programs are not required to have sufficient staffing to evaluate donors using their own attending physicians. Small programs may not have enough attending physicians to separately evaluate donors within their own programs. Physicians and licensed health care professionals outside of the program may perform this function, including a clinician who is a member of a different program, the donor's primary care physician (if they possess knowledge of the donation procedure), a general internal medicine clinic, or a clinic not directly associated with the program.

STANDARD:

B6.3.1.3 Autologous donors shall be evaluated and tested as required by Applicable Law.

Explanation:

Testing or screening of autologous donors in connection with cellular therapy product collection is not required by the Standards. However, testing required by local laws or regulations is required.

Clinical Programs may choose not to test autologous donors for infectious diseases or disease agents for their safety, or they may choose to test autologous donors with diagnostic tests. Positive screening tests for autologous donors must have the appropriate warning statements on their labels. It is important for the program to notify the Processing Facility so that the final product can be labeled in accordance with the Standards and Applicable Law.

STANDARD:

B6.3.2 The risks of donation shall be evaluated and documented, including:

B6.3.2.1 Possible need for central venous access.

Explanation:

Appropriate care should be taken to protect donor safety when a CVC is inserted solely for a collection procedure and that collection extends over more than one day. Donors need to be

assessed for the risks of CVCs, including significant complications such as hematomas, pneumothorax, hemothorax, and bacterial infections.

Example(s):

The WMDA Serious (Product) Events and Adverse Reactions (S[P]EAR) Committee has provided recommendations for policies in response to reported adverse events ([Document Reference: 0110824-CLWG-SEAR-August 2011, Version: 2](#)):

- Stem cell donor registries should review their policies concerning the placement of CVCs.
- If a stem cell donor registry does not have a policy concerning CVC placement, one should be written.
- Insertion of a CVC for PBSC collection should only be used in exceptional circumstances (i.e., only when peripheral venous access is not deemed feasible after skilled assessment or cannot be obtained or has failed).
- The policy should cover, at a minimum, the need for the following:
 - Requirement for careful peripheral venous assessment at the time of donor medical evaluation.
 - Evidence that alternative methods of donation have been discussed if appropriate.
 - Written justification for placement of a CVC.
 - Consenting procedures (and counselling) for CVC insertion, including who should obtain informed consent.
 - Qualifications and expertise of the person(s) permitted to insert the CVC.
 - Permissible sites for CVC insertion.
 - The requirement for radiological guidance for all CVCs inserted above the umbilicus, if locally available.
 - The need for care for all patients with CVCs, cared for by appropriately trained personnel.
 - The requirement for reporting adverse events or serious adverse events.

STANDARD:

B6.3.2.2 Anesthesia for cell or tissue collection.

Explanation:

Collection of HPC, Marrow or other tissue requires that evaluation occur for any medical condition that would expose the donor to the risk of the procedure including the need for anesthesia. This evaluation must be documented.

Evidence:

The donor's medical records for pre-collection workup results will contain evidence of compliance.

STANDARD:

B6.3.2.3 Mobilization for cell collection.

Explanation:

Mobilization requires that evaluation occur for any medical condition that would expose the donor to increased risk due to the mobilization agents (e.g., thrombotic events). This evaluation must be documented, including the pre-collection and collection time frames specific to growth factor administration.

Granulocyte colony-stimulating factor (G-CSF) is not advised for mobilization in patients with sickle cell disease or complex hemoglobinopathies. See [B6.3.6](#).

Evidence:

The donor's medical records for pre-collection workup results will contain evidence of compliance.

STANDARD:

B6.3.2.4 Other donor-specific risks.

Explanation:

The purpose of this Standard is to evaluate the donor for potential risks associated with the collection, such as anesthesia for collection of HPC, Marrow or central line placement. This evaluation is generally the responsibility of the Clinical Program, but the Collection Facility is responsible for verifying that appropriate testing and evaluation has been performed.

There should be a mechanism for independent review of suitability for vulnerable donors (e.g., children) and for donors at increased medical risk from donation (e.g., those with cardiac disease). The rationale and medical necessity should be discussed with the donor and recipient and documented within both medical records.

STANDARD:

B6.3.3 General or regional anesthesia, if required, shall be performed or supervised by a health care provider licensed and credentialed to administer anesthesia.

Explanation:

For patients requiring general or regional anesthesia during cellular therapy procedures, the anesthesia must be administered or supervised by a qualified healthcare provider who is both licensed and credentialed to administer anesthesia, such as an anesthesiologist or a qualified nurse anesthetist under appropriate supervision. This maintains patient safety and optimal outcomes during these complex procedures.

STANDARD:

B6.3.4 Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in the administration of these agents and management of complications in persons receiving them.

B6.3.4.1 Appropriate mobilization shall be used for the disease being treated and for the donor being collected.

Explanation:

Administration of hematopoietic mobilization agents is not free from side effects. There are reports of serious morbidity and mortality among recipients of hematopoietic growth factors. A licensed health care professional who is trained in dealing with complications of G-CSF must supervise its administration. Supervision can be exercised either directly, especially during the first injection, or indirectly (e.g., via phone contact with nursing personnel) for the subsequent injections, especially if self-administration is considered. The interim assessment of donor symptoms related mobilization agents and relevant laboratory tests should be performed, and dose adjustments made accordingly.

Evidence:

The inspector should verify that the licensed health care professional supervising administration of mobilizing agents is experienced in recognizing adverse reactions due to mobilization agents. When appropriate, donor side effects potentially attributable to mobilization agents should be reviewed by the inspector.

Example(s):

The patient record should show the doses of the mobilization agents to be administered and the person administering the agent.

G-CSF is not advised for mobilization in patients with sickle cell disease or complex hemoglobinopathies. See [B6.3.6](#).

STANDARD:

B6.3.5 A pregnancy test shall be performed for all donors with childbearing potential:

B6.3.5.1 For collections with mobilization, within seven (7) days prior to starting the donor mobilization regimen or undergoing anesthesia and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.

B6.3.5.2 For collections without mobilization, within seven (7) days prior to cellular therapy collection and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.

Explanation:

Pregnancy testing is required since the donation of cells from marrow or peripheral blood and anesthesia may pose a risk to the fetus. The intent is to confirm the donor is not pregnant before the initiation of the mobilization agent or administration of anesthesia and before the recipient starts the conditioning regimen. Childbearing potential is meant to include all donors ages, puberty through menopause, unless there is some definite medical indication that pregnancy is impossible (e.g., a past hysterectomy). The Clinical Program will define its policies for continuing with the collection when consent for the pregnancy test is refused.

The purpose of the required time frame is to prevent donor mobilization and recipient conditioning from occurring before finding out that the donor is pregnant. There are some obvious situations in which pregnancy testing would not occur within seven days prior to recipient conditioning. For example, if a cellular therapy product is collected from the donor and subsequently cryopreserved for administration weeks later, the donor does not have to be retested for pregnancy. However, if a recipient is on a 21-day conditioning regimen, a pregnancy test must be performed within seven days prior to beginning that regimen. The Clinical Program must be aware of situations where donor pregnancy screening may need to occur more than seven days in advance.

Evidence:

The inspector may look for the process or documentation of pregnancy testing of the donor.

Example(s):

In women determined to have potential for becoming pregnant (post/peri-pubertal, pre-menopausal females who have not undergone hysterectomy), a pregnancy test is required; serologic assays for human chorionic gonadotropin (HCG) or urine pregnancy tests should be used.

If a cellular therapy product is collected from the donor and subsequently cryopreserved for administration weeks later, the donor does not have to be retested for pregnancy.

If the recipient undergoes a preparative regimen for a long duration, a pregnancy test must be performed within seven days prior to beginning the regimen. The donor must be retested prior to collection to confirm there is no change in pregnancy status.

STANDARD:

B6.3.6 The donor shall be evaluated for the risk of hemoglobinopathy and, if indicated, tested.

B6.3.6.1 The evaluation shall occur prior to donor selection.

B6.3.6.2 The evaluation shall be verified prior to collection or administration of the mobilization regimen, if used.

Explanation:

Hemoglobinopathy assessment is required since administration of mobilization agents such as G-CSF may pose a risk to the donor as it was associated with morbidity (e.g., vaso-occlusive crisis) and mortality in donors with sickle cell disease (HbSS, HbSC), and also with compound hemoglobinopathies such as sickle beta-thalassemia (S/β thal). Testing is not required; however, if testing is not performed, the inspector should look for a thorough family history to evaluate the risk. The Clinical Program is to define how donor risk is evaluated.

Of note, medical literature reports that donors with sickle trait have been safely mobilized and collected. Although donors with the sickle trait did have higher symptom scores than control donors, there were no symptoms suggestive of sickle crisis. Thus, in this group, the risk is limited. References include:

- Fitzhugh CD, Hsieh MM, Bolan CD, Saenz C, Tisdale JF. [Granulocyte colony-stimulating factor \(G-CSF\) administration in individuals with sickle cell disease: time for a moratorium?](#) *Cytotherapy*. 2009;11(4):464-471.
- Rosenbaum C, Peace D, Rich E, Van Besien K. [Granulocyte colony-stimulating factor-based stem cell mobilization in patients with sickle cell disease.](#) *Biol Blood Marrow Transplant*. 2008;14(6):719-723.
- Kang EM, Areman EM, David-Ocampo V, Fitzhugh C, Link ME, Read EJ, et al. [Mobilization, collection, and processing of peripheral blood stem cells in individuals with sickle cell trait.](#) *Blood*. 2002;99(3):850-855.

Evidence:

The inspector may look for the process or documentation of risk evaluation in the donor. For example, hemoglobinopathy risk evaluation might include a relevant question in the Donor History Questionnaire.

Example(s):

Hemoglobinopathy risk assessment may include testing for the detection of Hemoglobin S (e.g., Sickle Dex) or an Hb-electrophoresis test, but a test is not required. An assessment may be performed by looking at the donor's medical history.

STANDARD:

B6.3.7 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, certified, or licensed in accordance with Applicable Law.

Explanation:

All laboratory tests must be performed by a laboratory accredited for the relevant tests.

Example(s):

Examples of relevant accreditation organizations include CLIA, CAP, ASHI, AABB, Joint Commission, CMS, EFI, United Kingdom Accreditation Service, and Royal College of Pathologists of Australasia.

STANDARD:

B6.3.8 The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.

B6.3.9 There shall be a written order from a physician specifying, at a minimum, anticipated date and goals of collection and processing.

B6.3.10 Collection from a donor who does not meet donor suitability criteria shall require documentation of the rationale for donor selection by the donor's physician and approval by the Collection Facility Medical Director.

Explanation:

These Standards require that donor data is reviewed prior to collection and that there is documentation in the record that the donor is appropriate for the intended recipient and is suitable to undergo the collection procedure. Critical factors impacting donor suitability must be included in the documentation (e.g., age, weight, co-morbidities).

Autologous donors in particular may have health-related issues that need to be known by Collection Facility staff in order to maximize the safety of the collection procedure. This information is important enough that it needs to be clearly communicated in writing in advance of the procedure so that appropriate precautions are taken.

Example(s):

Clinical Programs may include information regarding donor health issues on the collection order form, or they may communicate needed information by a documented note in the collection chart record. Such records may include the electronic medical record.

STANDARD:

B6.3.10.1 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.

Explanation:

Communication between the Clinical Program and the Collection Facility that pertains to the safety of the collection procedure must be in writing. Simply having access to a clinical note in an electronic health record is not sufficient or intuitive; therefore, the communication must be directed to the Collection Facility.

Evidence:

The inspector can review the method(s) used to convey the health status of the donor to the Collection Facility Staff and ask to review the SOP regarding donor follow-up.

STANDARD:

B6.3.11 There shall be written guidelines for communication between the Clinical Program and the Collection Facility or registry for the management of collection-related complications.

Explanation:

In the event of collection-related complications or post-donation events relevant to recipient safety, the Clinical Program must have guidelines for communication with both the Collection Facility and the registry.

STANDARD:

B6.3.12 There shall be policies or Standard Operating Procedures for the management of collection-associated adverse events and follow-up of donors.

B6.3.12.1 There shall be a process to track and trend collection-associated adverse events.

Explanation:

There should be a policy that provides guidelines for the post-collection care of donors. All donors should be monitored closely following the collection procedure.

Donor follow-up following the collection procedure can help to ensure donor safety and address collection-associated adverse events. These events should be assessed via a collaborative approach between the Clinical Program and Collection Facility and be addressed in accordance with the Clinical Program's QM Plan and shared with key stakeholders.

It is recommended that related donors are registered (e.g., EBMT, WMDA) and adverse events are recorded.

Example(s):

The World Health Organization *Guiding Principles of Human Cell, Tissue and Organ Transplantation* ([Guiding Principle 10](#)) recommends long-term follow-up of donors.

[*Allogeneic hematopoietic stem cell donation-standardized assessment of donor outcome data: a consensus statement from the Worldwide Network for Blood and Marrow Transplantation \(WBMT\)*](#) provides additional recommendations for donor follow-up (Halter, van Walraven, Worel, et al. *Bone Marrow Transplant*. 2013;48(2):220-225).

STANDARD:

B6.4 *ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS*

B6.4.1 Written criteria shall include criteria for the selection of allogeneic donors when more than one (1) donor is available and suitable.

B6.4.2 Information regarding the donation process, including the considerations for donation, should be provided to the potential allogeneic donor prior to HLA typing.

Explanation:

Sufficient information for allogeneic donors should be provided before the potential donor undergoes HLA typing to protect them from undue pressure should they be the only suitable donor. The Clinical Program may not always have control over the allogeneic donor consent process, but it should attempt to provide information to the donor if possible or review available documentation to verify that the donor received such information.

Considerations for donation may require a minimal health screening to determine if the donor is suitable (e.g., determine if the donor is pregnant, has an autoimmune disorder, cancer).

Example(s):

A full informational session regarding the donation process is not required to meet this Standard. Other acceptable methods include, but are not limited to, a brochure, pamphlet, or telephone conversation. Unrelated donor registries may be useful sources of information, such as the information on the websites of the [NMDP](#) and [Anthony Nolan](#).

STANDARD:

B6.4.3 A donor advocate shall be available to represent allogeneic donors who are minors or who do not have the capacity to give consent, as those terms are defined by Applicable Law.

Explanation:

A donor advocate is an individual distinct from the recipient's primary treating physician whose primary obligation is to help the donor understand the risks and benefits of donation and to promote the interests, well-being, and safety of the donor. The role of the advocate is to help safeguard that the consent is made without time pressure and with full information, to enhance the personal attention given to the donor during all procedures, to help prevent unnecessary inefficiencies and discomfort, to mobilize official expressions of gratitude after the donation, and to aid in the resolution of subsequent problems.

Donor advocates do not need to be routinely appointed for all donors who are not capable of full consent (such as donors who are minors or who are mentally incapacitated). However, a donor advocate process must be available at the Clinical Site, and donor advocates must be utilized with minor donors when the conditions necessary for minors to participate as donors are at risk of not being met (see circumstances below). In these circumstances, the donor advocacy role should be documented and should not be fulfilled by an individual involved in the recipient's care.

Evidence:

For Clinical Programs using minor or mentally incapacitated donors, there must be documentation that a donor advocate was involved in the donor assessment process in circumstances when the conditions necessary for minors to participate as donors are at risk of not being met. Circumstances in which a donor advocate should be considered during the minor donor assessment process include, but are not limited to, when:

- A potential donor is deemed to be at increased risk for physical injury due to the collection process.
- A potential donor may not experience psychological benefit from donating, such as might occur when the potential donor does not have an established relationship with the recipient, is not in the same household as the recipient, or is estranged from the family/recipient. Specific examples that illustrate this circumstance might include a donor who is emotionally distant from the recipient (e.g., a stepbrother who has never met the recipient) or when a possibly abusive relationship exists between the recipient and donor.
- A potential donor expresses in words or actions opposition to participation.
- A request for donation is made by the family or healthcare team.

Example(s):

Examples of donor advocates include chaplains, patient advocates, and social workers. The article [Family Donor Care Management: Principles and recommendations](#) provides recommendations for donor advocacy in the related transplant setting (van Walraven, Nicoloso-de Faveri, Axdorph-Nygell, et al. *Bone Marrow Transplant*. 2010;45(8):1269-1273). The ASTCT is also a source of information.

In the UK, the HTA provides guidance on third-party patient advocates in [Code G: Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation](#). This Code provides supplementary guidance to clinicians working in the field of allogeneic bone marrow and PBSC transplantation and HTA Accredited Assessors.

When Applicable Laws define donor advocate and specific requirements, those must be followed.

STANDARD:

B6.4.4 Allogeneic donor infectious disease testing shall be performed using donor screening tests licensed, approved, or cleared by the governmental authority.

Explanation:

Donors are often asymptomatic, and infectious disease tests must be sensitive enough to produce a positive result when a disease has not yet manifested in the donor. In some countries, the relevant governmental authorities may require use of approved or cleared tests for any tests performed in their jurisdiction, even if the recipient is in a different country. If such tests are not used, the donor eligibility is considered incomplete, but the donor may be used provided that all requirements for urgent medical need in the recipient's country are met. There may be countries where this requirement is not applicable. In the U.S., tests specifically licensed for donor screening must be used according to manufacturer's instructions.

Evidence:

The inspector will look for infectious disease markers testing results and verify they were performed according to Applicable Law. There may be regions where this requirement is not applicable.

STANDARD:

B6.4.4.1 Hemodilution in the donor prior to collection of blood samples for infectious disease testing should be assessed, and acceptance criteria should be defined.

Explanation:

Hemodilution could affect the results of communicable disease testing, and the Clinical Program may need to assess if the donor's blood is too diluted for testing. The scope of the FACT-JACIE Standards includes all donors, both living and cadaveric. [Eligibility Determination for Donors of](#)

[Human Cells, Tissues, and Cellular and Tissue-Based Products](#) (2007) states that transfusion or infusion might dilute plasma from a donor blood specimen, making test results unreliable. In January 2025, the FDA released additional draft guidance: [Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](#). A specimen taken before the transfusion or infusion may be tested, or if an adequate pretransfusion/infusion specimen is not available, an appropriate algorithm to determine whether plasma dilution is or is not sufficient to affect test results may be used. In the absence of an appropriate specimen to test under either of these options, the donor must be determined to be ineligible ([21 CFR 1271.80\(d\)\(2\)](#)). The UK's Department of Health & Social Care has provided Guidance ([Chapter 7: haemodilution, transfusion and donor testing](#)) that describes clinical situations impacting hemodilution in the context of infectious disease testing.

Example(s):

For example, the guidance states that for donors over 12 years of age, infusion of more than 2,000 milliliters of crystalloids within one hour immediately preceding the collection of samples is sufficient to affect the results of communicable disease agent testing. The Clinical Program should specify within SOPs the acceptance criteria for samples undergoing infectious disease testing. The Clinical Program may include test manufacturer's instructions within the SOP.

STANDARD:

B6.4.5 Allogeneic donors and allogeneic recipients shall be tested for ABO group and Rh type using two (2) independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

Explanation:

ABO group and Rh typing are performed on blood or cellular therapy products from allogeneic donors and recipients to avoid the unintentional use of ABO mismatched products containing RBCs that might result in a transfusion reaction. The Standards require testing on two independently collected samples. The timing of the collection of these samples is not specified; however, the entire process of collecting the two samples must be distinct from one another (i.e., different needle sticks and different phlebotomists if staff allows). It is not acceptable to collect the two samples at the same time. The results of both tests should be available to clinical, collection, and processing. The cellular therapy program determines who collects the samples and who performs the testing. Note that these are minimum requirements, and the cellular therapy program may elect to perform more testing, more frequent testing, or testing on the first day of collection as it determines to be appropriate. Testing and documentation should occur according to written SOPs. SOPs to manage ABO and Rh mismatches between the donor and recipient should also be established.

If cord blood products are selected for cellular therapy, two independent ABO tests can only be performed when additional cord blood samples are available for testing.

Example(s):

Allogeneic donors may be tested at the time they are initially evaluated for donor suitability and eligibility, and a second test may be performed at the time of cellular therapy product collection. Alternatively, both tests may be performed prior to collection.

STANDARD:

B6.4.6 An RBC antibody screen shall be performed on allogeneic recipients.

Explanation:

Red blood cell (RBC) antibody screening is important for recipients who receive cellular therapy products containing RBCs. RBC antibodies other than those that naturally occur in relation to the recipient's ABO blood group can cause hemolysis of RBCs that bear the antigens the antibodies recognize. Not all recipients have RBC antibodies other than those to ABO antigens. The only way to know if the antibodies are present is to test a panel of RBCs using serum from the recipient to detect them. Recipients only develop antibodies to RBCs other than anti A or anti B if they have been previously exposed to RBCs bearing other blood group antigens they lack. Pregnancy can immunize a woman, and previous blood transfusions can immunize women or men. It is far less likely that a healthy donor will have antibodies to other blood group antigens, and even if they do, the antibodies are rarely potent enough (i.e., in high enough concentration) to cause a reaction if administered with the product. The rare times this could be a problem do not justify testing all allogeneic donors.

Evidence:

Records of ABO and Rh typing results and antibody screening in the clinical records provide documentation of compliance.

Example(s):

Tests can be performed on the cellular therapy product itself, although the plasma that would be available for RBC antibody screening is diluted, potentially causing weak but significant antibodies to be missed.

STANDARD:

B6.4.7 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.

Explanation:

Cellular therapy products can transmit disease agents even after being extensively manipulated. Such agents may be difficult to detect in the product itself and so are best detected using blood samples from the product donor. There are time periods when a virus might be present but at levels

undetected by testing; therefore, physical examination, medical record review, and screening are also needed.

Evidence:

The medical records should document that allogeneic donors were tested for these infectious agents within the specified time period and that the results were obtained prior to the initiation of the cellular therapy procedure. Donor eligibility determination must be recorded.

Example(s):

For donors of allogeneic cellular and tissue-based products, the FDA regulations on donor eligibility determination require that donor evaluation includes risk factor screening by health history questionnaires, review of medical records, physical examination, and testing for relevant communicable disease agents and diseases. The donor is determined to be eligible if they are 1) free from risk factors for and clinical evidence of relevant communicable disease agents and diseases, 2) free from communicable disease risks associated with xenotransplantation, and 3) tests negative or non-reactive for relevant communicable disease agents within the specified timeframe for the product. It is the responsibility of the Clinical Program to document that donor evaluation procedures are in place to protect the recipient from the risk of disease transmission from the donor.

STANDARD:

B6.4.8 The medical history for allogeneic donors shall include at least the following:

B6.4.8.1 Vaccination history.

B6.4.8.2 Travel history.

B6.4.8.3 Blood transfusion history.

B6.4.8.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the applicable governmental authority.

B6.4.8.5 Questions to identify persons at risk of transmitting inherited conditions.

B6.4.8.6 Questions to identify persons at risk of transmitting a hematological or immunological disease.

STANDARD:

B6.4.8.7 Questions to identify a history of malignant disease.

B6.4.8.8 Allogeneic donors shall confirm that all the information provided is true to the best of their knowledge.

Explanation:

The Standards require that all donors be screened for medical history and risk factors for human transmissible spongiform encephalopathy, Creutzfeldt-Jakob disease (CJD), and potential transmissible infectious disease agents through xenotransplantation as there are no tests for these agents. Travel history is essential for this screening. Information about areas of the world where CJD is a risk factor should be established using trusted sources, such as national or international health agencies' websites or publications.

Evaluation of risk factors for disease transmission by medical history, physical examination, and examination of relevant medical records must be done within an appropriate period of time according to Applicable Law. If the particular period of time has passed, the risk factors for disease transmission must be updated.

Other risks may be associated with unlicensed vaccines, receipt of human-derived growth hormone or clotting factor concentrates, or hepatitis B immune globulin. Prospective donors should be questioned about these issues.

In some donors, risks assessments may be necessary based on the donor medical history. In the case of child donors born of mothers with human immunodeficiency virus (HIV), hepatitis C, hepatitis B, or human T-cell lymphotropic virus (HTLV) infection, the evaluation of risk of transmitting infection should include consideration of the age of the child, history of breastfeeding, and results of infectious disease marker testing; eligibility criteria must be in accordance with Applicable Law.

There are standard deferral times after immunization for allogeneic blood donation that can be used to determine the potential risk that may exist. Blood donors are typically deferred for four weeks after attenuated live virus vaccines such as oral polio, herpes zoster, and measles. In those cases in which a potential donor has recently been vaccinated, both the reason for the vaccination and the time interval should be evaluated to estimate the potential risk to a recipient. There should be specific SOPs for dealing with donors who had received smallpox vaccination. Donors must be screened for travel to areas that would put them at risk for malaria, human transmissible spongiform encephalopathy, severe acute respiratory syndrome (SARS) during periods of world-wide prevalence, or rare strains of HIV, which may not be detected by current screening tests.

Evidence:

Donor medical examination notes and questionnaire records can be reviewed to determine if all of the required screening elements were included in the eligibility determination.

Example(s):

It is recommended that the Clinical Program utilize a screening tool used by an unrelated donor registry even for related donors, such as the NMDP's "Donor Health History Screening Questionnaire."

Information about areas of the world where CJD is a risk factor can be obtained from the interorganizational "Donor History Questionnaire-HPC, Apheresis and HPC, Marrow" and the algorithm that accompanies it. This tool is available on the [FACT website](#).

Specific diseases for which screening is required by the FDA can be found in [21 CFR 1271.75](#).

Additional FDA requirements are described in [Testing Human Cells, Tissues, and Cellular and Tissue-Based Product \(HCT/P\) Donors for Relevant Communicable Disease Agents and Diseases](#) (2024).

STANDARD:

B6.4.9 Allogeneic donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests required by Applicable Law:

Explanation:

The purpose of this Standard is to prevent transmission of communicable diseases from the donor to the recipient in the allogeneic setting. A Clinical Program may wish to also perform such testing on autologous donors for patient care issues or for additional protection of personnel; however, this is not required unless mandated by Applicable Law. If an autologous donor is not tested for transmissible disease, or if testing is performed and found to be positive, the applicable labeling requirements apply.

In some cases, such as resistant disease or relapse/progressive disease, it may be medically necessary to administer donor lymphocytes or other cellular therapy products before availability of repeat transmissible disease testing. The recipient must be informed of this deviation, and the discussion of the deviation with the recipient must be documented in the medical record.

Testing must occur in accordance with written SOPs and using appropriate donor-screening tests licensed, approved, or cleared by applicable government authorities in accordance with the manufacturer's instructions. The results of donor eligibility determination must be recorded. For cellular therapy products in which donor testing results are not yet available, these products should be quarantined until the results are available.

Cellular therapy products from autologous donors known to be positive for agents listed in these Standards must be labeled in the same fashion but do not require the statement "Warning: Advise Patient of Communicable Disease Risks" since the patient is already infected with the agent. However, autologous donors with a positive communicable disease test are not considered to be ineligible, and such products do not require physician notification or patient consent for release for

allogeneic donors. Clinical Program personnel are required to adhere to universal precautions and should treat all products as potentially infectious.

Evidence:

Medical records and lab results will provide evidence of when and what testing was performed.

Example(s):

It is recommended that Clinical Programs and their testing laboratories use the most advanced tests available for these diseases and disease agents to minimize the window period.

The FDA announces additional relevant communicable diseases through published guidance. [Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products](#) (2007) is one such document. In January 2025, the FDA released additional draft guidance: [Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](#).

The FDA considers the following factors in naming a disorder a “relevant communicable disease”:

- There might be a risk of transmission through a cellular therapy product.
- It is sufficiently prevalent to affect the potential donor population.
- There could be fatal or life-threatening consequences as a result of transmission.
- Effective screening mechanisms or an approved screening test for donor specimens have been developed.

Other communicable disease tests should be added to the donor evaluation as they become available and recommended.

STANDARD:

B6.4.9.1 Human immunodeficiency virus, type 1.

B6.4.9.2 Human immunodeficiency virus, type 2.

B6.4.9.3 Hepatitis B virus.

B6.4.9.4 Hepatitis C virus.

B6.4.9.5 Treponema pallidum (syphilis).

STANDARD:

B6.4.10 If required by Applicable Law, allogeneic donors shall also be tested for evidence of clinically relevant infection by the following disease agents:

B6.4.10.1 Human T cell lymphotropic virus I.

B6.4.10.2 Human T cell lymphotropic virus II.

B6.4.10.3 West Nile Virus.

Explanation:

In the U.S., human cells, tissues, and cellular and tissue-based products (HCT/P) donors must be tested for HTLV I and HTLV II. Clinical Programs in EU member states are required to perform a risk assessment to determine if testing for HTLV I and II or other diseases is appropriate for their patient populations. In the U.S., testing for West Nile Virus is required on a seasonal basis. Testing results may influence the timing of recipient conditioning (when using autologous or allogeneic donors) or lead to selection of an alternative donor when possible.

STANDARD:

B6.4.10.4 Trypanosoma cruzi (Chagas Disease).

B6.4.11 Blood samples for testing for evidence of clinically relevant infection shall be drawn and tested within timeframes required by Applicable Law.

B6.4.11.1 Blood samples from allogeneic donors of HPC, Apheresis or HPC, Marrow for communicable disease testing shall be obtained within thirty (30) days prior to collection.

B6.4.11.2 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, or in accordance with Applicable Law.

B6.4.12 Allogeneic donors shall be tested for CMV unless previously documented to be positive.

Explanation:

Cytomegalovirus (CMV) is not a relevant communicable agent or disease. However, allogeneic donors still must be tested for evidence of infection with CMV, although the time frame for this testing is not restricted. A prospective donor who was previously positive for anti-CMV should be considered to be a seropositive donor. Use of CMV-seropositive donors is permissible, and a positive CMV test alone does not make a donor ineligible. Such a cellular therapy product may be

used so long as the Clinical Program has a clearly defined policy or SOP that addresses the use of CMV-seropositive donors. Product labels from CMV positive donors do not require the statements or biohazard label required for products positive for the other agents listed in these Standards. However, there must be a SOP for communicating test results of donors who are positive or reactive for CMV antibody.

Example(s):

CMV testing results may accompany the cellular therapy product as part of the administration form or other information available at product release.

STANDARD:

B6.4.13 Additional tests shall be performed as required to assess the possibility of transmission of other infectious and non-infectious diseases.

Evidence:

Medical record documentation will demonstrate that a risk assessment (e.g., based on season, geography, time/day of testing, U.S. Centers for Disease Control and Prevention/EU/World Health Organization reports) was conducted to determine the need for additional donor testing.

STANDARD:

B6.4.14 Allogeneic donors and recipients shall be tested for HLA alleles by a laboratory accredited by the American Society for Histocompatibility and Immunogenetics, European Federation for Immunogenetics, College of American Pathologists, 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

Explanation:

This Standard applies to all allogeneic donor sources, including cord blood. For cord blood transplants, some cord blood banks may not test for all HLA loci or at the level of resolution required by the Standards. In this situation, the Clinical Program must test for these requirements using a cord blood unit sample if one is available.

High resolution is defined as the first and second fields, as defined by World Health Organization nomenclature, and which encode the same protein sequence within the antigen binding site. HLA accrediting organizations standards continue to evolve, and the program must ensure they are utilizing the most up-to-date version.

The term “alleles” does not imply high resolution, but it does imply DNA typing. There are various levels of resolution, allowing for reporting of a low-resolution allele level typing by DNA which often times is misinterpreted as an antigen level typing.

Evidence:

HLA typing results must be available to the inspector to verify the use of the appropriate resolution and the performance of verification typing.

Example(s):

Clinical Programs performing allogeneic cellular therapy are encouraged to create broad policies and SOPs related to the various HLA typing that may be relevant to a variety of specific settings.

While only the HLA loci specified in this Standard are required, testing other loci may be useful for selecting donors. For example, typing for additional loci may be useful for assigning alleles and narrowing down the number of potential donors to test at high resolution. There may even be future studies demonstrating that other loci have an impact on patient outcomes. However, there is no clear mandate for testing additional loci at this time.

STANDARD:

B6.4.14.1 DNA high-resolution molecular typing shall be used for HLA typing.

Example(s):

In the case of related donors, it may be possible to deduce that parents are heterozygous for DRB1 at low resolution when all four parental haplotypes are identified. HLA accrediting organization standards allow for this assessment by testing enough relatives to determine genotypes for recipient and donor. The Clinical Program may wish to use this approach for related donors so long as it is in accordance with HLA typing accreditation guidelines and follows the planned deviation process.

STANDARD:

B6.4.14.2 Verification typing shall be performed on the recipient and selected allogeneic donor using independently collected samples. Results shall be confirmed prior to administration of the preparative regimen, mobilization, or cellular therapy product collection, whichever is earliest.

B6.4.14.3 There shall be a policy or Standard Operating Procedure to confirm the identity of cord blood units if verification typing cannot be performed on attached segments.

Explanation:

Verification typing does not need to be performed on all potential donors, but it is required for the final selected donor. Results must be available and confirmed prior to administration of the preparative regimen so that any discrepancies may be resolved in advance. Verification typing should be performed according to ASHI, EFI, CAP, or other appropriate organization standards. Repeat testing of HLA-A, B and DRB1 is usually sufficient to establish identity.

Verification typing is not required to be completed at the Clinical Program and may be completed through a different facility.

STANDARD:

B6.4.14.4 There shall be a policy or Standard Operating Procedure for anti-HLA antibody testing for mismatched donors and recipients.

Explanation:

This Standard refers only to the testing of the mismatched recipient for antibodies against the donor in the event there are mismatched donors and recipients. The Clinical Program must have a policy to define when the program performs such testing and who will be tested for specific antibodies.

Example(s):

Guidance regarding what details should be included in this policy can be found in the ASHI or EFI Standards. Examples include timeframe of testing and crossmatch testing.

STANDARD:

B6.4.15 Allogeneic donor eligibility, as defined by Applicable Law, shall be determined by a licensed health care provider after history, exam, medical record review, and testing. The donor eligibility determination shall be documented in the recipient's medical record before the recipient's preparative regimen is initiated and before the allogeneic donor begins the mobilization regimen.

Explanation:

Allogeneic donor eligibility is determined based on eligibility criteria set by government authorities and regulatory agencies and generally focuses on protecting recipient safety (e.g., prevention of transmission of communicable disease). Donor eligibility refers to a donor who meets all transmissible infectious disease screening and testing requirements. Donor eligibility determination may be made by properly trained healthcare professionals, including but not limited to physicians, APPs, or nurses.

STANDARD:

B6.4.16 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

Example(s):

For cellular therapy products that are manufactured in or distributed for use in the U.S., the FDA requires that an accompanying statement of authenticity be present for records translated into English.

STANDARD:

B6.4.17 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 their selection by the transplant physician, urgent medical need, and the informed consent of the donor and the recipient.

Explanation:

If chosen allogeneic donors are ineligible according to Applicable Law or do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented. While the risk of using an ineligible donation is apparent for the recipient, there are also risks to the donor. Donor risks can include guilt or a sense of responsibility for a poor outcome. There must be documentation in the medical record by the transplant physician of urgent medical need for the cellular therapy product.

Urgent medical need means that no comparable stem cell or cellular therapy product is available, and the recipient is likely to suffer death or serious morbidity without the stem cells or products. The product should be accompanied by a summary of records when sent to the Collection and Processing Facilities stating reasons the donor is ineligible, including results of health history screening, physical examination, and infectious disease testing.

FDA regulations and the Standards require labeling with a biohazard legend for cellular therapy products collected from ineligible donors with the statement "Warning: Advise patient of communicable disease risk" and in the case of reactive test results, "Warning: Reactive test results for (name of disease agent or disease)." This regulation for urgent medical need or labeling does not apply to an autologous donor. For additional information regarding labeling of products, see [Appendix II](#) of the Standards.

Evidence:

The rationale and informed consent for a specific donor who did not meet the institution's donor criteria should be available to the inspector for verifying the appropriate urgent medical need documentation and labeling.

Example(s):

In the setting of resistant disease, relapse, or progressive disease, it may be medically necessary to administer donor lymphocytes or other cellular therapy products before availability of repeat transmissible disease testing. The recipient must be informed of this deviation, and the discussion of urgent medical need must be documented in the medical record.

According to the U.S FDA guidance document [Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products](#) (2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in [21 CFR 1271.55](#). In January 2025, the FDA released additional draft guidance: [Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](#).

STANDARD:

B6.4.18 Allogeneic donor eligibility shall be communicated in writing to the Collection and Processing Facilities.

B6.4.19 Allogeneic donor records shall include donor suitability and eligibility determination, including the name of the responsible person who made the determination and the date of the determination.

Explanation:

There should be a written SOP covering the creation and retention of allogeneic donor records. The recipient records would be regulated by the clinical standards regarding patient care. The policy should address the following:

- For each donor, there should be a record containing:
 - The donor identification (first name, family name, and date of birth).
 - Age and medical and behavioral history (the information collected must be sufficient to allow application of exclusion criteria, where required).
 - Consent/authorization form(s).
 - Clinical data, laboratory test results, and the results of other tests performed.
 - The donor's eligibility and suitability. For unrelated donations, when the organization responsible for collection has limited access to recipient data, the Clinical Program must be provided with donor data relevant for confirming eligibility.
- All the records should be clear and legible, protected from unauthorized amendment, and retained and readily retrieved in this condition throughout their specified retention period in compliance with data protection legislation.
- Donor records required for full traceability must be kept for a minimum duration as dictated by institutional practice or governmental regulatory requirements.

Example(s):

It is recommended that a separate medical record be maintained for donors.

B7: RECIPIENT CARE

STANDARD:

B7.1 Recipient informed consent for the cellular therapy shall be obtained and documented by a licensed health care professional knowledgeable in the proposed cellular therapy.

B7.1.1 The informed consent process shall include information regarding the risks and benefits of the proposed cellular therapy.

Explanation:

Recipients of cellular therapy products must receive comprehensive information prior to initiating any preparative treatment. Consent can be in written form or documented verbal form, by health care professionals experienced in the proposed cellular therapy. Consent must include at a minimum the following:

- Rationale for treatment.
- The nature of the intervention.
- Who will have oversight of the treatment.
- The benefits and risks and anticipated outcome.
- Predicted adverse events and side effects.
- The alternatives treatment options and their anticipated outcome.
- Use of immunosuppression.
- The legal rights of the recipient.
- The protection of the recipient personal information and the data resulting from the treatment.

In addition, the recipient must be given the opportunity to ask questions and have those questions answered to their satisfaction. Consent must follow national legal and regulatory requirements.

The discussion that ensues is the most important part of the process of obtaining informed consent; however, it is the documentation of this process that can be easily audited. Informed consent is to be documented according to institutional standards and Applicable Law.

The information must be given by a trained person able to transmit it in an appropriate and clear manner, using terms that are easily understood. The health professional must confirm that cell therapy recipients have a) understood the information provided, b) had an opportunity to ask questions and been provided with satisfactory responses, and c) confirmed that all the information they provided is true to the best of their knowledge and documented in the medical record.

Evidence:

The inspector will review consent forms and any material routinely provided to recipients of cellular therapy. The inspector will also review completed consent forms and audits of the consent process performed by the Clinical Program.

STANDARD:

B7.1.2 For a cellular therapy product collected for a designated recipient, informed consent of the recipient for the therapy shall be obtained before collection of the product.

Explanation:

When a cellular therapy product is being collected specifically for a designated recipient—such as in autologous or directed allogeneic collections, it is important that the intended recipient provides informed consent for the therapy itself before the product collection occurs. This ensures that the patient fully understands the nature of, risks, potential benefits, and alternatives to the planned cellular therapy procedure, including how the cells will be used, stored, and infused.

Obtaining informed consent prior to collection safeguards against the risk of initiating procedures that may not ultimately be accepted by the recipient. It also avoids unnecessary exposure of the donor (who may be the recipient themselves in autologous settings) to collection-related risks when the therapy may not proceed.

Key components of this informed consent (as described in [B6.2](#)) include:

- The therapeutic intent and expected outcomes.
- Known risks and side effects of the cellular therapy.
- Alternatives to the proposed treatment.
- The voluntary nature of participation.
- The right to withdraw consent.

This process must be documented and conducted in compliance with institutional policies, these Standards, and Applicable Law.

STANDARD:

B7.2 The attending physician shall confirm the availability and suitability of a donor or cellular therapy product prior to initiating the recipient's preparative regimen.

Explanation:

Due to the potentially serious toxicity associated with preparative regimens, Clinical Programs must verify that cellular therapy products or suitable donors will be available prior to administering preparative regimens.

Evidence:

SOPs, standardized orders, and checklists (with signatures) are examples of pre-inspection documentation that may provide evidence this Standard is met. Alternatively, Clinical Programs may include a description of a process evident in dictated notes.

STANDARD:

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.

Explanation:

Cellular therapy products obtained from cord blood banks, registries or manufacturers outside of the cellular therapy program may differ in important ways for which the Processing Facility must be prepared. Required preparations may include special storage arrangements, necessary supplies and reagents, and developing personnel competency in order to process the product for administration while protecting cell viability and product safety.

STANDARD:

B7.2.2 The Clinical Program should obtain relevant information regarding the cellular therapy product from the manufacturer.

Explanation:

To assist the physician with determining the appropriateness of the cellular therapy product, the following items should be requested from the manufacturer:

- Total count of relevant cell.
- Viability and potency, as applicable.
- Microbial cultures from the cellular therapy product after processing prior to cryopreservation.
- ABO group and Rh type, if applicable.
- All HLA Class I and II typing results, if applicable.
- Communicable disease testing results performed on the donor.

- Final donor eligibility determination and risks of communicable and genetic diseases disclosed by the donor medical and genetic screening or clinical chart review, and the results of any investigation or further testing performed.
- The method of processing.
- Any variances in collection, processing, testing, cryopreservation, storage, and transport or shipping procedures that may influence the integrity and quality of the cellular therapy product.
- Size and shape of the cellular therapy product, including at a minimum the number and type of containers or compartments used for storage.

STANDARD:

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.

B7.4 There shall be policies or Standard Operating Procedures addressing safe administration of the preparative regimen, including lymphodepletion.

Explanation:

Preparative regimens encompass various modalities, such as biologic, radiologic, and chemotherapy. It is recommended that a tracking system regarding mixture, delivery, and completed administration be instituted for all of these regimens. Staff administering the preparative regimen shall be appropriately credentialed as defined by institutional policies and required by Applicable Law.

If there are differences between inpatient and outpatient processes, these should be addressed in applicable SOPs and specified on pre-printed or electronic orders used by the Clinical Program.

Example(s):

Policies must address the safe administration of chemotherapy in the preparative regimen. Context requires specific policies for safe administration due to the risk of adverse outcomes related to high doses. The policies must include timing and clearance of chemotherapy agents.

Melphalan is an example of a chemotherapy drug that requires careful timing of administration due to limited stability after preparation.

Oversight of the preparative regimen must be performed by an appropriately credentialed and experienced provider. Traceability in clinical administration of cellular therapies must follow

European Directorate for the Quality of Medicines & Health Care recommendations and [Directive 2006/86/EC](#) for donor-product-patient linkage.

STANDARD:

B7.4.1 The treatment orders shall include the patient's current height and weight, specific dates of administration, daily doses, if appropriate, and route of administration of each agent.

Explanation:

It is recognized that treatment orders must be approved by various individuals; however, the patient's height and current weight should be measured and recorded before treatment administration. The Clinical Program should also have a policy regarding when it is more appropriate to use body mass index (BMI), ideal body weight, or other calculations (e.g., adjusted body weight) on the treatment orders. Verification of body surface area (BSA), automated or verified by a second qualified designee (e.g., pharmacy), should be performed.

Evidence:

Pre-printed or completed order sets are appropriate examples of compliance with the Standard. Evidence of a measured, rather than a patient stated, height should be available.

STANDARD:

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.

Explanation:

A protocol or standard of care-specific set of orders that is pre-printed and readily available in written or electronic form is an important measure of control; however, it is still critical that the drug doses are verified and documented by an attending physician prior to transmitting the order to the pharmacy.

Evidence:

The inspector may review orders of patients currently receiving chemotherapy. There should be evidence that the orders were reviewed and approved by an attending physician.

STANDARD:

B7.4.3 The pharmacist verifying or preparing the drug shall check and document the dose 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 persons shall verify and document:

Explanation:

For purposes of this Standard, a qualified person is someone trained and competent to perform the task.

Evidence:

There should be written documentation by two staff members noting that they have verified the drug and dose against the orders and the protocol, as well as the recipient's identity.

While touring patient care areas, the inspector may also ask the pharmacists about their normal practice and if they retain ultimate responsibility for verification against the protocol or standard regimen listed on the orders. Nurses may be asked about the normal procedures for treatment administration to confirm this.

STANDARD:

B7.4.4.1 The drug and dose in the bag or pill against the orders and the protocol or standardized regimen.

B7.4.4.2 The identity of the recipient.

Explanation:

Even if a validated electronic system is used (e.g., bar coding), there must be a method to document the verification of the drug and dose in the final container against the orders and the protocol or standardized regimen, and the identity of the recipient to receive the chemotherapy by a qualified person. The dispensed drug could be in many forms, including intravenous and oral medications, and the actual drug in hand and number of doses must be verified.

Written instructions should be available for reconstitution, dilution, mixing, labeling, and packaging. There should be a standard process in place to retrieve the batch number and expiration of all drugs and diluents used in the preparation of the therapy regimens.

Evidence:

Copies of standard treatment or research protocols in areas of recipient care such as inpatient and outpatient units and the pharmacy can provide evidence of compliance. Specific patient charts can be used to check that treatment orders and documentation are compliant with the guidelines. In

case of time-sensitive chemotherapy agents (e.g., Melphalan), the inspector may review documentation of the time elapsed between drug reconstitution and administration.

STANDARD:

B7.5 There shall be policies or Standard Operating Procedures 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 recipient's diagnosis, relevant medical history including pre-existing comorbid 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 recipient 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 institutional radiation therapy standards.

B7.5.5 A final report of the details of the radiation therapy administered shall be documented in the recipient's medical record.

Explanation:

Information from the radiation oncology consultation, including factors that may increase the toxicity of the radiation, should be discussed with the patient, and informed consent must be documented. Records can come from internal radiation/oncology documentation.

Evidence:

Information available to the radiation oncologist, the radiation oncology consult, and the radiation report at the end of treatment can be reviewed in the recipient's chart. Documentation that the radiation was given on a specific date and its dose can be compared to the consultation documentation. The inspector can also ask to see copies of treatment protocols that include radiation and verify the protocol by comparing it to patient charts.

STANDARD:

B7.6 There shall be policies or Standard Operating Procedures addressing safe administration of cellular therapy products.

Explanation:

This Standard applies regardless of the therapeutic intent of the cellular therapy product. Clinical Programs need to determine the composition of the product to determine how it should be prepared for administration. Characteristics of the product, including the cell source (e.g., marrow, peripheral blood, cord blood), type of product (e.g., DLIs, IECs, mesenchymal stromal cells [MSCs]), and cell counts should be taken into consideration. Unless otherwise specified, the B7.6 standards apply to all products. Programs should work with their Processing Facilities to verify appropriate processing and preparation of products for administration.

Clinical Programs must identify appropriate timeframes between the end of the preparative regimen and administration of the cellular therapy product to confirm that the administered product is not affected by the preparative regimen. The program must verify that the preparative regimens were given at the scheduled time and delay administration of the cells if required. Programs are responsible for communicating with the Processing Facility regarding any delayed administration.

Non-cryopreserved (often referred to as “fresh”) cellular therapy products, whether intended as hematopoietic stem cell grafts or for immunotherapy, must be administered within the time specified by the Clinical Program’s policies, registry and tissue bank requirements, and Applicable Law. When using frozen stem cell products, individual bags should be thawed and infused before thawing subsequent units to reduce the amount of time thawed products are left standing.

Evidence:

Staff should be prepared to discuss their normal practice and their training in the administration of cellular therapy products. Specific patient charts can be used to determine that two persons checked the product and that the documentation in the chart is complete. If there is time and an administration is scheduled on the day of inspection, the inspector should be notified so that they may watch parts of the procedure. If not, a mock procedure should be performed for inspector observation.

Example(s):

Frozen cellular therapy products may include administration of significantly higher doses of dimethyl sulfoxide (DMSO), and allogeneic bone marrow may include administration of significantly higher numbers of ABO-mismatched RBCs.

It is important to have a clear communication pathway between the Clinical Program and the Processing Facility, or the manufacturer if applicable, regarding the date and time of administration. If plans change, updated information is provided to the laboratory or the manufacturer prior to the planned day of administration.

Monitoring of vital signs is generally part of routine hospital policy for blood products; however, given the potential for administration reactions (e.g., hypoxia, bradycardia, hypertension), the Clinical Program should monitor vital signs at least one hour after administration. Some cellular therapies are known to elicit early adverse reactions.

STANDARD:

B7.6.1 There shall be policies or Standard Operating Procedures for determining the appropriate volume and the appropriate dose of RBCs, cryoprotectants, and other additives.

Explanation:

Clinical Programs need to determine the appropriate volume, DMSO (and other additives), and RBC load for recipients. Volume issues will differ depending on the cellular therapy product. Clinicians must consult with the Processing Facility to make clinical decisions based on methods of cellular therapy product preparation.

STANDARD:

B7.6.2 There shall be policies or Standard Operating Procedures for the infusion of ABO-mismatched RBCs in allogeneic cellular therapy products.

Explanation:

In order to avoid major hemolytic reactions, RBC or plasma reduction may be necessary when utilizing ABO-mismatched marrow products. The Clinical Program must have policies or SOPs regarding ABO-mismatched products ([B5.1.9](#)). Similarly, the Processing Facility must have policies and SOPs regarding ABO-mismatched products ([D5.1.4](#) and [D8.13](#)), including exceptional release ([D5.1.9](#)). Clinician awareness and concordance of policies between the Clinical and Processing Facilities is necessary for optimal patient care.

Example(s):

Clinical SOPs addressing the use of ABO-mismatched RBCs should be available for review.

STANDARD:

B7.6.3 There shall be policies or Standard Operating Procedures for preparation and administration of cellular therapy products according to manufacturer specifications.

Explanation:

Precise preparation and administration of products are critical to ensuring patient safety, therapeutic efficacy, and regulatory compliance. This standard requires that formal, written policies

and procedures be established and followed for all aspects of product handling—from receipt through administration or final disposition based explicitly on the manufacturer’s specifications.

Manufacturers provide validated instructions for product preparation, including storage conditions, thawing procedures, dilution (if applicable), time windows for infusion post-preparation, and required ancillary materials. These instructions are based on product-specific characteristics such as cell viability, potency, and stability. Deviations from these specifications may compromise product integrity and lead to reduced efficacy or patient harm.

STANDARD:

B7.6.4 There shall be consultation with the Processing Facility regarding cord blood preparation for administration.

B7.6.4.1 Cord blood units that have not been RBC-reduced prior to cryopreservation shall be washed prior to administration.

B7.6.4.2 Cord blood units that have been RBC-reduced prior to cryopreservation should be diluted or washed prior to administration.

Example(s):

For cord blood units, the NMDP requires washing of RBC replete cord blood units due to reported unexpected adverse events. See [Donor and cord blood unit selection guidelines](#) for more information.

STANDARD:

B7.6.5 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.

B7.6.6 When administering cellular therapy products from more than one (1) donor, each cellular therapy product shall be administered safely prior to administration of subsequent cellular therapy products.

Explanation:

When using more than one cellular therapy product (e.g., double cord blood transplant), the Clinical Program must wait to administer the second product until it is determined that the first one was administered safely with no adverse events.

Example(s):

For double cord blood transplants, preferably the second unit should not be thawed until administration of the first unit is completed and the Clinical Program is reasonably certain that no adverse reactions are occurring.

STANDARD:

B7.6.7 There shall be documentation in the recipient's medical record of the unique identifier of each cellular therapy product and dose administered, initiation and completion times of administration, and any adverse events related to administration.

B7.6.8 A Circular of Information, Investigator's Brochure, or other product-specific information for cellular therapy products shall be available to staff.

Example(s):

The inter-organizational [Circular of Information for the Use of Cellular Therapy Products](#) may be used to fulfill this requirement and can be found on the FACT website. A Circular of Information is defined as "an extension of container labels that includes the use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations." An investigator's brochure or package insert may contain this information.

Clinical Programs are responsible for communicating to staff where the current version of the Circular of Information is and what information is included in it.

Evidence:

The inspector may ask staff members of the Clinical Program if they know where the Circular of Information is and what its use is.

STANDARD:

B7.7 There shall be policies or Standard Operating Procedures addressing appropriate follow-up of recipients after administration of preparative regimens and cellular therapy products, including, at a minimum:

Explanation:

Administration of preparative regimens and cellular therapy products is known to be associated with diverse and potentially serious complications. Clinical Programs are expected to have a system in place to monitor for these complications and provide appropriate courses of action if they occur. Written policies and SOPs addressing appropriate management plans, developed after critical review of current literature and thoughtful deliberations, will enable the clinical team to have increased consistency in its management approach and enhanced quality improvement. To allow for the flexibility often needed in clinical practice, the program may choose to address these critical elements of post-therapy management in the form of clinical guidelines rather than SOPs.

STANDARD:

- B7.7.1 Management of nausea, vomiting, pain, and other discomforts.*
- B7.7.2 Monitoring of blood counts and transfusion of blood products.*
- B7.7.3 Monitoring of infections and use of antimicrobials.*
- B7.7.4 Monitoring of organ dysfunction or failure and institution of treatment.*
- B7.7.5 Monitoring of graft failure, prolonged cytopenia, and institution of treatment.*
- B7.7.6 Regular assessment for evidence of acute GVHD using an established staging and grading system.*
- B7.7.7 Regular assessment for evidence of chronic GVHD using an established staging and grading system.*

Explanation:

GVHD is a potential risk, particularly with allogeneic recipients. Adverse events attributable to acute or chronic GVHD occur within and outside of the 100-day post-cellular therapy administration window. GVHD must be assessed at the Clinical Program, with close communication with the referring physician. Weekly assessment for the first three post-cellular therapy administration months for acute GVHD as clinically indicated is generally recommended. Thereafter less frequent assessment and documentation is widely accepted as standard of care; however, a minimum frequency of at least every three months during the first-year post-cellular therapy administration is recommended for assessment of chronic GVHD and late effects.

GVHD staging and grading and post-cellular therapy administration surveillance for late effects should be documented in the recipient's medical record.

Example(s):

Examples of established GVHD grading systems include the National Institutes of Health consensus criteria for chronic GVHD and the CIBMTR data management guidelines.

STANDARD:

- B7.8 There shall be policies or Standard Operating Procedures addressing the administration of IECs and management of complications, including the use of cytokine-blocking agents and corticosteroid administration.*

Explanation:

IEC therapy is increasingly being used for clinical treatment of refractory or relapsed malignancies with promising outcomes. While there are different forms of IEC therapies being used, they share

important immune-related features that Clinical Programs should be cognizant of and prepared to manage. The risk of severe CRS following such therapy is an example, which could occur after either IEC therapy or transplant of HPC replete with IECs. The best practices for IEC therapy are still being developed by practitioners in the field and are expected to change with experience, but programs that administer IEC therapy must have current policies and SOPs that address critical aspects of such therapy to promote the safety of its recipients.

Example(s):

Additional tools for Clinical Programs administering IECs include:

- Maus, MV, Nikiforow, S. [The why, what, and how of the new FACT standards for immune effector cells](#). *J Immunotherapy Cancer*. 2017;5:36.
- Fesnak AD, Suhoski Davis MM, Levine BL. [Production of chimeric antigen receptor \(CAR\) T cells](#). *Nature Protocols*. 2017;12(4).
- Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. [ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells](#). *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

STANDARD:

- B7.8.1 There shall be a consultation with the referring physician prior to initiation of IEC therapy to review the goal and plan of the treatment.*
- B7.8.2 There shall be regular assessment of the recipient to detect complications, including CRS and neurologic dysfunction.*

Explanation:

There are well-established operational guidelines available detailing the anticipated complications arising from the use of IECs and HCTs. These should be incorporated into SOPs, clinical charts, management procedures.

Evidence:

Evidence may include completed risk assessments of individual IECs, operational documents, SOPs, and clinical notes recording recipient clinical observations post treatment. Audits of compliance with institutional SOPs and treatment algorithms also demonstrate that the Standard has been met.

Example(s):

In addition to IND requirements, investigator experience may generate ideas for detecting complications. Attending physicians may want to request additional laboratory testing, such as C-reactive protein, lactate dehydrogenase, ferritin, and fibrinogen. For example, evaluating fibrinogen periodically after CAR administration may be useful for early detection of severe CRS.

STANDARD:

B7.8.3 There shall be a written plan for rapid escalation of care, increased intensity of monitoring, and relevant workup to address complications.

B7.8.3.1 Communication to the clinical staff, intensive care unit, emergency department, and pharmacy shall be timely.

Explanation:

In cellular therapy programs such as CAR T-cell therapy, HCT transplantation, or other advanced cellular products, patients are at risk for sudden and severe complications, including CRS, ICANS, infections, and organ dysfunction.

To manage these risks effectively, programs must maintain a written, institutionally approved escalation plan. This plan should be readily accessible to the clinical team and tailored to the types of complications expected with the specific cellular therapy products used. It is a critical component of risk mitigation, early intervention, and optimal patient outcomes.

Effective interdisciplinary communication is essential for the escalation plan to succeed. All relevant departments and personnel must be promptly notified when a patient's condition deteriorates or when specific therapies (e.g., tocilizumab, steroids, vasopressors) may be required on an urgent basis. This timely communication can ensure that ICU staff are prepared for transfer and management of critical care needs, the ED is informed in case of off-hours or direct admissions, the pharmacy can release or prepare time-sensitive medications, and the primary clinical team remains in the loop to coordinate and oversee care transitions.

Delays in communication can result in treatment setbacks, preventable harm, and poor outcomes, especially in time-critical scenarios like CRS or sepsis. Therefore, clear protocols, timely communication systems (e.g., paging systems), and real-time documentation tools should support immediate and efficient information flow.

STANDARD:

B7.9 There shall be policies or Standard Operating Procedures in place for planned discharges and provision of post-transplant or post-cellular therapy care.

B7.9.1 When a recipient is discharged prior to engraftment or recovery of peripheral blood cell counts, the Clinical Program shall verify that the following elements are available:

B7.9.1.1 A consult between the attending physician and the receiving health care professionals regarding the applicable elements in Standard [B7.7](#).

STANDARD:

B7.9.1.2 Facilities that provide appropriate location, adequate space, and protection from airborne or surface microbial contamination.

Example(s):

One way to protect cellular therapy recipients from airborne microbial contamination is to verify that the receiving facility has the ability to rapidly secure a private room for a recipient upon arrival to the facility (e.g., ED, clinical unit).

STANDARD:

B7.9.1.3 Appropriate medications, blood products, and additional care required by the recipient.

Explanation:

Discharges should normally take place after hematopoietic engraftment. A Clinical Program may adopt a policy for discharging recipients before engraftment, with ongoing inpatient care undertaken at another facility. It may be necessary to collaborate with health care providers in local or regional facilities to provide a portion of post-transplant care. This may not involve direct provision of care but must work operationally within the QM systems of the facility.

Evidence:

The working relationships between the Clinical Program and receiving facility shall be clearly documented, including explicit criteria for transfer back to the program. Communication used to fulfill the requirement for a consult must be documented and available for inspectors.

The Clinical Program QM Plan should describe the process for collaborative care arrangements, including criteria for participation by specific patients, health care providers, and facilities. Recipient outcomes under this type of arrangement must be monitored.

Inspectors will determine if receiving facilities are adequately assessed for post-transplant care. They will evaluate the receiving facility to verify all elements are met through documentation (e.g., consult notes, agreements, SOPs). If an inspector determines that an on-site assessment of a collaborating facility is necessary or desirable, specific arrangements must be made in advance through the FACT or JACIE office.

Example(s):

A shared care arrangement may be justified by a balance of clinical, economical, and geographical factors that clearly benefit overall patient care without compromising safety and outcome.

STANDARD:

B7.9.2 The Clinical Program shall provide appropriate instructions to recipients prior to discharge.

B7.9.2.1 There shall be a process to provide transplant and cellular therapy-specific instructions for post-discharge care to the recipient, caregivers, and other health care providers who may provide care.

Explanation:

The period following hospital discharge is critical to patient safety, recovery, and long-term outcomes. Patients may still be at high risk for complications such as infection, graft failure, relapse, or delayed immune reconstitution. As such, it is essential that the Clinical Program provides clear, comprehensive, and personalized discharge instructions before the patient leaves the hospital or treatment center.

These instructions should include, but are not limited to:

- Medication regimens and adherence requirements.
- Signs and symptoms that warrant urgent medical attention.
- Infection prevention measures (e.g., hygiene, dietary precautions, mask use).
- Activity restrictions and lifestyle modifications.
- Follow-up appointment schedules and laboratory monitoring.
- Contact information for urgent questions or emergencies.

Providing this information in a format that is understandable, accessible, and tailored to the patient's condition promotes safe transitions of care and empowers patients to manage their health effectively.

STANDARD:

B7.10 There shall be policies or Standard Operating Procedures addressing indications for and safe administration of ECP if utilized by the Clinical Program.

Explanation:

ECP is a leukapheresis-based immunomodulatory therapy used in the treatment of acute and chronic GVHD, along with other non-transplant indications involving the separation of leukocytes by apheresis and additional treatment steps.

There are different methodologies for ECP that include both closed and open circuits. In the former, which is the most common, collected leukocytes remain integral to the circuit of the cell separator, while a minority of ECP procedures involve detaching the leukapheresis product at some point (e.g., for addition of psoralen and/or UV irradiation). It is probable that inspectors will increasingly

encounter the use of ECP within and associated with transplant programs undergoing inspection, both within and outside of clinical trials.

STANDARD:

B7.10.1 There shall be a consultation with the facility or physician that performs ECP prior to initiation of therapy.

Explanation:

If ECP is a part of therapy for GVHD or other indications for bone marrow transplant patients within a Clinical Program or Collection Facility applying for FACT or JACIE accreditation, the activities must meet the Standards as they apply. However, it is quite common for patients requiring ECP to attend a hospital or unit (such as dermatology) that may have no other relationship with the program aside from the provision of ECP. If ECP is performed at a site not applying for accreditation, then the program must be able to demonstrate a written agreement that meets the requirements in [B4.6](#).

The term “consultation” in this Standard is interpreted broadly. Clinical Programs that perform ECP within their own programs must still review the patient’s medical status in relation to how it presents a need for ECP and how the therapy should be administered.

STANDARD:

B7.10.2 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.

B7.10.3 A report of the details of ECP administered, including an assessment of the response, shall be documented in the recipient’s medical record.

Explanation:

The provision of ECP is not required of Clinical Programs; however, if it is used as a treatment for cellular therapy patients, it must comply with the Standards.

It is acceptable for the transplant physician to rely on the ECP provider to create the therapy plan; however, the physician must confirm that a treatment plan has been established and agree to the details prior to the intended procedure.

If national or international standards in ECP are available, they should be incorporated into organizational or transplant program policies and SOPs.

Evidence:

Inspectors should review patient medical records of ECP, both in the instance of an internal or external service, to determine the requirement for administration and response assessment are met. The inspector is not required to review records on-site if the facility is external. However, the therapy plan and documentation of the date and regimen of administered ECP must be included in the recipient's medical record and can be compared to the consultation documentation. The inspector can also ask to see copies of treatment protocols that include ECP and verify the protocol by comparing it to patient medical records.

Example(s):

The Clinical Program may decide the frequency with which to report ECP in the patient's medical record. This will depend on the therapy plan; for example, depending on the length of the therapy regimen, reports may be created after every procedure or monthly.

STANDARD:

B7.10.4 The facility performing ECP shall be qualified to meet FACT-JACIE requirements.

Explanation:

Clinical Programs performing ECP must have an SOP for the ECP procedure. For those programs referring patients to external facilities, written agreements should require that the facilities follow a written procedure including a written informed consent. The intent is not to dictate how ECP is performed, but that it is performed in accordance with established processes.

Example(s):

Clinical Programs may perform ECP within their own facilities, utilize a separate unit of the hospital, or refer patients to an external facility. When not performed within the program itself, written agreements must require compliance with the Standards.

STANDARD:

B7.11 There shall be policies or Standard Operating Procedures in place for provision of appropriate long-term follow-up, treatment, and plans of care.

Explanation:

Long-term follow-up care is a critical component of the comprehensive care that the Clinical Program is responsible for providing to cellular therapy recipients. Long-term follow-up is essential for detecting and managing late effects of cellular therapy, and it requires expertise that is different from that for acute care of recipients.

Late effects may include endocrine and reproductive function (e.g., new onset diabetes, thyroid dysfunction, hypogonadism), osteoporosis, cardiovascular risk factors (e.g., hypertension, dyslipidemia, metabolic syndrome, lifestyle factors), respiratory function, chronic renal impairment,

and secondary cancers. Growth and development-related late effects should specifically be monitored in pediatric patients. Infections are common and can be severe, especially in long-term survivors suffering from chronic GVHD. Prevention of infections can be achieved by anti-microbial prophylaxis, administration of immune globulin, or vaccinations. Appropriate advice when travel is planned is also important for long-term survivors.

The establishment of a dedicated survivorship clinic for cellular therapy survivors is highly recommended but not required, as long as the medical issues outlined in the Standards can be adequately addressed. The Clinical Program shall have the responsibility to either perform long-term follow-up by themselves or monitor long-term follow-up data of its former recipients already discharged to the referring physicians. In the latter case, it will still be the responsibility of the program to coordinate the long-term care with the referring physicians so that the recipients will not be lost for follow-up.

Example(s):

The following publications may be used as references when establishing long-term follow-up guidelines for care of patients after receiving cellular therapy:

- Majhail NS, Rizzo JD, Lee SJ, et al. [Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation](#). *Biol Blood Marrow Transplant*. 2012;18(3):348–371.
- Hashmi S, Carpenter P, Khera N, et al. [Lost in Transition: The Essential Need for Long-Term Follow-Up Clinic for Blood and Marrow Transplantation Survivors](#). *Biol Blood Marrow Transplant*. 2015;21(2):225–232.
- Hashmi S, Litzow MR. [Late Effects after Allogeneic Hematopoietic Stem Cell Transplantation](#). In: Savani BN, ed. *Blood and Marrow Transplantation Long-Term Management: Prevention and Complications*. 2013:21–23.
- Puckrin R, Jamani K, Jimenez-Zepeda VH. [Long-term survivorship care after CAR-T cell therapy](#). *Eur J Haematol*. 2024;112(1):41–50.

STANDARD:

B7.11.1 There shall be policies or Standard Operating Procedures in place for post-transplant vaccination schedules and indications.

Explanation:

SOPs should include post-transplant vaccination schedules and indications, as well as procedures for monitoring late effects. Find the Centers for Disease Control and Prevention vaccination recommendations for post-transplant and post cellular therapy treatment patients at <https://www.cdc.gov/vaccines/hcp/imz-schedules/adult-notes.html>.

STANDARD:

B7.11.2 There should be policies or Standard Operating Procedures in place for psychosocial follow-up care.

Explanation:

Psychological challenges are common both pre- and post- cellular therapy treatment. Psychosocial support refers to the provision of assistance for cellular therapy recipients to enable them to better cope with the psychological and social challenges that occur before, during and after treatment. The Clinical Program can define the type of psychosocial services it provides. Psychological needs can be met by a psychologist or through alternative forms of supportive care.

Psychosocial evaluation before cellular therapy treatment is important for identifying risk factors for inferior outcomes. Cellular therapy treatments can result in challenges including compliance, depression, anxiety, and diminished quality of life for both the recipient and their caregivers. Consequently, there is a need for psychosocial support for both parties in the early post-cellular therapy treatment period, as well as continued support and evaluation for issues that may negatively impact recipient and caregiver outcomes.

References:

- Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN. [Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature](#). *Psycho-Oncology*. 2009;18(2):113–127.
- Janicsák H, Ungvari GS, Gazdag G. [Psychosocial aspects of hematopoietic stem cell transplantation](#). *World J Transplant*. 2021;11(7):263–276.

Example(s):

Patients experiencing anxiety, or post-traumatic stress disorder related to receiving cellular therapy care are examples of individuals who may benefit from psychosocial services.

STANDARD:

B7.11.3 There shall be policies or Standard Operating Procedures for monitoring by appropriate specialists of recipients for post-cellular therapy late effects, including at a minimum:

B7.11.3.1 Endocrine and reproductive function and osteoporosis.

B7.11.3.2 Cardiovascular risk factors.

B7.11.3.3 Respiratory function.

STANDARD:

B7.11.3.4 Chronic renal impairment.

B7.11.3.5 Secondary malignancies.

B7.11.3.6 Growth and development of pediatric patients.

B7.11.3.7 Assessment for psychosocial needs.

B7.11.3.8 Neurological and neurocognitive complications.

B7.11.4 There shall be policies or Standard Operating Procedures describing the transition of long-term pediatric recipients to adult care as appropriate.

B8: CLINICAL RESEARCH

STANDARD:

B8.1 Clinical Programs shall have formal review of investigational protocols and consent forms by a process that is approved under institutional policies and Applicable Law.

B8.1.1 Those Clinical Programs utilizing investigational treatment protocols shall have a pharmacy in place that is 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 Clinical research protocols shall be conducted in accordance with institutional policies and Applicable Law.

B8.2.1 The Clinical Program shall maintain:

B8.2.1.1 Documentation of approval by the IRB, Ethics Committee, or equivalent.

B8.2.1.2 If applicable, documentation of approval by the IBC or equivalent.

STANDARD:

B8.2.1.3 Correspondence with regulatory agencies.

B8.2.1.4 Audits and any adverse events, including their resolution.

Explanation:

The purpose of these Standards is to confirm that the Clinical Program is obtaining appropriate review of clinical research protocols. These Standards apply to all clinical research performed by the Clinical Program. This includes research performed under an IND or Clinical Trial of an Investigational Medicinal Product (CTIMP) sponsored by the institution, industry, or any other entity for whom the program is conducting the research.

Investigational drugs should be secured in storage dedicated to investigational products and clearly labeled as investigational products. The length of time for which documentation of approvals and associated quality documents must be maintained varies depending on the type of clinical research and the study sponsor. The Clinical Program must also comply with Applicable Law. Labeling for those products in Europe should conform to [Directive 2004/23/EC](#) and use the EU SEC as per [Commission Directive \(EU\) 2015/565](#).

Evidence:

The inspector may ask about the process for review of protocols, determine how research ethics approval is obtained, and examine the regulatory binder for a specific study to review evidence of IRB or Research Ethics Committee approval. A signed consent form from a patient's chart can be used to crosscheck approval dates with IRB or applicable regulatory agency documents. If the Clinical Program carries out any Clinical Trials of Investigational Medicinal Products, studies under IND or IDE applications, or equivalent, the regulatory binder for such studies should be available.

Example(s):

A Clinical Program may use its host institution's shared resources to manage its regulatory files and clinical research operations or have its own clinical research office that manages all aspects of its clinical research studies. Aspects requiring management include clinical research monitoring by institutional monitors, independent monitors contracted by industry, national cooperative group monitors, and lead research center monitors.

There are a variety of ways to manage cellular therapy products. Clinical Programs may choose to manage cellular therapy products in the Processing Facility. The management in a cellular therapy Processing Facility is influenced by staff experience, storage facilities, and validated procedures. Similarly, Clinical Programs may choose to manage cellular therapy products in hospital pharmacies and take responsibility for safe handling to protect the product and recipient. These processes should be appropriately described in policies and SOPs.

Cellular therapy research protocols should be under the supervision of the appropriate governmental authorities, including the Office for Human Research Protections under the

Department of Health and Human Services or the FDA in the U.S. and the National Research Ethics Committees in Europe.

STANDARD:

B8.3 For clinical research, informed consent shall be obtained from each research subject or legally authorized representative, in a language they 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, have their questions answered to their satisfaction, and 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 Law:

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.

B8.3.2.6 A statement of whether the participant will receive compensation for participating in the study or if it will cost the participant to be in the study.

B8.3.2.7 A statement stating who is sponsoring the study.

B8.3.2.8 A statement of whether there is a potential conflict of interest.

Explanation:

These Standards address appropriate elements of informed consent for subjects treated on clinical research protocols. Language the research subject can understand shall be conveyed via the process of informed consent following institutional policies and Applicable Law.

Evidence:

The informed consent document can be used to confirm that it is compliant with applicable regulatory requirements.

Example(s):

A Clinical Program may use template consents that cover all elements provided by a sponsor, IRB, Ethics Committee, or equivalent or write its own consents.

STANDARD:

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.

Explanation:

The purpose of this Standard is to require that the Clinical Program has a conflict-of-interest policy. Examples of conflicts include financial, academic, or any other incentive that would unduly influence the clinical investigator to enroll patients on clinical research protocols.

Evidence:

Management plans for identified conflicts of interest shall exist according to institutional policies and SOPs and in compliance with Applicable Law. The inspector may request to review the Clinical Program's or institution's conflict-of-interest policy to evaluate whether it is consistent with regulatory requirements.

Conflict-of-interest policies and SOPs shall be reviewed in conjunction with informed consent processes. Plans for managing identified conflicts of interest may vary according to Applicable Law.

Example(s):

The Clinical Program may follow its institution's policy on conflicts of interest or develop its own policy.

A clinical research investigator may have a potential conflict of interest in a product used in a clinical trial in which the investigator is participating, such as stock ownership, advisory boards, speaker's bureaus, or research funding. A conflict-of-interest management plan might include divulging the information to participants, depending on governmental and institutional mandates.

In the U.S., [21 CFR Part 54](#) applies.

B9: DATA MANAGEMENT

STANDARD:

- B9.1 The Clinical Program shall define staff responsible for collecting and reporting data.*
- B9.2 The Clinical Program shall collect and maintain complete and accurate data necessary to complete the Transplant Essential Data Forms of the CIBMTR or the Data Collection Forms of the EBMT.*

Explanation:

Maintenance of complete and accurate transplant data is essential for self-assessment and outcome analysis in individual Clinical Programs, for outcome reporting and research, and for compliance with these Standards. Clinical Programs are expected to comply with the rules of the relevant registry(ies) and Applicable Law in regard to data collection and maintenance. When a patient does not consent to use of their data, Applicable Law applies.

There are different processes for verifying complete and accurate data between FACT and JACIE. JACIE audits a small sample of data on behalf of the EBMT data registry using the Data Collection Form. FACT and CIBMTR administer a collaborative data assessment program to assist FACT-accredited programs to improve data management. There is an emphasis on the implementation of corrective action plans, intensified support between inspections, and follow-up to document continuous improvement.

For Clinical Programs audited by CIBMTR, FACT clinical inspectors do not perform a data audit during the on-site FACT inspection. The CIBMTR audit teams on site perform all verification of the accuracy of data against source data according to their current practices and schedules. Programs respond to the CIBMTR auditor according to the timelines defined by CIBMTR. FACT receives information from programs annually related to the results of these audits and manages the processes on an ongoing basis, depending on the needs of the program.

The FACT-CIBMTR Data Audit Committee reviews CIBMTR Data Audit reports. If CIBMTR requires a corrective action plan related to data accuracy, the Data Audit Committee also reviews the program's corrective action plan, progress on implementation of corrective actions, and internal audits assessing the effectiveness of corrective actions (see [B4.8](#) for elements of an audit report).

To be compliant with this Standard and achieve or maintain FACT accreditation, Clinical Programs must maintain all error rates in the satisfactory range as defined by CIBMTR and must actively participate in submission of required corrective action plans and progress reports. Accredited programs with a history of less-than-optimal CIBMTR results are given a grace period to demonstrate improvement. During this time, programs are expected to learn from prior audits, design appropriate investigations, implement effective corrective actions, and follow up to ensure

that improvements are made and sustained. This collaborative process is designed to help programs identify the issues that may be barriers to improvement and to develop strategies to be successful.

The FACT-CIBMTR Data Audit Committee reviews the program's past performance and determines the requirements for the FACT on-site audit. If deficiencies are found in data accuracy or completeness, these will be cited under Standard B9.1, and a corrective action plan will be required. The FACT-CIBMTR Data Audit Committee will assess the plan, the program's progress on the implementation of the corrective action, and internal data audits demonstrating improvement (see [B4.8](#) for the required elements of an audit report).

FACT and CIBMTR will apply consequences according to the same schedule. At the time of publication of this manual, the critical field error rate required by CIBMTR is $\leq 3.0\%$. Consequences may be applied if a program's critical field error rate is $> 3.0\%$ for two consecutive CIBMTR audits. Clinical Programs with CIBMTR consequences do have options for interim CIBMTR audits as defined by CIBMTR.

Evidence:

FACT clinical inspectors will have access to CIBMTR data reports during the inspection. The FACT-CIBMTR Data Audit committee will provide the FACT clinical inspectors with specific items to review (e.g., current internal data audit, progress on implementation of the corrective action plan). The clinical inspector should focus on adequacy of corrective actions and quality improvement. Where data management is outstanding and there are no CAPAs to review, the on-site inspectors may ask to see commendable practices that have resulted in exemplary data management.

The Clinical Program must also provide evidence of its own periodic data audits to determine if data are accurate for evaluation of patient outcomes as specified in [B4](#). The choice of data to be audited is a decision for the program but should include those listed in [B4](#) at a minimum.

Example(s):

As the CIDR program sunsets, cellular therapies activities will shift under Adoptive Cellular Therapies (ACT), which will include other cell and gene therapies (more information about this is available at <https://cibmtr.org/CIBMTR/About/Administrative-Committees/Adoptive-Cellular-Therapies-ACT-Council>). [CIBMTR's data collection forms](#) (both the Transplant Essential Data forms and the Cellular Therapy Essential Data forms) and [EBMT's data collection forms](#) are easily accessible online.

Clinical Programs applying for accreditation of their cellular therapy programs should use the appropriate CIBMTR forms for these therapies. Programs should use the forms that are appropriate for the cellular therapy products they administer.

Data registries may have basic data forms and expanded forms intended for research. Both of these types of forms are acceptable under this Standard.

STANDARD:

B9.2.1 Clinical Programs shall submit the data specified in B9.2 for allogeneic and autologous transplants to a national or international database.

Evidence:

In the event that the Clinical Program does not submit data to CIBMTR or EBMT, it should provide reasonable explanations for not submitting the data.

The Clinical Program should furnish evidence of its own periodic data audits to determine if data are accurate for evaluation of patient outcomes as specified in [B4](#). The choice of data to be audited is a decision for the program but should include those listed in [B4](#) at a minimum.

Example(s):

Allogeneic transplant patient information and outcomes are to be reported to the [Stem Cell Therapeutic Outcomes Database \(SCTOD\)](#), managed by the CIBMTR, by all U.S. centers according to law. Clinical Programs in the U.S. may also receive transplant outcome data from the Stem Cell Therapeutic Outcomes Database.

STANDARD:

B9.2.2 Clinical Programs shall collect and submit the data specified in B9.2 for all patients for at least one (1) year following administration of the cellular therapy product.

B9.2.3 Clinical Programs should meet accuracy criteria established by FACT or JACIE, and CIBMTR or EBMT.

B9.2.3.1 If data accuracy criteria are not met, the program shall implement a Corrective Action Plan that meets FACT or JACIE requirements.

B9.3 The Clinical Program should collect and submit all data elements included in the Cellular Therapy Essential Data forms of the CIBMTR or the Data Collection Forms of the EBMT.

Explanation:

This Standard, B9.3, is a recommendation to collect and submit data to registries applicable to cellular therapy products other than those intended for transplantation for hematopoietic reconstitution, such as IECs. Programs may choose a national OR international database they wish to submit to; FACT does not mandate which database they submit data to. For programs which report quality data to an organization other than CIBMTR or EBMT, the recommendation is to collect the same information found in the Cellular Therapy Essential Data forms of the CIBMTR or the Data Collection Forms of the EBMT. When a program submits a compliance application and the Data Audit Committee is made aware of which database they are submitting to, the committee will determine if the data being submitted is adequate (equivalent to the standard).

Clinical Programs providing non-transplant cellular therapy programs (such as CAR T-cell products or regenerative medicine) should use the appropriate CIBMTR or Data Collection forms for the cellular therapy products they administer. Some of these therapies have very specific forms and some are included in general cellular therapy forms.

Example(s):

CIBMTR collects data for IECs via Adoptive Cellular Therapies (ACT), and their data collection forms are available on their website ([CIBMTR Data Collection Forms](#)). EBMT's cellular therapy data collection forms accommodate IECs and should be used for these cellular therapy products ([EBMT Data Collection Forms](#)).

B10: RECORDS

STANDARD:

B10.1 There shall be a records management system for cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

Explanation:

A record is defined as documented evidence that activities have been performed or results have been achieved. A record does not exist until the activity has been performed. Each Clinical Program has the flexibility to develop an individualized system of organizing and maintaining records as long as certain objectives are achieved. The record keeping system must be documented and should include at a minimum:

- Location of new and completed forms.
- Method of error correction that prevents obscuring the original entry and indicates the identity and date of the individual modifying the record.
- Method to prevent destruction or loss of the record.
- Method of documenting modifications and distribution.
- Time of retention and proper storage location.
- System to secure confidentiality of records.
- Methods for filing and transfer of records to archival storage.

Each Clinical Program has the flexibility to develop individualized systems of maintaining and organizing records as long as the objectives of the Standards are achieved. The methods for filing and transferring records to archival storage should be specified in the quality manual.

STANDARD:

- B10.1.1 A records management system shall be established and maintained to facilitate the review of records.*
- B10.1.2 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.*
- B10.1.3 Records shall be maintained to ensure their integrity, preservation, and retrieval.*

Explanation:

Records may be maintained in more than one location, provided that the records management system is designed to safeguard prompt identification, location, and retrieval of all records. The methods for filing and transfer of records to archival storage should be specified in a policy or in the SOP manual.

Example(s):

It is recommended that recent records be kept on-site and archived records are readily accessible within a reasonable time frame.

Records may be maintained as original paper records, electronic files, photocopies, digital images, or on microfiche or microfilm. Electronic records must be backed up on a regular basis and stored to prevent their loss when records are maintained in common electronic portable formats. Examples of common formats include but are not limited to portable document format (PDF), extensible markup language (XML), or standard generalized markup language.

STANDARD:

- B10.1.4 Records shall be accurate and legible.*
- B10.1.5 Written records shall be indelible.*
- B10.1.6 Safeguards to secure the confidentiality of all records and communications among the clinical, collection, and processing staff and with donors and recipients shall be established and followed in compliance with Applicable Law.*

Example(s):

Breaches in policy that might compromise confidentiality include the following:

- Unsecured patient records.
- Patient charts left unattended in areas where unauthorized personnel or visitors may have access or unattended computer screens displaying patient information in such areas.

- Patient charts or records, in hard copy or electronic format, involuntarily displayed during video conference or video calls.
- Indiscriminate discussions using patient-specific identifiers in the presence of unauthorized personnel or visitors.
- Patient information posted on chalk or bulletin boards that is potentially visible to unauthorized personnel or visitors.
- Release of confidential information without appropriate consent and approval.

Confidential storage may consist of maintaining the records in a locked room with access restricted to authorized personnel or the use of locked file cabinets. The Clinical Program must have SOPs describing the maintenance of donor and recipient confidentiality (see [B5.1.1](#)).

STANDARD:

B10.2 The Clinical Program shall define and follow good documentation practices.

Explanation:

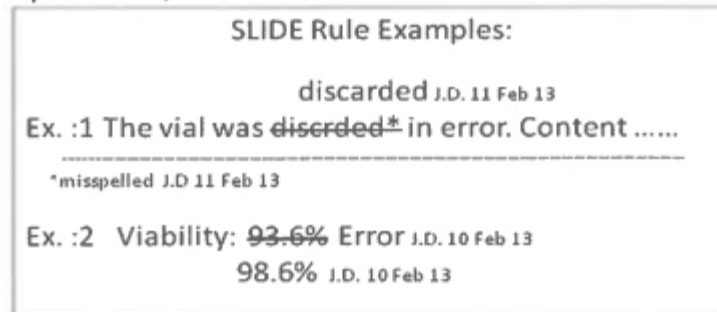
Good documentation practices are the guidelines that ensure records are created and maintained in a consistent manner, legible, indelible, accurate, and allow traceability to the person, date, and if applicable, time, of each event and entry. Good documentation practices should be used for all controlled documents and facility records, including forms, worksheets, training records, calibration logs, cleaning logs.

Example(s):

Examples of good documentation practices include:

- Data entry must be clear and legible.
- Use indelible blue or black ink. Avoid gel pens, felt tip pens, or pencils.
- Make record entries at the time the task was performed (i.e., concurrently).
- Do not use ditto marks or continuation lines to include several data entry fields.

- Do not use correction fluid, correction tape, or overlay of labels.
- Use the example below to correct errors:
 - **Single Line** – Draw a single line through the error. The cross-out must permit the reading of the original information.
 - **Initial and Date** – Add initial of person making correction and date of correction.
 - **Errors** – Explain errors, if reason is not obvious.



Each facility should have an SOP that describes the details of the expected practices. Facility-specific SOPs may include such issues as a standardized format for date and time, expectations for attaching a label or printout to records, or other details. Good documentation practices can be found via the U.S. Pharmacopeia or clinical research offices.

STANDARD:

B10.3 RECORDS TO BE MAINTAINED

B10.3.1 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 after the creation of the record or according to Applicable Law.

Explanation:

QM records include all of the items referred to in [B4](#), including the results of audits, Occurrence Reports, complaints, and outcome analysis.

Personnel training and competency records include all of the items referred to in [B3](#) (Personnel), for all attending and consulting physicians, APPs, all letters documenting initial training, all competencies for procedural skills as routinely practiced in their facility, nursing training records, and the names of key individuals responsible for support services (coordinators, pharmacy, dietary, social services, physical therapy, and data management).

Facility maintenance records include all of the items referred to in [B2](#) (Clinical Unit), including documentation of facility testing and validation for control of air quality and microbial contamination; dates and extent of repairs on mechanical systems; dates and extent of renovations

and new construction; preventive maintenance on equipment; personnel responsible for cleaning and additional training records when required; safety training for biological, chemical, and radiation exposure or disposal; and the outcome of any building or clinical unit inspections for safety or compliance with governmental or other agencies.

Facility management records are comprised of management issues related to facility maintenance, including a list of responsible individuals and their respective job titles, areas of oversight, and resolution of facility problems.

General facility records include global policies for the entire institution of which the Clinical Program is a part. These may include disaster plans; fire response and safety plans; biological, chemical, and radiation disposal policies; and confidentiality requirements.

Evidence:

It is suggested that Clinical Programs have readily accessible records for at least quality control and personnel training and competency for the last three years for inspector review. A written SOP should indicate the methods for filing and transfer of records to on- or off-site archival storage and how and for how long records are archived.

Example(s):

An example of a records management system is the electronic medical record. Electronic records must be backed up on a regular basis and stored to prevent their loss. The Clinical Program must make provisions for all records to be maintained for the required period in the event that the program ceases operation.

STANDARD:

B10.3.2 Records of validation studies for a clinical procedure shall be retained at a minimum until the procedure is no longer in use.

Explanation:

Validation studies must be retained in the event of occurrences that require retroactive investigation. Electronic storage of validation studies is acceptable. Documentation includes the procedure that was validated, the validation plan and data, and the validation results.

STANDARD:

B10.3.3 Employee records shall be maintained in a confidential manner and as long as required by Applicable Law.

B10.3.4 Cleaning and sanitation records shall be retained for at least three (3) years or longer in accordance with Applicable Law or by a defined program or institution policy.

Explanation:

An exception to the 10-year requirement for retention of Clinical Program records is for the documentation of cleaning and sanitation. These records only need to be retained for at least three years after creation but should include cleaning schedules, methods, and identification of personnel responsible for cleaning. There should also be documentation for the initial training and retraining of personnel as needed.

Evidence:

If documentation of cleaning and sanitation is performed directly by the Clinical Program's institutional environmental services department, then the Clinical Program should have knowledge of this documentation and the ability to show that it is complete.

STANDARD:

B10.3.5 Records to allow tracking and tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, or as required by Applicable Law, whichever is latest.

Explanation:

Records related to cellular therapy products should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for collection is critical for tracing purposes in the event of a problem, recall, or adverse event.

Evidence:

The inspector should ask who is responsible for records and where these records are maintained and determine if an organized system is in place that allows timely retrieval.

Example(s):

In the U.S., NMDP requires that records pertaining to the traceability and tracking of all aspects of the manufacture of the products managed by them to be retained indefinitely, as should records of adverse reactions and post-donation complications, treatment interventions, and recovery.

Per the EU [Directive 2004/23/EC](#) (see Article 8), tissue establishments must keep the data necessary to ensure traceability at all stages. Data required for full traceability must be kept for a minimum of 30 years after clinical use.

STANDARD:

B10.3.5.1 These records should include the product code and unique numeric or alphanumeric identifier.

Explanation:

In order for the records to allow tracking and tracing of cellular therapy products, it is recommended that the Clinical Program will keep the product code and unique numeric or alphanumeric identifier of part of the record. Records must be accessible upon request. For products where ISBT 128 coding and labeling practices were not used, an alternative unique identifier should be used.

STANDARD:

B10.3.6 Recipient and donor records including, but not limited to, consents and records of care, shall be maintained in a confidential manner as required by Applicable Law for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, whichever is latest.

Explanation:

Allogeneic donor eligibility determination files, including results and interpretation of testing and screening, are part of patient and donor files. These can be stored electronically or as hard copies. These records must be maintained with a secure system that guarantees absolute confidentiality and is in compliance with regulations and Applicable Law on confidentiality and data protection. The inspector should be alert to breaches in policy or security that potentially compromise patient confidentiality.

Patient and donor records must be maintained for a period of at least 10 years after administration (or if not known, after distribution, disposition, or expiration) or longer if required by Applicable Law.

Example(s):

In EU Member States, donor records required for full traceability must be maintained for a period of 30 years per [Directive 2006/86/EC](#). Consequently, records must be maintained for the duration of follow-up. In the U.S., Health Insurance Portability and Accountability Act (HIPAA) regulations on confidentiality and data protection apply.

STANDARD:

B10.3.7 Research records shall be maintained in a confidential manner as required by Applicable Law for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

Explanation:

Research records should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. If research records are stored independently of patient records, the same considerations regarding confidentiality apply. The sponsor of the research and/or governmental authorities may place specific requirements for long-term maintenance of research records. In addition to maintaining research records for a duration as required by Applicable Law, research records should also comply with GxPs.

STANDARD:

B10.4 ELECTRONIC RECORDS

B10.4.1 The Clinical Program shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures. For all critical electronic record systems:

Explanation:

The definition of an electronic record is "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." This Standard requires Clinical Program to establish and maintain a current listing of all critical electronic record systems specific to cellular therapy treatment. As facilities utilize more electronic systems, it is important that they maintain a list of which ones are critical.

Electronic record systems are considered critical when they are used in any of the following manner:

- As a substitute for paper.
- To make decisions based upon the data stored or created by the electronic record system (including outcome analysis).
- To make calculations via automated functions.
- To create or store information that is input into critical processes (whether the electronic record system is used during critical processes or used as source data for critical procedures).

It is not the intent of the Standards to include hospital-based systems and clinical medical records. These systems are typically inspected by hospital-based regulatory and accrediting organizations. Furthermore, Clinical Programs may not have the authority to direct validation studies on these systems. Any data system that does exist within the scope of control of the Clinical Program is required to meet these Standards.

Each Clinical Program must determine in advance whether the staff will depend on an electronic or paper record to perform a regulated activity. This determination should be documented for all records created and maintained by the facility.

Evidence:

Inspectors should assess the Clinical Program's list of critical electronic record systems to confirm it includes all electronic record systems used by the facility that meet the criteria in this Standard. Additionally, a list that matches critical record types to specific record systems should be provided pre-inspection (e.g., electronic laboratory record versus paper eligibility record).

The inspector should determine the scope of electronic records used by the Clinical Program and any circumstances in which the electronic record is used as a substitute for a paper record.

If electronic records are used in addition to paper records, the inspector should evaluate the electronic records to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.
- The system has limited access by authorized individuals.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.
- Documentation that the individuals performing the development, maintenance, or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- The electronic system is not the sole method for storing or retrieving needed records.

Example(s):

Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

If an electronic record of the location of a cellular therapy product in storage is printed for the chart and the information is verified by a signature or initials, and this printed record is then used by personnel to retrieve the product at the time of distribution, the electronic record is not considered to have been used as a substitute for a paper record.

If a computerized system (word processor) is used to generate SOPs, validation is not required since the quality and safety of a cellular therapy product would not be directly affected. However, if a computerized system is used to make a critical calculation (e.g., T cell dose, DMSO concentration, CD34 cell recovery) and the electronic calculation is the only calculation performed, validation is required to ensure that the calculation is always performed correctly under any circumstances. However, if the computerized calculation is used to confirm a manual calculation, and the manual calculation is used for manufacturing purposes, the extent of validation need not be as extensive as in the previous example.

In the U.S., for electronic records used as a substitute for paper, the inspector should refer to the FDA document [Part 11, Electronic Records; Electronic Signatures - Scope and Application](#) (2003), for guidance to assess the validation procedures, as well as the applicable requirements of HIPAA. In the EU, the inspector should refer to the Modular Requirements for Electronic Records and Document Management ([MoReq](#)).

STANDARD:

B10.4.1.1 There shall be policies, Standard Operating Procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

B10.4.1.2 There shall be a means by which access is limited to authorized individuals.

B10.4.1.3 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

Explanation:

In case of error or ambiguity, a method must exist to allow traceability of data entered into the electronic record system to the staff member who performed the entry. This may take the form of an audit trail maintained internally by software, or it may take the simple form of a login sheet on which staff members record their session with the electronic record system and identify what data was entered in that session.

Example(s):

To identify individuals responsible for record entries, several options exist. Examples include using a sign-in sheet when using the system or using a worksheet to create an audit trail of each data element. More sophisticated systems usually have an automated system that tracks record entry based upon an individual's login credentials.

STANDARD:

B10.4.1.4 There shall be written policies and Standard Operating Procedures for record entry, verification, and revision.

B10.4.1.5 A method shall be established or the system shall provide for review of data before final acceptance.

Explanation:

The final review and acceptance of entered data do not require a second individual to verify the data. Nor does the identification of individuals responsible for record entries need to be automated. The intent of the Standard is to be certain all data is verified to be correct and to maintain documentation of who has entered pieces of information.

STANDARD:

B10.4.1.6 There shall be documented training of personnel in the system's use.

B10.4.1.7 There shall be a defined process for continued competency of personnel in the system's use.

Explanation:

Personnel must be trained to appropriately use all critical electronic record systems (including record entry, verification, and revision) and backup processes when the critical systems are not available. This training must be continuous, including initial training and ongoing training as SOPs are revised and issues with the use of critical electronic record systems are identified.

As with all other cellular therapy treatment activities, the staff members who utilize the electronic record system must be trained for such use. Moreover, just as SOPs are required for cell manipulations, SOPs must also be in place to describe how to enter, process, and retrieve data using the electronic record system. Competency of staff using the system must be documented on a regular basis (annually at a minimum) and must also be documented with changing versions of the systems in use.

STANDARD:

B10.4.1.8 There shall be a defined process for the use of electronic signatures.

Explanation:

The term "electronic signature" shall be clearly and precisely defined. The definition shall specify what constitutes a valid electronic signature and delineate how the electronic signature will be used and interpreted. The policy defining electronic signature shall include the following elements: the method of creating the signature (e.g., typing a name, using a mouse to draw, clicking an "accept" button), the elements included (e.g., first and last name, role/title, time and date stamp), a statement

that the electronic signature is legally binding, and the type of records to which the signature applies (e.g., manufacturing batch records, regulatory documents, audits, validations review, contracts, agreements). The method of creating a signature and the intended use may vary among Clinical Programs.

The Clinical Program needs to define when, under what conditions, and for which programs it is appropriate to utilize electronic signatures.

STANDARD:

B10.4.1.9 Unique identifiers shall be maintained.

B10.4.1.10 There shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

B10.4.1.11 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

B10.4.1.12 All system modifications shall be authorized, documented, and validated prior to implementation.

B10.4.2 For all critical electronic record systems under the control of the Clinical Program, there shall be processes for and documentation of.

Explanation:

Establishment of an electronic record keeping system that meets one or more of the criteria for a critical electronic record system requires validation. The extent of validation is somewhat dependent upon whether the computerized system was developed in-house, custom-built by an outside vendor or consultant, or developed from off-the-shelf software.

Validation procedures of critical electronic systems include, as appropriate, such elements as:

- Documentation of development requirements and function.
- Verification that calculations are performed correctly.
- Evidence that records reproducibly contain the desired information.
- Tests of system functions under “worst case” scenarios such as system overloads (e.g., too many simultaneous users, too many simultaneous processes being performed [such as too many programs open on a Windows desktop]), and power failures.
- A method for data verification before final entry.
- Internal consistency checks to verify that values are within defined ranges.
- Restricted entry of data to match predefined value limits.
- Required entry of data with field information limited with choices for data consistency.

- Source data is derived from pre-defined sources such as fixed forms. "Monitoring for data integrity" means establishing assurances that data has not been changed either by accident or by intent, and this requires access to original documents whenever possible, along with a plan for verification of the electronic system data by comparison to original data.
- Evidence of a schedule of regular backups that includes storage of backup data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the backup copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include the information entered into the database, acceptable sources of the entered data, and a description of system maintenance and development history.
- Formal and documented training in system use requirements for all personnel.
- Evidence of SOPs in place for computer record-keeping systems.
- Regular quality audit trails.
- A mechanism to report deviations and to ensure that problems are reported and resolved.
- Evidence that changes to records do not obscure previously entered information.
- Documentation that deleted electronic files have been converted to non-electronic media such as microfilm, microfiche, or paper in a manner that preserves the content and meaning of the record.

Evidence:

While details of the validation system may be located in an institutional department of information services or elsewhere, the Clinical Program shall have a summary of the validation available to the inspector.

If electronic records are used in addition to paper records, the inspector should evaluate the electronic record system to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.
- The system has access limited to authorized individuals and that documentation is generated to identify which individuals have accessed the system and made record entries.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.

- Documentation that the individuals performing the development, maintenance or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- Procedures are in place to provide for record keeping in the event of failure of the electronic record system, and that the staff members who may have to follow these procedures are trained in their use.
- A process for generating backups of records maintained electronically is in place.

STANDARD:

B10.4.2.1 Prospective validation of systems, including hardware, software, and databases.

B10.4.2.2 Installation of the system.

B10.4.2.3 Numerical designation of system versions, if applicable.

B10.4.2.4 Authorization and validation of all system modifications prior to implementation.

B10.4.2.5 Systems development including the verification of calculations and algorithms.

B10.4.2.6 System maintenance and operations.

B10.4.2.7 Monitoring of data integrity.

B10.4.2.8 Backup of the electronic records system on a regular schedule.

B10.4.3 For each critical electronic record system, there shall be an alternative system to allow for continuous operation of the Clinical Program if the critical electronic record system is not available. The alternative system shall be validated, and clinical personnel shall be trained in its use.

STANDARD:**B10.5** *RECORDS IN CASE OF DIVIDED RESPONSIBILITY*

B10.5.1 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.

Explanation:

Most, but not all, Clinical Programs will have some of the activities or services covered by the Standards performed by another entity in the same institution or in another institution. In such cases, the conditions under which the activity or service is performed must be documented through written agreements. When the facilities are within the same institution, the responsibilities may be written in a policy or other type of document.

These agreements should clearly define roles and responsibilities for critical tasks. All such agreements should be dated, reviewed and renewed on a regular basis, and include provision for the maintenance of records following termination of the agreement. How such agreements are executed is a function of the type of Clinical Program.

The agreements must clearly define the role and responsibility of the contracted facility to comply with all governmental regulations and Standards that are applicable to the performed services. The contracted facility must also adhere to critical processing, storage, and distribution standards defined by the contracting facility, although the contracted facility does not have to be accredited by FACT or JACIE. The contracting facility must have implemented a process to verify that services are performed in compliance with all applicable Standards and regulations.

The Clinical Program's records should include relevant contracts and agreements, and the Clinical Program is responsible for compliance with the Standards. The entire record of the outside facility(ies) need not be duplicated for the facility record. However, the facility record should allow tracing and tracking of relevant information to the correct source. For example, the facility may manufacture products for multiple clinical programs.

The facility record should indicate where the product was collected, stored, and/or administered but does not need to contain a record of the supply and reagent lot numbers used for steps performed at the Collection Facility or Processing Facility. The facility should verify that such relevant and appropriate records will be maintained by the facility that performs the work. Records of allogeneic donor eligibility screening and testing must be provided to the facility.

Maintenance of records must be specified in the SOPs, and it must be clear who is responsible for maintaining records. In general, records should be sufficiently detailed to enable tracking and tracing from a donor to a recipient or final disposition and vice versa.

Donor and recipient confidentiality must be maintained through the use of identifiers whenever the identity of the unrelated donor must remain anonymous. The location of each facility must be known to the relevant personnel at each facility but should not be known to the recipient. To that end, the Clinical Program may not know the identification or location of the Collection Facility in the case of a product obtained through an unrelated donor registry. Facilities that participate in programs such as NMDP or other donor registries will have well-defined procedures for divided responsibility. Applicable rules and regulations regarding the sharing of confidential information must be followed.

QM Plans must include the concept of written agreements even if no agreements are currently in place at the Clinical Program. The purpose is to outline the general process for establishing agreements should the need arise. Extensive detail is not required, but the plan must minimally describe who is responsible for reviewing and approving agreements and require that agreements include the external facility's responsibility to comply with the Standards in their activities relating to the Clinical Program.

In the event the Clinical Program (or entities with which the facility has agreements) terminates its activities, it is essential that traceability data and material concerning the quality and safety of the cellular therapy products be provided to the relevant parties.

Evidence:

The inspector should review the process for establishing agreements or contracts with entities outside of the Clinical Program that participate in product collection, testing, storage, transport or other critical services that might affect the quality of the product. In the case of donor registries, they should be accredited by the WMDA. If agreements exist, examples should be reviewed by the inspector for adherence to the facility's established process. In all cases, a process must exist for the development and implementation of such agreements. The inspector should verify that there is a process in place to assess compliance with the requirements and that this process is effective. Copies of those agreements should be available to the inspector on the day of the inspection.

Example(s):

Written agreements should be reviewed every two years, similar to SOPs, although a greater or lesser time interval may be appropriate under some conditions. The effective dates of an agreement could be specified within the agreement itself. It would be helpful to have a list of written agreements to inventory whether each one is reviewed and renewed appropriately.

For services provided with the same institutions, shared policies or procedures that address expectations and performance quality can be interpreted as agreements. For Clinical Programs receiving products facilitated through donor registries, agreements may be through those registries.

Such agreements may include, but are not limited to donor qualification, determination of donor suitability and eligibility (allogeneic donors only), collection of the product, donor or product testing, and long-term storage.

Stand-alone facilities may carry out agreements directly with the service providers (or institutions for which they provide services), whereas agreements involving Clinical Programs in academic institutions may be between the institution and the service provider.

Audits of external facilities may be accomplished by reviewing the Clinical Program's internal and external audit reports, performing on-site inspections for compliance, receiving period performance reports from the facility, or the Clinical Program can audit its experience with the contracted facility using data that it defines and collects. There may be other alternatives, but the contracting facility must verify that their contracted services are meeting requirements.

STANDARD:

B10.5.2 The Clinical Program shall furnish outcome data related to the safety, purity, or potency of the cellular therapy product to other facilities involved in the collection or processing of the cellular therapy product.

Explanation:

This Standard applies to both in-house and contracted collection, processing, or administration. Records need not be duplicated as part of the clinical record. Generally, relevant and appropriate records will be maintained by the Clinical Program, Collection Facility, or Processing Facility that performs the work. Maintenance of records must be specified in the SOPs, and it must be clear who is the party responsible for maintaining records. The clinical record should allow tracing and tracking of relevant information to the correct source.

It is expected that the Clinical Program will have an arrangement with a Collection or Processing Facility that meets FACT-JACIE Standards as the main source of cells. Cells may also come from other places, such as third-party manufacturers. In those situations, it is the responsibility of the Clinical Program to clearly outline what the other facilities' (e.g., third-party manufacturer) requirements are to help achieve quality cellular therapy.

Donor and recipient confidentiality must be maintained through the use of identifiers when this is required by unrelated donor registries. The location of each Collection or Processing Facility must be known to the relevant personnel at both, but it does not need to be known to the recipient or donor. Collection or Processing Facilities that participate in programs such as NMDP will have well-defined procedures for divided responsibility. Where applicable, Applicable Law regarding data confidentiality must be followed. In the case of the NMDP, the appropriate Limited Data Set Use Agreement should be in use. NMDP's *Data Use and Processing Policy* is available at <https://network.nmdp.org/policies-protocols> (under Transplant centers, Additional resources).

Evidence:

If divided responsibility occurs regarding any aspect of the cellular therapy process, a relevant patient file can be used to confirm that an appropriate mechanism is in place to track and trace the

process from beginning to end and vice versa. A written SOP should describe specific responsibilities of each party of the divided responsibility.

There should be SOPs regarding dissemination of outcome data, and the process must be in place accordingly.

Example(s):

Clinical Programs that consist of pediatric and adult services at different hospitals may perform cellular therapy product collections at one institution that are used for a patient at another institution. An example would be if a child received a haploidentical transplant from a parent and the donor cells were collected at the adult hospital and administered to the recipient at the pediatric hospital. Another example would be if a patient with non-Hodgkins Lymphoma had autologous PBSCs collected in first remission at one hospital and these cells were transferred to a second hospital for an autologous transplant.

Donor eligibility is another example in which responsibility is typically divided. Clinical Programs are usually responsible for performing donor eligibility determination. Those programs must provide donor eligibility records to the Collection Facility so that the collection staff can verify that an eligibility determination was made. It should be obvious in the record who performed each of these responsibilities.

Data to be provided to other facilities involved in the collection or processing of the cellular therapy product includes adverse effects of administration, other adverse events related to the product such as transmission of infection, and engraftment data. Other data, such as temperature on arrival of products, may be required by the Collection or Processing Facilities.

PART C: COLLECTION FACILITY STANDARDS

- [C1:](#) General
- [C2:](#) Collection Facility
- [C3:](#) Personnel
- [C4:](#) Quality Management
- [C5:](#) Policies and Standard Operating Procedures
- [C6:](#) Allogeneic and Autologous Donor Evaluation and Management
- [C7:](#) Coding and Labeling of Cellular Therapy Products
- [C8:](#) Equipment, Supplies, and Reagents
- [C9:](#) Process Controls
- [C10:](#) Cellular Therapy Product Storage
- [C11:](#) Cellular Therapy Product Transportation and Shipping
- [C12:](#) Records

PART C: COLLECTION FACILITY STANDARDS

C1: GENERAL

STANDARD:

C1.1 These Standards apply to all collection, storage, and distribution activities performed in the Collection Facility for cellular therapy products.

Explanation:

Part C of the Standards applies to all activities on a cellular therapy product obtained by apheresis, peripheral blood, marrow, and other tissue collections, which include storage and distribution. Once a product has been collected, it is stored until it is distributed from the Collection Facility. Distribution after collection may be directly to the Clinical Program, to a third-party manufacturer, or to the Processing Facility for further processing and storage.

When a Collection Facility has multiple sites, the structure of the facility must allow for integrated and regular interaction among all members of the collection team. All sites must operate under one QM Program; the Collection Facility Director must have a presence at each site; and consistent processes for regulatory compliance, personnel training and competency, document control, review of outcomes analysis, and product efficacy must be established.

Additional Standards may apply to certain cell collections, such as collection of marrow from cadaveric or beating heart donors. It is not the intent of these Standards to encompass all professional standards or Applicable Law for beating heart donors; however, FACT or JACIE accredited Collection Facilities performing activities with these types of donors must comply with the Standards as they apply to these circumstances.

STANDARD:

C1.2 The Collection Facility shall abide by Applicable Law.

Explanation:

FACT and JACIE are voluntary inspection and accreditation organizations that develop professional standards designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with the Standards does not guarantee compliance with Applicable Law. Governmental regulations must also be followed. It is the responsibility of the individual Collection Facility to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the facility may apply; for example, when a facility is sending or receiving cellular therapy products from outside of its immediate jurisdiction. In the EU, Collection Facilities must comply with [Directives 2004/23/EC](#), [2006/17/EC](#), and [2006/86/EC](#), which define quality and safety standards for the donation, procurement, and testing of human tissues and cells.

Compliance with other organizations' standards or governmental regulations does not ensure that the Standards have been met. Governmental regulations supersede any organization's standards if those regulations set a higher standard or are inconsistent with a specific standard. However, if a standard is more rigorous than a governmental regulation, that standard must be followed.

Evidence:

While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with Applicable Law. Evidence of compliance with the Standards will require pre-inspection information identifying prevailing governmental authorities and documentation of certificates, permits, or licenses.

Example(s):

In the U.S., minimally manipulated cellular therapy products from first- or second-degree related donors are regulated under the [21 CFR Part 1271 Subpart D](#) GTP regulations and section 361 of the Public Health Service Act, with the exception of products collected from bone marrow as a source of cellular therapy products. A cellular therapy product that is extensively manipulated, obtained from an unrelated donor, combined with a drug or device, or used for non-homologous use (i.e., does not perform the same function in the recipient as in the donor) is regulated as a drug, device, and/or biological product under section 351 of the Public Health Service Act and other applicable regulations in [Title 21](#) of the CFR. It is the responsibility of the Collection Facility to verify that the contracting entity for whom it performs services possesses an approved IND or BLA.

In the Member States of the EU, both HPCs and T cells fall under the European [Directive 2004/23/EC](#) of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, as well as the implementing Directives [2006/17/EC](#) and [2006/86/EC](#). Under these Directives, a tissue establishment license from the Competent Authority is required, and the tissue establishments need to notify the Competent Authority of serious adverse events and reactions of tissues and cells. Additionally, some member states require specific authorizations delivered by the Competent Authority for minimally manipulated cell products that are not classified as MPs.

[Directive 2001/83/EC](#) regulates products that are classified as MPs for human use. This includes somatic cellular therapy MPs and gene therapy MPs. The TMP-[Regulation \(EC\) No 1394/2007](#) entered in force on December 30, 2007 to include tissue-engineered products. The consequence of classification as an MP is that a GMP environment is required for the production of these cells. Furthermore, each Member State in the EU may add additional regulations to the directives that also must be followed. Member State-specific regulations will not be detailed here. The current EU Directives will be replaced by [Regulation \(EU\) 2024/1938](#) of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application. The regulation will be fully applicable from August 7, 2027.

STANDARD:

C1.2.1 The Collection Facility shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

Explanation:

Applicable Law may require registration or certification with the government or may require accreditation from professional organizations for the activities performed within the facility.

Evidence:

Documentation of registration with the relevant governmental authorities will be sent to the FACT or JACIE office with the accreditation application materials. The inspector may also ask to see it on-site. A copy may not be immediately available in the Collection Facility; however, the Collection Facility Director or Medical Director should know who in the institution is responsible for the registration and where a copy may be obtained. It is not appropriate to request a faxed copy from the regulatory authority during the on-site inspection.

Example(s):

Any facility that is involved with the collection, procurement, screening, testing, packaging, processing, storage, labeling, or distribution of cellular therapy products in the U.S. may be required to register with the FDA annually ([21 CFR Part 207](#), [Part 807](#), and [Part 1271](#)). This registration requires a listing of the activities in which the Collection Facility engages and a listing of each applicable type of cellular therapy product that is regulated under GTP or regulated as a medical device, drug, or biological drug. More information regarding the requirements and process for FDA registration can be found on the FDA webpage [Tissue Establishment Registration](#) (2021). Note that each activity performed by the institution must be registered, regardless of who performs the activity. A Collection Facility that is within a larger institution such as a hospital or medical center may combine its registration with other services related to the same regulations. Activities that may be performed by a Collection Facility include the screening of donors for infectious disease risk to determine eligibility or temporary storage of the collected material.

In the EU, the Competent Authorities in the Member States shall ensure that all tissue establishments have been accredited, designated, authorized, or licensed and that these establishments have implemented the EU Directive and other national regulations, where applicable.

Examples of verified compliance with regulations include acceptable FDA audits, hospital accreditation, (e.g., Joint Commission, DNV, HFAP) state licensure, licensing of tissue establishments by the Member State in the EU, CLIA certification, OSHA inspections, or accreditation by the AABB, CAP, or any other applicable accreditation body.

STANDARD:

C1.3 The Collection Facility shall have a Collection Facility Director, a Collection Facility Medical Director, a Quality Manager, and a minimum of one (1) additional designated staff member. The designated team shall have been in place and performing cellular therapy product collections for at least twelve (12) months preceding initial accreditation.

Explanation:

Facilities that are active in the collection of licensed blood products or therapeutic procedures may have significant collection experience from these activities; however, the facility and personnel must document specific experience in cellular therapy product collection.

Evidence:

Current employee files and CVs should document evidence of length of employment and experience with cellular therapy product collections.

In collection of tumors, the quality team overseeing the clinical activities could have oversight of the collected tumor tissues.

Example(s):

For marrow collections, the Quality Manager does not have to be solely dedicated to the Marrow Collection Service and will often oversee other areas of the organization.

STANDARD:

C1.4 The Collection Facility shall use cell processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Collection Facility.

Explanation:

Collection Facilities, including mobile apheresis services or donor centers that provide donor management or cell collection activities, must use cell processing facilities that meet the requirements of the Standards in order to be eligible for accreditation. The Processing Facility is not required to be formally acknowledged as FACT or JACIE accredited; however, even if not pursuing accreditation, the facility must comply with the Standards.

Evidence:

Processing Facilities must be inspected to ascertain that they meet the Standards in regard to their interactions with the Collection Facility. If a Processing Facility is already FACT or JACIE accredited to provide services to multiple facilities, this may satisfy the inspection requirement. If a facility is not FACT or JACIE accredited to provide these services, it must provide evidence of compliance with the Standards, including compliance with Applicable Law. Evidence includes pre-inspection documentation and on-site inspection.

Example(s):

Collection Facilities perform collection procedures for a variety of reasons. In addition to collecting cellular therapy products for transplantation, facilities may perform collection in support of research or products that require further manufacturing. Collection for these other purposes must be incorporated into the facility's QM Program. Facilities that only collect products for further manufacture may seek accreditation with this designation. This is a restricted accreditation, and any marketing must truthfully and completely disclose the limitations of the accreditation.

STANDARD:

C1.5 The Collection Facility shall meet the minimum number of cellular therapy product collections as defined in [Appendix V](#).

Explanation:

This Standard refers specifically to the number of collection procedures for cellular therapy products, not the number of donors from whom cells were collected, and may include both allogeneic and autologous donors. New facilities that want to gain the required experience needed for initial accreditation may conduct validation runs and use healthy volunteers for collection of cellular therapy products that are never to be administered. These would count toward the goal of 10 cellular therapy products collected by apheresis; however, those types of collections (healthy volunteers for products that are never to be administered) are not accepted for renewal accreditation.

Because of the risks to cellular therapy product integrity resulting from the many changes of product custody and risks to recipient safety related to administration, only procedures for therapeutic intent count towards the number of required procedures. This includes products that will be transplanted or distributed for further manufacture and ultimate administration. These products have increased requirements for teamwork, informed consent, and product handling.

A Collection Facility consists of one team of collectors, staff, and procedures. If a cellular therapy program applies for accreditation at two different collection sites, this minimum number of collection procedures applies to a single team. If there is little to no interaction between the sites, both sites must meet this minimum number.

This Standard allows Collection Facilities to apply for accreditation prior to meeting the minimum volume, but this is intended for exceptional circumstances. In this scenario, there must be adequate QM data to demonstrate compliance with the Standards, and the facility's team must be experienced (see [C3 Personnel](#)). Accreditation will not be awarded until the minimum volume is met. The facility must decide if it is in a position to accept the risk of not meeting the minimum volume (and not becoming accredited) within the accreditation timeline.

Evidence:

A review of current Collection Facility statistical reports can be used to ascertain whether the Collection facility has complied with the required minimum number of collection procedures performed based on the type(s) of cellular therapy product collection it performs (e.g., apheresis, marrow, other tissue).

Example(s):

FACT and JACIE will use the average number of collections per year over the accreditation cycle to determine if a Collection Facility meets the minimum collection volume. For example, if a FACT or JACIE accredited facility performs six apheresis collection procedures in the first year, 17 in the second, and then seven in the third, the program will have performed an average of 10 procedures per year during the accreditation cycle and will have met the Standard.

Cellular therapy programs performing adult and pediatric apheresis collection may collect from adult donors in one facility and pediatric donors in another. If different individuals perform collections at each of the sites, then both sites must perform a minimum average of ten collections per year within each accreditation cycle. Meeting this requirement at just one of the sites and not the other does not comply with the intent of the Standard.

STANDARD:

C1.6 *There shall be a process to qualify the sites for cellular collections, including at a minimum ensuring Chain of Identity.*

C1.7 *There shall be written criteria for each collection site that define the level of donor risk that can be safely managed.*

Explanation:

The Collection Facility, when collecting for both autologous and allogeneic donors, must have a process to verify that the facility is qualified to manage the acuity of the donor across an array of physical and psychological health concerns. Cell collection organizations, especially apheresis centers, may collect cells for administration or for further manufacturing at various sites. Some collection sites may be within an inpatient hospital or outpatient clinic; others may be free-standing collection sites. The Standard does not require that all sites be equivalent. Collection sites may vary in capabilities, capacity, potential for donor isolation, staffing, access to transfusion services, interventional radiology, or support for pediatric patients. Some collection sites may be relatively distant from the main facility and be most appropriate for collections from healthy adult donors without CVCs.

The intent of these Standards is that the Collection Facility must define what type of donors can be safely managed at each collection site. Variables to consider should include, at a minimum, ensuring Chain of Identity, expertise in central venous line management, expertise in pediatrics (if applicable), availability of blood components if needed for priming an apheresis device, and ready capability to

manage comorbidities such as obesity, cardiac dysfunction, or hypertension. It is acceptable to limit certain sites to specific types of donors.

Evidence:

The donor criteria for each collection site should be documented in the facility's QM plan, specific site description, or elsewhere.

Example(s):

The following are example statements that could indicate criteria for a collection site:

- Donors less than 25 kg must have collections performed at the collection site in the pediatric transplant unit.
- Donors at this specific site must have a platelet count above 100,000/mm³.

C2: COLLECTION FACILITY

STANDARD:

C2.1 There shall be secured and controlled access to designated areas appropriate for collection of cellular therapy products and for storage of equipment, supplies, reagents, cellular therapy products, and records.

Explanation:

Storage areas for cellular therapy products must be designated to specific personnel and have controlled access to prevent mix-ups and contamination regardless of the duration of the storage. Storage includes temporary holding of a product after collection and prior to transport to a Processing Facility. It is critical that the storage area be, at a minimum, secure and temperature-controlled and that the products be appropriately labeled and segregated, particularly for those products that may be held in the Collection Facility overnight and transported the following day.

Supplies and reagents used for collection must be stored in a manner that preserves their function and sterility. Upon receipt of supplies, kits, and reagents, inspection for acceptability must be documented. For items requiring storage at a specified temperature or humidity range, the temperature and/or humidity of the storage area must be monitored and documented.

For collections of marrow and other cellular products, the Standards may need to be applied differently between collection procedures performed in an operating room for hematopoietic reconstitution versus smaller outpatient collection environments for regenerative medicine regarding risk to the donor, equipment, space for personnel, etc.

Evidence:

Collection Facilities must submit a floor plan of the facility prior to the on-site inspection. Inspectors use these floor plans to gain a preliminary understanding of the designated areas and the flow of activities. The inspector will tour the Collection Facility during the on-site inspection, including all locations where cellular therapy products are collected, stored, and distributed. The areas should be designed to facilitate proper workflow and cleanliness. Observation of the organization, design, location, and amount of space available in the facility can determine if it is adequate for the number and types of collections it performs and if the collection environment is adequate to minimize the risk of product contamination. The inspector should also evaluate the inventory control system to determine if it is adequate to prevent the use of outdated or damaged supplies and reagents.

The inspector should observe storage areas and confirm that supplies and reagents are stored under the conditions specified by the manufacturer. When refrigerators are used to store cellular therapy products, supplies, or reagents, the inspector should look for evidence that each is appropriately labeled and adequately separated so as not to cause confusion or compromise the integrity or sterility of the contents.

Operating rooms are often subject to other accreditation and facility management requirements. Documentation of compliance with other accreditation or governmental agencies (e.g., CMS, the Joint Commission) may assist inspectors with verifying compliance with the Standards.

If there are no collection procedures occurring on the day of the on-site inspection, the inspector could ask that a mock collection be demonstrated. This allows assessment of the adequacy of the environment as well as the procedural details and staff knowledge.

The inspector should also verify that the other procedures performed using the same staff, instruments, and/or space do not put recipients or donors at increased risk of disease transmission. An example would be an infusion room where patients with infectious diseases are treated.

Example(s):

Adequate storage can be accomplished by storing cellular therapy products and supplies on a designated, temperature monitored shelf that is appropriately labeled for that purpose, utilizing designated labeled compartments, or by other procedures. It is recommended that outdated products and reagents and those not intended for clinical use be stored in a separate unit from those designated for patient care if possible. When this is not possible, outdated and research material must be clearly separated from clinical material and appropriately labeled.

A first in, first out system is one that is most commonly encountered. This mechanism can be tracked on paper or via a computer program.

STANDARD:

C2.1.1 *The designated area for collection shall be in an appropriate location of adequate space and design to minimize the risk of microbial contamination.*

Explanation:

There is no definition of adequate size; however, the size of the collection area should at least allow for safe practice and, in case of emergencies, allow for adequate room for resuscitation. There should be appropriate space between each donor or patient and an isolation room in order to prevent cross contamination, especially when the facility is also performing other therapeutic procedures.

STANDARD:

C2.1.2 *The collection area shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.*

Explanation:

A demonstration by personnel of where each of these activities is typically performed, how a cellular therapy product moves through the facility, and how products and associated paperwork are segregated if more than one product is present in the facility can demonstrate compliance. Inspectors should note safeguards in place to prevent mislabeling, inappropriate product release, or mix-ups. The physical facility should be orderly and organized according to a defined workflow.

Although there is no standard for the amount of space necessary to provide a safe environment for collection, the inspector should evaluate this issue. The inspector should investigate what other activities are performed on the equipment and in the space with the same staff. It is also helpful to see results of surveys submitted by donors and recipients.

STANDARD:

C2.1.3 *There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of cellular therapy products.*

Explanation:

The space used for collection and storage of cellular therapy products should be well-defined and adequate, and there should be designated space for preparation and storage of reagents and equipment.

Example(s):

Where applicable, [21 CFR 211.42\(b\)](#) in the U.S. requires that facilities have adequate space and segregation measures for the orderly placement of equipment and materials to prevent mix-ups and contamination between different components, including cellular therapy products. Separate or

defined areas, or other control systems, must be in place for operations as necessary to prevent contamination or mix-ups.

STANDARD:

- C2.1.4 *There shall be suitable space for confidential donor examination and evaluation.*
- C2.2 *The Collection Facility shall provide adequate lighting, ventilation, access to sinks for handwashing and to toilets to prevent the introduction, transmission, or spread of communicable disease.*

Explanation:

The layout and design of the Collection Facility must minimize the risk of error and permit effective cleaning and maintenance in order to avoid cross-contamination and mix-ups. The facility should be situated in an environment that presents minimal risk of causing contamination of materials and products and allows personnel to perform their duties safely. In the U.S., facility regulations are detailed in [21 CFR 211.52](#).

Evidence:

The inspector will observe the Collection Facility to determine if the collection environment is adequate to minimize the risk of introduction, transmission, or spread of communicable disease.

STANDARD:

- C2.3 *Environmental conditions shall be controlled to protect the safety and comfort of donors and personnel.*
- C2.4 *There shall be a written assessment of critical Collection Facility environmental parameters, including storage areas, that may affect cellular therapy product viability, integrity, contamination, or cross-contamination during collection.*
- C2.4.1 *The written assessment shall include temperature and humidity at a minimum.*
- C2.4.2 *Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.*
- C2.4.3 *If using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled, monitored, and recorded for air quality and surface contaminants.*

Explanation:

The intent of this Standard is not to require continuous monitoring. The Collection Facility must perform an assessment of conditions to determine if any parameters need to be controlled,

monitored, and recorded. This includes parameters that may directly affect the cellular therapy product and also conditions that would diminish equipment or personnel performance, such as extreme humidity. Some equipment has operating limits, but others do not. Each facility needs to define acceptance criteria ranges and verify that parameters are within those ranges.

Environmental monitors for measures of air quality, such as particle counts or microbial colony counts, may be recommended, but Applicable Law may not require specific air quality classification where collections are performed using closed systems.

Evidence:

If no parameters are controlled, the Collection Facility is requested to provide documentation of its reasoning prior to the inspection. It is the inspector's responsibility to determine while on-site if the parameters affecting cellular therapy product viability, integrity, contamination, or cross-contamination identified by the facility are appropriate. If the inspector believes a parameter not identified should be controlled, this will be indicated in the inspector's report and included for discussion by the FACT or JACIE Accreditation Committee.

Example(s):

Collections are typically performed in facilities that operate with unclassified air but may require control of temperature and humidity at a minimum to safeguard donor and personnel comfort in addition to cellular therapy product safety. Adverse temperatures and humidity levels may result in aborted collections and suboptimal personnel performance. Temperatures below freezing may damage products. Cellular therapy products collected in higher temperatures may have poor potency. High humidity can lead to the growth of mold or other organisms that could pose a threat to product sterility. However, this Standard does not specifically require control of temperature and humidity. For example, the facility may use humidity and temperature ranges recommended by equipment manufacturers to set limits. The facility may also reference facility management policies, such as the use of an air conditioning unit (which controls humidity in addition to temperature) that is maintained by the institution.

Contamination in the Collection Facility can be minimized through air filtration and by ensuring that the air pressure within the facility is positive to the surrounding areas (room pressure monitors should be used).

STANDARD:

C2.5 *The Collection Facility shall document facility cleaning and sanitation and shall maintain order sufficient to achieve adequate conditions for operations.*

Explanation:

Collection Facility cleaning and sanitation must be performed on a regular basis in order to prevent contamination and cross-contamination of cellular therapy products. There should be an approved method of cleaning of the facility and the equipment, and that cleaning should be documented.

The Collection Facility must define how documentation will occur, and this may vary depending upon location, such as apheresis collection areas and operating rooms. The methods used must be specified by an SOP. While the benchtop and equipment surfaces are most often cleaned and disinfected by facility personnel, other surfaces that may be cleaned by outside vendors such as floors, walls, and ceilings are also subject to this Standard. The facility, together with the cleaning services vendor, must establish SOPs for this activity.

Beds and chairs must be cleaned between patients. If an institutional policy is followed for the cleaning and sanitation of beds and chairs, the policy must be referenced within the Collection Facility's SOP, and the facility must be able to provide documentation that the cleaning and sanitation of the beds and chairs between patients has been completed.

For some collection procedures, equipment or instruments that come into contact with the cellular therapy product may require cleaning and sterilization between use. When this is the case, the Collection Facility must verify that the cleaning and sterilization methods used remove infectious agents.

The Collection Facility should follow local policies regarding cleaning and sanitation. These policies will usually be from the hospital covering the operating room.

Evidence:

Collection Facility cleaning must be documented and the records maintained for the period of time specified in institutional policies, the FACT-JACIE Standards, or by Applicable Law. The inspector will observe the Collection Facility and look for signs of cleanliness, sanitary practices, and orderly arrangement. If documentation of cleaning and sanitation is performed directly by the Clinical Program's institutional environmental services department, then the program should have knowledge of this documentation and the ability to show that it is complete.

In the U.S., documentation of Joint Commission or similar agency accreditation may be used supportively to demonstrate that the Collection Facility meets requirements for cleaning and sanitation; however, it is still incumbent on the inspector to fully observe and review the facility during the on-site inspection.

Example(s):

A checklist to document that facility cleaning and sanitation was performed according to SOPs can be left for the cleaning staff to complete when cleaning is performed after business hours.

STANDARD:

- C2.6 *The Collection Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, caregivers, and volunteers.*
- C2.7 *The Collection Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease and to chemical, biological, radiological, electrical, or fire hazards.*

Explanation:

The Collection Facility's policies and SOPs, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to Applicable Law regarding safety. It is critical that the program has a safety manual and that staff members have ready access to instructions for prompt response in case of exposure to hazardous materials. If an institution-wide manual is used, safety, infection risks, and biohazard waste disposal procedures that are unique to the program must be covered in the program's safety manual. The use of electronic training programs that cover safety and infection control is acceptable, but there must be evidence that the staff has completed all relevant training satisfactorily.

Collection Facilities should post warning signs wherever radioactive materials are in use. Activities such as eating and drinking must be restricted in the Collection Facility.

Evidence:

Ideally, the inspector should observe a collection to verify that personnel use appropriate protective clothing and observe other biosafety precautions. If there is no collection procedure underway, a mock procedure can be demonstrated. The inspector should examine selected employee files for training in biological, chemical, radiation, electrical, and fire safety (when appropriate). Compliance with state and federal regulations should be addressed by the Collection Facility and verified by the inspector. The inspector should also be alert during the tour for the presence of unused or inappropriately stored supplies or equipment that may contribute to an unsafe environment.

Example(s):

Safety training, including universal precautions for handling blood, is a requirement of OSHA in the U.S.

The safety manual may be an institution-wide document available by hard copy or electronically. Access to the institutional safety manual solely by computer is not acceptable without a written policy describing how to access the information in the event of a computer failure or down time. An SOP that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice.

A condensed or summarized hard copy of the institutional safety manual should be kept in the facility. In this case, there must be written documentation of how the condensed version is kept

updated with institutional safety manual revisions. Such a document should focus on those hazards that are most likely to occur in the facility, such as needle sticks or handling patients and recipients or donors with a known communicable disease.

STANDARD:

C2.8 *All waste generated by the Collection Facility's activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with Applicable Law.*

Explanation:

Poor management of medical waste exposes personnel, waste holders, and the community to injuries, infections, and toxic effects. Hazardous waste generated by the Collection Facility's activities includes a broad range of materials, including used supplies, sharps, and chemicals. All medical waste must be discarded in a safe manner according to written protocols for the disposal of biohazard waste and in accordance with Applicable Law. Contaminated materials shall be placed in appropriate bags and containers marked with the international infectious substance symbol. Radioactive and chemical waste must be discarded using methods approved by appropriate governmental agencies.

Evidence:

The inspector should examine how medical waste and chemicals are handled and discarded (e.g., incinerator, waste field) and compare their observations with the written protocols.

Example(s):

Contaminated materials may typically be discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, through the use of a sanitary landfill. Sharps (e.g., needles, blades) should be considered highly hazardous healthcare waste and placed for disposal in puncture-proof containers, whether or not they are infected. Chemicals, such as cytostatic drugs used in purging procedures, shall be discarded in accordance with Applicable Law.

STANDARD:

C2.9 There shall be a written policy for personal hygiene and the use of personal protective equipment and attire.

C2.9.1 The policy shall define the protective clothing to be worn upon entering the work area and while working within it.

C2.9.2 The policy shall define personal protective equipment appropriate for the activities and classification of the environment to be worn while handling biological specimens.

C2.9.3 Such personal protective equipment shall not be worn outside the designated work area.

Explanation:

PPE is equipment worn to reduce exposure to hazards that could cause injury or illness in the workplace, and to protect the cellular therapy product from exposure to hazards that could cause injury or illness to the recipient. Personal hygiene includes hand hygiene that is undertaken to reduce disease transmission.

Collection Facilities must follow their institutional policies regarding appropriate PPE (e.g., gowns, goggles, plastic aprons, gloves) that must be worn when connecting patients, blood sampling, during disconnection at end of procedure, or any other situation when handling potentially hazardous substances. The type of exposure that may be encountered will determine the appropriate protection. If aerosol exposure is likely, a mask, goggles, and gowns or aprons should be worn. Gloves must be worn whenever potential infectious exposure exists. To prevent the spread of hazardous substances, PPE must be removed before leaving the workspace.

Evidence:

One way to demonstrate compliance with hygiene is for the program to have a policy on handwashing.

STANDARD:

C2.10 There shall be access to an intensive care unit or emergency services.

Explanation:

The Standards aim to protect patient, recipient, and donor safety in rare emergency situations. The Collection Facility must have documentation that there is ready access to an ICU or equivalent coverage in an immediate fashion for its patients or recipients and donors when appropriate. This requires the ability to provide multisystem support, including assisted respiration and/or circulatory support. Ordinarily, this would be within the institution; however, contractual arrangements with

another institution may be considered if transfer SOPs are in place to ensure prompt service and patient safety.

Evidence:

The inspector should verify that personnel are appropriately trained to respond to emergency situations and that there is emergency equipment available and in working condition. A review of protocols for emergency response, personnel training and competency files, and a contract or a letter of understanding with local emergency services can be performed.

Example(s):

A combined adult and pediatric Collection Facility may have an ICU within its institution; however, it may not have personnel trained in pediatrics. It may be more beneficial for a pediatric patient to be transferred to a pediatric hospital's ICU. This is acceptable if the transfer is timely and there is a written agreement defining the responsibilities of each party.

The ED may be acceptable when other outpatient facilities are unavailable, if the physical space and physician coverage are adequate to ensure that the patient (donor or recipient as appropriate) is evaluated promptly and not exposed to risk of infectious disease transmission, including respiratory pathogens. For example, a busy trauma center may be inadequate to provide these safeguards.

Examples of appropriate training and emergency equipment include an electrocardiograph, crash cart, code team (in the hospital), or ACLS (advanced cardiac life support)- and/or CPR (cardiopulmonary resuscitation)-trained individuals (in freestanding Collection Facilities). If the only emergency response available to the facility is a community-based emergency service (such as 911 in the U.S. or 112 in the EU), the inspector should be able to verify that such an option is feasible and provides for a reasonably safe collection. Ideally, there should be documentation that the emergency response system was tested, particularly when community-based services are used, to verify it is working as intended.

C3: PERSONNEL

STANDARD:

C3.1 *COLLECTION FACILITY DIRECTOR*

- C3.1.1** *There shall be a Collection Facility Director with a degree in a relevant science and a minimum of two (2) years of experience in management and oversight of the Collection Facility.*

Explanation:

The Collection Facility Director must be an individual with a relevant degree. A Medical Doctor (MD) degree qualifies as a relevant doctoral degree; a non-physician Collection Facility Director may hold a doctoral or baccalaureate degree (or international equivalent) in any of the biological sciences. A person with a diploma (such as nursing) can be the Collection Facility Director if they have sufficient documented experience in directing a facility.

The Collection Facility Director may also serve as the Collection Facility Medical Director, if appropriately credentialed.

Evidence:

The inspector should review several pieces of documentation, such as the Collection Facility Director's degree or diploma, postgraduate training experience, or CV for director experience. This is at the discretion of the inspector and ultimately of the Accreditation Committee to decide if the director's experience is sufficient.

Example(s):

Documentation of evidence may include a medical school diploma, residency or fellowship certificates, or the Collection Facility Director's CV indicating director experience. Examples of a relevant post-graduate (beyond baccalaureate) science degree could be in nursing, chemistry, or biology.

STANDARD:

- C3.1.2** *The Collection Facility Director shall be responsible for all Standard Operating Procedures, technical procedures, performance of the collection procedure(s), supervision of staff, administrative operations, and the QM Program, including compliance with these Standards and Applicable Law.*

Explanation:

The Collection Facility Director is responsible for all administrative and technical aspects of the Collection Facility. This includes development and implementation of SOPs; training of personnel;

design and execution of validation studies and audits; development of and compliance with the QM Program; maintenance of equipment; data analysis and reporting; and compliance of the Collection Facility with the Standards and Applicable Law.

The term “supervised” in this Standard differs from the supervision of staff during training or directly observing collection procedures. The term refers to the Collection Facility Director’s supervision of the procedures by ensuring the staff is appropriately trained and have reviewed and follow the SOPs. The Collection Facility Director is also responsible for reviewing the staff worksheets and verifying procedures which satisfactorily result in efficacious cellular therapy products.

The Collection Facility Director may have other responsibilities, but they should be available at all times when the Collection Facility could be operational.

Evidence:

The inspector should review the Collection Facility’s organizational chart to verify compliance with the Standard in addition to the job description and areas of responsibilities as described in SOPs, QM Plan, and other documents.

Example(s):

Documentation of evidence may include the Collection Facility Director’s signature for reviewing SOPs and the QM Plan. Documentation of the procedures performed or supervised must be available.

STANDARD:

C3.1.3 The Collection Facility Director shall participate in a minimum of ten (10) hours of educational activities annually.

C3.1.3.1 The Apheresis Collection Facility Director shall participate in educational activities related to the field of HPC transplantation, quality management, or cellular therapy.

C3.1.3.2 The Marrow Collection Facility Director shall participate in educational activities related to the field of HPC transplantation, quality management, or cellular therapy.

STANDARD:

C3.1.3.3 The Collection Facility Director for Other Tissue shall participate in educational activities related to the field of cellular therapy, quality management, or relevant therapeutic disease areas.

Explanation:

The purpose of this Standard is to ensure that licensed staff receive continuing education in cellular therapy. Areas may include QM, regulatory issues, and technical aspects of the cellular therapy procedure.

The Collection Facility Director must participate regularly in educational activities related to cellular therapy and transplantation to broaden the scope of knowledge and keep up with current advancements in the field.

Evidence:

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not a Collection Facility Director meets this Standard. Recognized educational activities include both certified CME credits (preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are referenced in this Accreditation Manual and may include topics specific to cellular therapy and diseases in which cellular therapy is a therapeutic option.

To assess the appropriateness of the amount and type of continuing education, Collection Facilities must submit the following information for each of the completed continuing education activities within each accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, grand rounds).
- Topic of activity demonstrating relevance to cell therapy (e.g., hematology, cell transplantation).
- Date of activity.
- Approximate number of hours of activity.

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Use of a formalized CPD record such as the FACT [Educational Activities Form](#) or equivalent is recommended. Use of this form is not required, but it can be used to document compliance with continuing education requirements.

Example(s):

Evidence of compliance may include formal or informal study. Educational activities do not necessarily require large financial resources. The Collection Facility may choose to establish its own

guidelines for the number of hours from each type of activity that can be counted toward the minimum requirement in this Standard.

Examples of appropriate continuing education activities include:

- The annual meetings of professional societies (such as those representing apheresis, transfusion medicine, cellular therapy, and scientific research) that include information directly related to the field.
- Grand Rounds, if specifically related to cellular therapy or diseases for which cellular therapy is a therapeutic option. The continuing education log must include the title, subject, and date of the presentation.
- Presentation of CME or CPD lectures.
- Presentation of a paper at a scientific meeting, such as abstracts and oral presentations.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or online tutorial.
- Review of articles in the medical literature related to cellular therapy, including those where the journal offers CME credits.
- Local or regional journal club, potentially including the preparation time.
- Morbidity and Mortality conferences.

ASTCT also offers an [online Learning Center](#) that hosts recordings from its many educational events. Additional educational opportunities are provided by ESH and EBMT through their respective e-learning programs ([ESH](#) and [EBMT](#)).

STANDARD:

C3.2 *COLLECTION FACILITY MEDICAL DIRECTOR*

C3.2.1 *There shall be a Collection Facility Medical Director who is a licensed physician with a minimum of two (2) years of postgraduate education, training and practical experience in cellular therapy product collection, and relevant experience in transplantation.*

C3.2.1.1 *The Apheresis Collection Medical Director shall have performed or supervised a minimum of five (5) cellular therapy product apheresis collection procedures in the twelve (12) months preceding initial accreditation and a minimum average of five (5) cellular therapy product apheresis collection procedures per year within each accreditation cycle.*

STANDARD:

C3.2.1.2 The Marrow Collection Medical Director shall have performed a minimum of 10 (ten) marrow harvests in their lifetime and performed or supervised an average of one (1) per year within each accreditation cycle.

C3.2.1.3 The Collection Medical Director for Other Tissue shall have performed a tissue collection procedure.

Explanation:

The Collection Facility Medical Director should be a physician licensed to practice medicine in the state, province, or country in which the Collection Facility is located and have postdoctoral training in cellular therapy product collection, transplantation, and administration. For programs collecting tissues such as tumor infiltrating lymphocytes (TILs), the Medical Director must have training in the methods required for cellular therapy product collection or diseases treated by cellular therapy products. The Medical Director does not need to be licensed in other jurisdictions in which satellite collection facilities are located (e.g., when the primary facility and its satellites are in different states).

The Collection Facility Medical Director for Other Tissue must have surgical skills and have demonstrated competence in carrying out a minimum of one tissue collection procedure, either for diagnostic or therapeutic purposes or to support further manufacturing. If they have not carried out a collection procedure to support onward manufacture, they must have knowledge of the differences between tissue collection procedures for this purpose and those for diagnostic or therapeutic purposes.

The Collection Facility Medical Director may also serve as the Collection Facility Director (or vice versa), if appropriately credentialed.

If there has been an extended time period since a collecting individual has performed a collection, there should be a reassessment of their training and competency. Documentation of procedures performed or supervised must be available.

Evidence:

To fulfill this Standard, the Collection Facility Medical Director must provide a copy of their current state, provincial, or national license. Since documentation of the medical degree is required to obtain a medical license, the license will be considered to be documentation that the Medical Director is a physician.

The Marrow Collection Facility Medical Director is required to submit a CV that demonstrates training and experience prior to the on-site inspection. The inspector should review this information in advance and request additional information if there are questions. Evidence of experience should be apparent.

Example(s):

Experience can include training as part of a residency or fellowship program, specific training in another facility, or on-the-job training.

STANDARD:

C3.2.2 The Collection Facility Medical Director shall be responsible for the medical care of donors undergoing collection, including performance of the collection procedures, pre-collection evaluation of donors at the time of donation, and management of complications resulting from the collection procedure.

Explanation:

The Collection Facility Medical Director may have other responsibilities, but they should be available at all times when the Collection Facility could be operational. The Collection Facility Medical Director's responsibilities should be specifically documented.

Providers can delegate responsibilities for care as they deem appropriate. For the medical care of donors undergoing cell collections, the requirements for care may be delegated to the appropriate healthcare professionals.

In programs that collect marrow or other tissue, the Collection Facility Medical Director is directly responsible for the medical care of donors during the collection procedure, including the pre-collection evaluation of the prospective donor at the time of donation, performance of the collection procedure, training and supervision of assistants for the procedure, care of any complications resulting from the collection procedure, and compliance with the Standards. The Medical Director is not usually responsible for the initial selection of the donor or for the determination of donor eligibility. These are usually the responsibility of the clinical transplant team or donor registry.

Evidence:

The inspector should review the Collection Facility's organizational chart to verify compliance with the Standard in addition to the job description and areas of responsibilities as described in SOPs, the QM Plan, and other documents.

Example(s):

Collection charts documenting the pre-collection evaluation of the prospective donor at the time of donation and care of any complications resulting from the collection procedure may also provide documentation of compliance.

STANDARD:

- C3.2.3 *The Collection Facility Medical Director shall participate in a minimum of ten (10) hours of educational activities related to the field of HPC transplantation, cell or tissue collection, quality management, or cellular therapy annually.*

Explanation:

The Collection Facility Medical Director must participate regularly in educational activities related to cellular therapy product collection and transplantation to broaden the scope of knowledge and keep up with current advancements in the field.

Recognized educational activities include both certified CME credits (preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are referenced in this Accreditation Manual and may include topics specific to cellular therapy and diseases in which cellular therapy is a therapeutic option.

Evidence:

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. A total of ten hours of a combination of these topics is required. Each topic does not need to be covered in ten hours individually, however hours in each category will be assessed. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not a Collection Facility Medical Director meets this Standard.

For additional Evidence and Examples related to continuing education, see the guidance following [C3.1.3.3](#).

STANDARD:

- C3.3 **QUALITY MANAGER**

- C3.3.1 *There shall be a Collection Facility Quality Manager to establish and maintain systems to review, modify, and approve all policies and Standard Operating Procedures intended to monitor compliance with these Standards or the performance of the Collection Facility.*
- C3.3.2 *The Collection Facility Quality Manager should have a reporting structure independent of cellular therapy product collection.*

Explanation:

The title held by this individual may differ among facilities and is not relevant as long as the duties include those described in the Standards. The Collection Facility Quality Manager under ideal circumstances would be an individual with at least an undergraduate degree or equivalent in the field of health sciences or biological sciences and will have training in the field of cellular therapy product collection. However, individuals with education or experience with either QM or cellular

therapy product collection may still be regarded as fulfilling the minimal qualifications for the job as long as the Collection Facility Director can verify the proficiency of the individual to serve in this capacity. The Quality Manager may be shared with other portions of the cellular therapy program or the institution.

The Quality Manager must have an active role in preparing, reviewing, approving or implementing QM policies and SOPs and must confirm that the SOPs are in compliance with the Standards and Applicable Law before implementation. A key role of the Quality Manager is to develop systems for auditing Collection Facility activities to ascertain compliance with the written policies and SOPs.

Formal training and certification in one or more aspects of QM is encouraged but not required. Formal training may include practical work experience in a facility, fellowship, or certification program. Additional information related to certification in quality is available from the [American Society for Quality \(ASQ\)](#) and the [National Association for Healthcare Quality \(NAHQ\)](#). Finally, resources are available on both the FACT and JACIE websites to assist Quality Managers in advancing their knowledge and skill sets.

The Quality Manager should have a degree of autonomy from operational departments within an organization, allowing them to objectively assess and report on quality issues without being influenced by pressures to prioritize production or other factors that could compromise quality standards; essentially, they should be able to function independently to ensure the highest quality is maintained.

A Quality Manager may have an operational role in the Collection Facility as long as they do not audit their own work. In this scenario, it is acceptable for the individual's job description to state "other duties as assigned," rather than specifically list out QM responsibilities as long as there is documentation of who is assigned the role.

Evidence:

The inspector should look for documentation (e.g., audit reports) that a Quality Manager is in place and performs or oversees the functions covered in the QM section of the Standards. During inspection, the inspector may want to inquire about SOPs in place to avoid bias when Quality Managers must review their own work.

Example(s):

Formal training may include documented practical work experience in a facility, fellowship, or a certification program. Additionally, the Quality Manager's CV, job description, organizational chart, audit reports, or proficiency test reports (if applicable) are all examples of documentation that may demonstrate compliance.

The [FACT Quality Handbook](#) and the [FACT Quality Management Series webinars](#) are resources available through the FACT website. Additionally, JACIE offers [Quality Management and Certification in Hematopoietic Stem Cell Transplantation and Cellular Therapy: The JACIE Guide](#). These are all excellent resources for Quality Managers.

STANDARD:

C3.3.3 The Collection Facility Quality Manager shall participate in a minimum of ten (10) hours of continuing education activities which include cellular therapy, cell collection, and quality management annually.

Explanation:

The amount of activity required to meet this Standard depends on the type and frequency of the educational activities.

The Quality Manager must participate regularly in educational activities related to cellular therapy product collection, transplantation, and QM to broaden their scope of knowledge and keep up with current advancements in the field.

Recognized educational activities include both certified CME credits (preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are referenced in this Accreditation Manual and may include topics specific to cellular therapy and diseases in which cellular therapy is a therapeutic option.

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. A total of ten hours in combination of these topics is required. Each topic does not need to be covered in ten hours individually. The inspector should assess the documented number and content of the continuing education activities and use their judgment to determine whether or not a Quality Manager meets this Standard.

For additional Evidence and Examples related to continuing education, see the guidance following [C3.1.3.3](#).

STANDARD:**C3.4 STAFF**

- C3.4.1 The number of trained and competent collection personnel shall be adequate for the number of procedures performed and shall include a minimum of one (1) designated trained individual with an identified trained and competent backup individual to maintain sufficient coverage.*

Explanation:

This Standard requires that there be an adequate number of trained personnel available for the collection of cells relative to the workload. The number of staff available and other responsibilities of the staff will vary from institution to institution based on the size and scope of the facility, and no specific numbers of staff members are required by the Standards. There should be sufficient staff present to manage in the event of any donor emergency without neglecting ongoing collections. A designated backup, trained individual is required, but this does not require the Collection Facility to hire an additional employee. There are many options to train personnel from other departments who are qualified to perform the necessary tasks should they be needed.

The Collection Facility Director should indicate personnel responsible for specific activities in the Collection Facility and confirm that they are appropriately trained and competent to perform those activities, including confirmation that they have been trained in appropriate age-specific issues for the recipient and donor population they serve. Personnel should be retrained as necessary to remain up to date on current collection methods.

Evidence:

The inspector will make a judgment of the adequacy of the staff support, including a review of the plan for staffing in the event of absences. The inspector should observe and inquire about the number of donors for whom one staff member is responsible at one time.

Documentation of initial training, continuing education, and periodic competency testing of all personnel is required. Documented training at the time of initial employment is expected of all new staff hired at the time of and following application for FACT or JACIE accreditation. Records of initial training may not be available for long-term employees of the facility; however, documentation of continued competency on a periodic basis should be available for all staff.

The inspector may request review of personnel records demonstrating competency and experience. The inspector should not request or be given confidential information such as staff medical records (e.g., vaccinations, health records).

Example(s):

Competency testing may include observation of performance of a procedure by a supervisor or coworker, oral or written examination of expected areas of performance, or participation in proficiency testing programs.

Insufficient staffing may be indicated by excessive overtime, rapid turnover of personnel, incomplete record keeping, or an increase in adverse events.

STANDARD:

C3.4.2 For collection activities involving pediatric donors physicians and collection staff shall have documented training and experience with pediatric donors.

Explanation:

Pediatric collections might require additional training or documented experience in this special population of donors. SOPs addressing special situations that apply to pediatrics should be in place with appropriate staff training and experience.

Evidence:

The inspector may request review of dated personnel records demonstrating training and competency in managing pediatric donors.

STANDARD:

C3.4.3 There shall be attending physician oversight if general medical physicians, physicians-in-training, or APPs provide care to the cellular therapy donors.

C3.4.3.1 The scope of responsibility of general medical physicians, physicians-in-training, or APPs shall be defined.

C4: QUALITY MANAGEMENT

STANDARD:

C4.1 There shall be a QM Program that incorporates key performance data.

C4.1.1 The Collection Facility Director shall have authority over and responsibility for ensuring that the QM Program is effectively established and maintained.

Explanation:

The QM Program includes quality assurance, control assessment, and improvement activities. The strategy (QM Plan) and associated policies and SOPs drive the operation of the QM Program. Marrow Collection Facilities that operate independently must comply with the requirements in [B4](#) to confirm their activities are monitored under a QM Program.

The Collection Facility must define what key performance data it will analyze. Minimally, this should include data necessary to complete the QM activities required by these Standards.

Evidence:

Records to demonstrate an active QM Program with oversight of the Collection Facility should be available to the inspector.

Example(s):

The Collection Facility may choose to participate in an existing QM Program in its affiliated hospital, participate in the Clinical Program's QM Program, use portions of those QM Programs in its own program, or have a stand-alone QM Program. An example of an independent Marrow Collection Facility is one that collects only for NMDP or other donor registries.

STANDARD:

C4.2 The Collection Facility shall establish and maintain a written QM Plan.

Explanation:

The QM Plan is the written document that outlines how the QM Program is implemented.

The QM Plan must detail all key elements that affect the quality of recipient and donor care and cellular therapy products. The specific controlled documents for each of these elements do not have to be fully described in the QM Plan, but they must be referenced within the plan and linked to the appropriate document(s) where the details are described.

The QM Plan does not necessarily need to be stand-alone, serving only the Collection Facility. If a QM Plan is shared, it must include all elements required by the Standards and clarify the nature and extent of participation by other areas or institutions.

Evidence:

The written QM Plan for the Collection Facility will be provided to the inspector prior to the on-site inspection. If policies and SOPs are referenced in the QM Plan, they may be requested in advance to enable the inspector to review the details of the QM Program. The inspector is expected to evaluate implementation of the QM Plan at the facility and assess the understanding of QM by the staff.

When the QM Plan is broad (e.g., a shared plan covering an entire Transfusion Medicine department), all aspects of collection of cellular therapy products need to be addressed.

STANDARD:

C4.2.1 The Collection Facility Director shall be responsible for the QM Plan as it pertains to the Collection Facility.

Explanation:

The Collection Facility Director is in charge of the elements of the QM Plan that are directly related to the facility. A designee must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. Delegation to a qualified designee must be documented, either in the QM Plan or in controlled documents related to it.

Evidence:

QM Plan review and approval should provide evidence of the Collection Facility Director's involvement.

Example(s):

A designee can be a member of another department, such as an institutional Quality Assessment and Improvement or Compliance Department, who devotes some time to the QM activities of the Collection Facility, or they could be a member of the collection facility's team. The same person may be responsible for QM of all components of the cellular therapy program or each individual area (clinical, collection, processing) and may have a distinct individual responsible for QM, as long as there is a mechanism for sharing information to all participating entities.

STANDARD:

C4.3 The QM Plan shall include, or summarize and reference, an organizational chart of key positions, functions, and reporting relationships within the Collection Facility.

C4.3.1 The QM Plan shall include a description of how these key positions interact to implement the quality management activities.

Explanation:

The organizational chart must include titles of key positions and the reporting structure of the Collection Facility and the QM Program. In addition, these charts must illustrate relationships with Clinical, Collection, and Processing Facilities that meet these Standards. Lines of responsibility and communication must be clearly defined in a way that is understood by all involved.

If a Collection Facility contracts services to or from an extended clinical or processing service, the organizational chart must include the contracted service(s) and summarize the reporting structure in the QM Plan.

Evidence:

The organizational chart for the Collection Facility will be provided to the inspector prior to the on-site inspection. The inspector will verify that the organization and daily function are as described in the chart and QM Plan (e.g., meetings, participants, schedule, reporting, documentation).

Example(s):

Organizational charts for matrix programs, where an individual may report to different people for different duties (i.e., to the facility supervisor for technical duties and to the Quality Manager for quality duties), should reflect the sphere of influence of individuals rather than only the lines of legal authority.

STANDARD:

C4.4 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Collection Facility. Personnel requirements shall include at a minimum:

Explanation:

The QM Plan, as approved by the Collection Facility Director, identifies the key personnel for whom documentation of training, competency, and continuing education is expected. This must include all individuals responsible for critical elements of the Collection Facility. Documentation of training for each individual must include all procedural skills routinely practiced. These requirements are detailed in [C3](#). These requirements apply to all personnel in these positions, including those not directly employed by the Collection Facility but who perform collection services.

Evidence:

The inspector should review training records to verify compliance with these Standards. Organization-specific issues and safety training are generally covered by orientation programs and continuing education programs, but inclusion of this content should be confirmed by the inspector. The inspector should review policies or SOPs describing the elements of staff training and continued competency.

The inspector should review the records of one or more personnel to confirm that all of the required elements have been documented.

Example(s):

Although only one job description is needed for each key position, documentation for each staff member is on an individual basis. For example, a staff nurse position will have one job description for that position, but each individual nurse needs their own information on file that includes documentation of qualifications, new employee orientation, training, assessment of continued competency, and continuing education as outlined in Standards [C4.4.2.1](#)–[C4.4.2.6](#).

EU regulations contain some specific requirements for personnel training that are not specifically stated in the Standards that include:

- Information sufficient for an understanding of the scientific and technical processes and principles relevant to their designated tasks.
- Information on the organizational framework, quality system, and health and safety rules of the establishment in which they work.
- Information concerning the broader ethical, legal, and regulatory context of their work.

The following resources from the HTA provide further guidance for programs in the UK:

- [Code G: Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation.](#)
- [HTA Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment.](#)

STANDARD:

C4.4.1 A current job description for each position.

C4.4.2 A system to document the following:

C4.4.2.1 Initial qualifications.

Explanation:

Initial qualifications generally include minimal educational requirements, formal training that is either required or preferred, and licensing or certification (e.g., registered nurse, bachelor's degree).

STANDARD:

C4.4.2.2 New employee orientation.

Explanation:

New employee orientation refers to training employees on general organizational issues upon hire, such as safety, training, or benefits.

Evidence:

Organizational issues are generally covered by institutional orientation programs, but this should be confirmed by the inspector.

STANDARD:

C4.4.2.3 Initial training, competency, and retraining when appropriate for all procedures performed.

Explanation:

Initial training documentation must include all specific procedures that an individual staff member will perform (as defined in the job description) and should clearly indicate when that staff member has been approved to perform each procedure or function. Initial training should also include:

- Relevant scientific and technical material specific to individual duties.
- Organizational structure, quality systems, and health and safety rules specific to the organization.
- Ethical, legal, and regulatory issues specific to the organization.

Example(s):

Training and its documentation may be accomplished in a variety of formats. Training may be facilitated through formal or informal presentations, self-learning by reading suggested materials on a topic, or reviewing previously presented audio or visual presentations. Documentation may include attendance rosters, attestation statements of attendance, certificates of attendance, or competency assessments following the training.

STANDARD:

C4.4.2.4 Continued competency for each critical function performed, assessed annually at a minimum.

Explanation:

Competency is the ability to adequately perform a specific procedure or task according to direction. Collection Facilities must have a system for documenting competency and retraining, when appropriate, for each critical function performed by a staff member (see [A4](#) for the definition of "critical").

Evidence:

The inspector should review records of employees' initial and annual competencies. The inspector should review policies or SOPs describing the elements of staff training and continued competency assessment and the records of one or more employees to determine whether all of the required elements are documented.

Example(s):

Competency may be assessed by direct observation, the use of written tests, successful completion of proficiency surveys, review of collection procedure endpoints, or as determined by the Collection Facility Director.

STANDARD:

C4.4.2.5 Annual training in applicable GxP.

Explanation:

GxP is an abbreviation that stands for “good practice” following various quality standards (such as [ISO 9001:2015](#)) and regulations (such as U.S. [21 CFR Part 211](#)). The “x” is variable, with further definition of good practices defined by different countries, fields, and laboratories. The type of work that is being performed will define which GxPs should be followed.

The extent and level of GMPs implemented is dependent on the type of manufacturing that is performed (e.g., manufacturing of minimally manipulated HPC cellular therapy products versus investigational and licensed cellular therapy products). GTPs are rooted in GMPs; in other words, the relevant GMPs are included in GTP regulations.

Training topics will depend on the type of work performed in accordance with Applicable Law. There will be local variations depending on Applicable Law for a particular jurisdiction. Comprehensive training on every aspect of GxPs each year is not expected; rather, there must be some training based on a GxP topic annually.

Evidence:

Many of the procedures performed by personnel already require training in GxPs to perform the work; therefore, GxP training is not required to be separate. However, documentation must provide evidence that the GxPs were included. For example, training in environmental control could include an overview of GTPs or GMPs, the relevant requirements based on the work to be performed, and the specific tasks performed by personnel.

Example(s):

These Standards require training in GxP as they are required by Applicable Law. Third parties such as commercial manufacturers may have different expectations. For example, Applicable Law may not require compliance with GMPs for the collection of mesenchymal stromal cells, but manufacturers might expect that of the Collection Facility. This responsibility should be defined in the written agreement with the manufacturers.

Collection and Processing Facilities in the U.S. follow a variety of GxPs:

- Good Tissue Practice (GTP) according to [21 CFR Part 1271 Subpart D](#).
- Good Manufacturing Practice (GMP or cGMP) as it pertains to the activities performed.
- Good Documentation Practice (GDP) and data integrity practices.

The [Guide to the Quality and Safety of Tissues and Cells for Human Application](#) (5th Edition, 2022) published by the European Directorate for the Quality of Medicines & Health Care provides guidance on Good Practice Guidelines based on current scientific knowledge, expert opinion, and the results of many international projects. The use of this guide is becoming more commonplace

throughout Europe, including both EU member states and non-EU states who are members of the council (47 countries with approximately 820 million inhabitants). Many competent authorities use it as part of their inspections. The information provided may be applied to HPC transplantation, IEC therapy, and other novel cellular therapies.

STANDARD:

C4.4.2.6 Continuing education.

Explanation:

Staff should adhere to local and governmental continuing education requirements.

Evidence:

The inspector should find evidence of educational opportunities for staff related to their duties, such as quality-related meetings, webinars, or FACT or JACIE training sessions, if applicable.

STANDARD:

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

Explanation:

Document control is the Collection Facility's method of establishing and maintaining critical documents required by the Standards or deemed necessary for the effectiveness of the QM Program. The hierarchy and number of documents or extent of documentation is dependent on the processes, size and complexity of the Collection Facility and will differ from one program to another.

Controlled documents serve multiple purposes for the QM Program and can consist of different document types, such as policies, SOPs, worksheets, or forms. Controlled documents provide the structure needed for quality assurance through applicable policies and SOPs. Controlled documents also ensure consistent quality control when using forms, worksheets, audit reports, outcome analyses, training records etc. The QM Program must identify which documents are critical and describe how they are controlled.

STANDARD:

C4.5.1 There shall be identification of the types of documents that are considered critical, and these shall comply with the document control system requirements. Controlled documents shall include at a minimum:

C4.5.1.1 Policies, Protocols, Standard Operating Procedures, Manuals, and Guidelines.

STANDARD:

C4.5.1.2 *Worksheets.*

C4.5.1.3 *Forms.*

C4.5.1.4 *Labels.*

Explanation:

The QM Program must maintain a controlled document hierarchy which provides identification of the types of documents considered critical. A critical document refers to an internal document that is directly related to and could impact patient care or cellular therapy product safety, purity, potency, identity, or integrity. For example, all manuals, SOPs, forms, worksheets, and labels required by these Standards must be considered to be critical documents within the program and must be controlled. Collection Facilities may call documents by different names (such as guidelines instead of protocols) and may identify additional types of documents as critical within the scope of the document control system.

It is up to each program to define which documents are controlled under the QM Program. Documents and manuals that are the property of other institutions (e.g., a commercial CAR-T apheresis manual) should not necessarily be controlled by the program. However, programs must ensure that they are referring to the current version of such documents and manuals.

Evidence:

The inspector should review a listing of which documents fall under the document control system. For example, quality manuals, safety manuals, procedural SOPs, and technical guidance are all controlled documents authored by the program which must be available at the inspection.

Example(s):

Examples of such documents include the quality manual, SOPs, forms, practice guides and work sheets.

STANDARD:

C4.5.2 *There shall be policies or Standard Operating Procedures for the development, approval, implementation, distribution, review, revision, and archival of all controlled documents.*

Evidence:

The inspector should review active controlled documents to ensure they have been written correctly, approved by the appropriate staff before being implemented, and comply with the document control system and the Standards. The inspector will observe how the Collection Facility controls modifications of documents and maintains accurate archival systems.

STANDARD:

C4.5.3 The document control system shall include:

C4.5.3.1 A standardized format for controlled documents.

Explanation:

The Collection Facility should be consistent in the format or design of controlled documents, including a standardized date format. The facility should define acceptable date formats for documents where no specific date format is mandated by the form.

The Clinical Program must have an SOP outlining the method by which the Clinical Program creates, approves, implements, reviews, and revises its SOPs (the "SOP for SOPs"). Documents authored by the Collection Facility should follow the document management system; however, departmental and institutional documents may differ.

Evidence:

The inspector must verify that all elements of a controlled document are present as defined in the document control system and that there is consistency in format from one controlled document to another.

STANDARD:

C4.5.3.2 Assignment of a numeric or alphanumeric identifier, version, and title to each controlled document.

Explanation:

The document control system must include a system for numbering and titling that allows for unambiguous identification of documents. The numbering system must allow for identification of revisions of a document with the same title by creating a new unique identifier (e.g., numerical, alpha numerical). Worksheets and forms must also be controlled documents and contain a title, unique identifier, and version identifier.

Evidence:

The inspector must verify that controlled documents are consistently identified, titled, and versioned as defined in the document control system.

STANDARD:

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

Explanation:

The individual approving documents must have the appropriate qualifications and responsibility for the document being approved.

The effective date of a controlled document is the day the new version of a document is implemented and the previous version has been recalled or archived.

Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate individual entered the signature.

Evidence:

The inspector must verify that records indicate consistent approval of controlled documents.

STANDARD:

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

Explanation:

The methods of document distribution and storage should control or prevent unwanted or unauthorized document modification or duplication. The intention of this Standard is to make sure that only the currently approved document is available for use.

Evidence:

The inspector should review the storage and accessibility of currently approved documents and archived documents to verify strict access control.

Example(s):

Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software (to lock specific areas or a specific document to prevent printing) or having copies clearly printed with an expiration date, watermarked as copies, or printed with a clear statement that printed copies may not be the current version, which can only be reviewed by going to source library.

STANDARD:

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

Explanation:

Review does not require an amendment of the version identifiers if the document is still current, but there must be clear evidence that the review has taken place. However, if changes to a controlled document are planned or have occurred since the last review the document should be changed immediately and should not wait for the two-year review.

Evidence:

The inspector should look for documentation of the biennial review. There shall be documentation of review by an authorized person even in the absence of changes.

Example(s):

When an SOP is reviewed, associated documents (e.g., forms, worksheets) must be reviewed concurrently to ensure alignment.

STANDARD:

C4.5.3.6 A system for document change control that includes a description of the change, version, signature of approving individual(s), approval date(s), communication or training on the change as applicable, effective date, and archival date.

Explanation:

A change control system must include at least the following elements: change proposal, review of proposed change, analysis of change for compliance with the Standards and Applicable Law, risk and impact assessment on existing process and controlled documents, approval of change and revision of documents, communication or training on the change as applicable, and implementation of the change. Changes in practice should not occur before change in the appropriate controlled document has been made and approved. If immediate implementation of a change is required prior to official document edits, then the department should issue a planned deviation documenting this deviation from routine practice. A copy of the new document reflecting the changes could suffice for a description of the change.

The effective date of a controlled document is the day the new version of a document has been implemented and the previous version has been recalled or archived.

A staff member may not perform a new or modified procedure until they have been notified of the change, reviewed the SOP, and, if applicable, completed required training and competency assessment. The amount and format of training and competency assessment may differ based on complexity of the changes. Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate person entered the signature.

Evidence:

The change control process should be reviewed to assess if it is effective to prevent unintended changes to processes or controlled documents.

STANDARD:

C4.5.3.7 A system for archival of controlled documents for a minimum of ten (10) years from archival or according to governmental requirements or institutional policy, whichever is longer. The system shall include the inclusive dates of use and their historical sequence.

Explanation:

Archival of controlled documents is essential to enable facilities to go back to previous versions to confirm historic practices and review operational changes and rationale for the change.

Evidence:

The inspector will examine how the Collection Facility archives controlled documents, whether retrospective review is possible, and whether previous documents can be identified (e.g., unique identifier, version, title).

Example(s):

The archival system must include items such as date removed, version number, reason(s) for archival, and identification of the individual who performed the archive.

STANDARD:

C4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

Explanation:

When controlled documents are updated, there needs to be a secure process in place to ensure that any electronic and hard copies of obsolete or inactive versions are not accessible for use.

Example(s):

There should be a system in place to rescind obsolete or inactive documents to prevent unintended use. For example, on paper copies, a visible watermark could indicate that the document may not be the current version and direct staff to the source library for the most current version. If paper copies are distributed, there must be a process to rescind obsolete or inactive controlled documents.

STANDARD:

C4.6 *The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the establishment and maintenance of written agreements.*

Explanation:

The Collection Facility must have policies and SOPs describing the requirement, development, and maintenance of written agreements or contracts with external organizations or individuals providing a critical service for the program (e.g., donor or recipient workup prior to treatment, collection, processing, testing, storage or administration of cellular therapy products, donor or recipient follow-up post-treatment). Agreements are also required when critical services are provided by the Collection Facility to external parties (e.g., donor or recipient workup prior to treatment, collection, distribution of cellular therapy products). This Standard does not apply to entities within the Collection Facility's own facility or institution.

When an agreement is required, the parties involved must define responsibilities as to who is required to initiate, maintain, and review the agreement.

The content, terms, and conditions within the agreement must be defined and accepted by all parties prior to signing and execution of the agreement.

Evidence:

Written agreements that match current practices must be available for the inspector to review on-site.

Example(s):

It is required that Collection Facilities only use Processing Facilities that meet the Standards. However, an accredited Collection Facility may collect cellular therapy products for one or more programs that are not FACT or JACIE accredited.

STANDARD:

C4.6.1 *Agreements shall be established with external parties providing critical services that could affect the quality and safety of the cellular therapy product or the health and safety of the donor or recipient.*

Explanation:

It is the Collection Facility Director's responsibility to determine which internal or external entities provide critical services that require an agreement.

Documented agreements must clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements must be dated and approved by both parties and legal counsel, if necessary. Agreements must also describe the maintenance or transfer of records and cellular therapy products following termination of the agreement.

Evidence:

Written agreements with external parties must be available for the inspector to review on-site.

Example(s):

External facilities may be defined as those that are a different legal entity or those whose activities are not under the control of the Collection Facility Director.

One form of written agreement that may be acceptable for closely related but separately operated units is a shared SOP that describes the collaborative arrangements.

STANDARD:

C4.6.2 Agreements shall include the responsibility of the external party performing any step in collection, processing, testing, storage, distribution, or administration to maintain required accreditations and to comply with these Standards and Applicable Law.

Explanation:

The Standard requires that agreements include defined responsibilities for critical tasks between the program and the external party.

Example(s):

The Collection Facility is responsible for verifying that an external party has maintained required accreditations. Agreements should include language requiring notification if accreditation is lost.

STANDARD:

C4.6.3 Agreements shall be established when the Collection Facility provides critical services to external parties.

Explanation:

The Collection Facility is responsible for ensuring that an agreement is in place with all external parties. The agreement can be generated and maintained by the external party; however, the Collection Facility must be able to demonstrate that it exists.

Example(s):

When formulating written agreements either for clinical trials or licensed cellular therapy products, the Collection Facility can add language to require that it be notified of information such as:

- If the collected product did not meet the appropriate cell dose (e.g., HPC-A). Receiving this information as feedback allows the facility to investigate the collection failure.
- Potential scheduling or shipping issues that impact patient care.

For agreements that provide critical collection services, language can be added to address communication pathways and notification timeframes. For example, the following are questions related to how relevant information will be communicated if the donor has a reaction or adverse event:

- Which type of reaction or adverse event during collection events requires urgent notification?
- What is the timeframe to notify the external party?
- Which medications were administered after the adverse event was noted?

STANDARD:

C4.6.4 Agreements shall be dated and reviewed on a regular basis, at a minimum every two (2) years.

Explanation:

Written agreements should be reviewed internally at least every two years, similar to SOPs, although greater or lesser time intervals may be appropriate under some conditions. The Collection Facility can define whether a formal review and approval is appropriate to complete with the external organization. The effective dates of an agreement could be specified within the agreement itself. It is helpful to have a list of written agreements to ensure each is reviewed appropriately.

Evidence:

The inspector should be able to view documentation that collection agreements have been reviewed or revised, and, if appropriate, approved every two years. There shall be documentation of review by an authorized person even in the absence of changes.

Collection Facilities should have an awareness of, and a review plan for all written agreements. This includes those that the facility does not control (i.e., does not develop or provide authorized signatures), but which are relevant to the clinical care of the patient or donor or impact the cellular therapy product.

Example(s):

A master list of written agreements and a checklist could assist with appropriate review and ensure that important elements are included and that a designee in the program is notified when changes are made.

STANDARD:

C4.7 The QM Plan shall include, or summarize and reference, policies and Standard Operating 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.

Explanation:

Outcome analysis is a process by which the results of a therapeutic procedure are formally assessed. Outcome analysis focuses on patient-related issues. Efficacy assessment focuses on cellular therapy products and determines if the cellular therapy products can be demonstrated to produce a desired or intended result.

Evidence:

The inspector should confirm documentation of all activities, from definition of expected outcome to process improvement, when indicated. There must be evidence of ongoing analysis of data in addition to mere data collection.

The inspector should ask to see the data analysis, formal statistical review and peer reviewed publications, meeting minutes, and Collection Facility review of the data, including the personnel in attendance and where data are presented.

Example(s):

Examples of policies can include those related to adverse events or microbial contamination.

STANDARD:

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

Explanation:

Outcome analysis involves the collection, evaluation, and distribution of patient outcome data.

Acceptable criteria such as cellular therapy product safety, product efficacy, and clinical outcome should be developed for each cellular therapy product by the Collection Facility in conjunction with the clinical team. This process must be defined in relevant SOPs. Evaluation of patient outcome is required to confirm that the product that was manufactured and distributed met expected specifications. Any unexpected outcomes must be investigated, including risk assessment, and a corrective action or process improvement plan should be implemented. The facility personnel should evaluate all aspects of the collection procedure related to any unexpected outcome, including delayed or failed engraftment.

Cellular therapy product efficacy based on outcome may be difficult to document. Where product efficacy cannot be established, it is expected that product safety will still be assessed. Minimally, the

QM Plan must address the need for the development of an outcome analysis policy that is appropriate for each product type and that adequately assesses that collection processes do not negatively impact outcome.

STANDARD:

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

Explanation:

Outcome analysis should include each individual product or recipient to assess efficacy or safety as appropriate; however, that assessment alone is insufficient to meet this Standard. The intent of the Standard is that similar recipients (e.g., diagnosis, donor type) of a similar product be assessed together for efficacy, safety, trends, and opportunities for improvement. Individual Collection Facilities will choose how to aggregate data based upon the size and complexity of the program.

Outcome analysis should not only be performed on individual cellular therapy products, but also on aggregate data as a whole to identify overall trends. A detailed statistical analysis should be performed, including descriptive statistics for the various cellular therapy products and procedures performed by the cellular therapy program. Product characteristics, especially cell dose, should also be considered in such analysis. These data can be used to identify changes that might require further investigation.

Example(s):

This information can be obtained and analyzed directly by the Collection Facility or presented by another section of the cellular therapy program at a common QM meeting where facility personnel are in attendance.

The Collection Facility may also consider the number of collections per patient, cell yield per collection, and duration of each collection in its analysis.

STANDARD:

C4.7.3 For HPC products intended for hematopoietic reconstitution, time to neutrophil and platelet engraftment following cellular therapy product administration shall be analyzed.

Explanation:

The responsibility for the collection and analysis of outcome data is an example of a QM requirement that may or may not be performed entirely within the Collection Facility. It is acceptable to share the same data between clinical, collection, and processing; however, the Collection Facility

is responsible for ensuring it has access to clinical outcome data to enable it to adequately assess that its processes do not negatively impact outcomes.

Example(s):

Timely engraftment of the HPC product in a recipient following a myeloablative regimen is directly related to the quality of that HPC product. Therefore, the Collection Facility personnel must be aware of the time to neutrophil and platelet engraftment for all recipients for whom they have supplied products. The facility should use a standardized definition of engraftment as per CIBMTR or EBMT. If delayed or failed engraftment occurs, it is important for the facility to be able to share results and trace back to the products source for information such as cell dose, cell type, sterility testing, and viability. It is not required for each section of the cellular therapy program to independently analyze engraftment, but it should be stipulated in the facility's policies or SOPs the responsibility each facility will assume, and the activity that will be undertaken by the Collection Facility.

STANDARD:

C4.8 *The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for, and a schedule of, audits of the Collection Facility's activities to verify compliance with the QM Program, policies and Standard Operating Procedures, these Standards, and Applicable Law.*

Explanation:

The purpose of a Collection Facility audit is to gather objective evidence to verify whether collection activities comply with applicable standards, guidelines, and SOPs. In addition, a collection audit may provide information on potential improvements that the process owner may want to consider.

The audit process should occur throughout the year in accordance with the Collection Facility's QM Plan and schedule, with reporting of Collection Facility audit results, corrective action, and follow-up on a regular schedule (at least once a year). There must be regular auditing of critical collection activities; frequency will depend on the importance of these activities, and to some extent on the results. Where there are published studies, these should be used to help assess audit results. Additionally, responsibilities of the audit for external parties who provide critical services must be detailed in a written agreement as described in [C4.6](#).

A schedule of prospective collection audits is expected. Required audits for the Collection Facility are listed in [C4.8.5](#), but there may be other audits required in response to specific occurrences. Review by the Collection Facility Director is to be documented. There should be evidence that audit reports are shared with the collection staff, the Clinical Program Director, and the Processing Facility Director as appropriate and that any open audits are assessed.

Further information is available in the [FACT Quality Handbook](#) and [The JACIE Guide](#).

Evidence:

The Collection Facility should facilitate the on-site inspection with a concise presentation of recent audits, supported by policies and SOPs, and include documentation of CAPA and follow-up. Examples of how results are trended and presented to relevant directors and staff are also helpful. The inspector should review audit results and schedule of planned audits, but it is not the intent to use a facility's audits to identify deficiencies during an inspection, and the inspector shall maintain the confidentiality of the information.

The inspector should expect to find, at a minimum, a written audit plan, assessment and audit results, actions taken, and follow-up assessments and audits.

Example(s):

Required audits in the Collection Facility are included in [C4.8.5](#) and [C4.8.6](#).

STANDARD:

C4.8.1 Collection Facility audits shall be conducted by an individual with sufficient knowledge in the process and competence in auditing to identify problems but who is not solely responsible for the process being audited.

Explanation:

The individual performing an audit does not need to be external to the Collection Facility, but they should not have performed the actions being audited.

The Collection Facility auditor must be knowledgeable in the process and competent in auditing techniques. Sufficient knowledge must include auditing and the subject matter. The organization must demonstrate how they assess auditor competency.

STANDARD:

C4.8.2 An audit plan for each audit shall include:

C4.8.2.1 Title.

C4.8.2.2 Name of individual(s) to complete the audit.

C4.8.2.3 Audit purpose.

C4.8.2.4 Audit scope.

C4.8.2.5 Documentation of review and approval by the Collection Facility Director and the Quality Manager.

STANDARD:

C4.8.3 An audit report shall include:

C4.8.3.1 Approved audit plan.

C4.8.3.2 Identification of auditor.

C4.8.3.3 Date started and completed.

C4.8.3.4 Records or processes audited.

C4.8.3.5 Summary of results to include findings, assessment of the underlying cause of errors, recommendations, and conclusions.

C4.8.3.6 Plan for follow-up, if appropriate, including a timeline.

C4.8.3.7 Documentation of review and approval by the Collection Facility Director and Quality Manager.

Explanation:

Audit reports are an important tool to provide inspectors evidence of adherence to the Standards and effectiveness of implemented CAPAs; to provide management guidance on future actions and decisions; and to document the evaluation process plans and decisions made in response to issues detected.

An acceptable Collection Facility audit report contains the elements described in Standards [C4.8.2–C4.8.3.7](#), and may also include the following elements:

- Audit type (e.g., Yearly Key Element, 2-Year Key Element, Focused, Follow-up).
- Audit location (e.g., Collection site).
- Date audit is assigned, including name and title of staff who assigned the audit.
- Title of staff assigned to complete the audit.
- Audit period (date range).
- If errors were found but not included in the final analysis, an explanation must be provided.
- Development of an appropriate CAPA, which should be included in the audit report to demonstrate that an appropriate corrective action plan was implemented.
- Auditor signature and date.
- Documented staff review and date of review.
- Quality meeting results presentation date, if required.

Initially, the audit report is completed by the auditor (e.g., quality coordinator) and reviewed and approved by the appropriate personnel (e.g., Quality Manager and Collection Facility Director). At this stage in the audit process, the report does not contain evaluation of the results (determination of the root cause) or the corrective actions, but it may contain recommendations from the auditors. The approved audit report is distributed to the manager of the audited area. It is the responsibility of the manager of the audited area to evaluate the findings and recommendations to determine the appropriate CAPA, including a timeline, and sign the audit. The audit report is considered complete when the CAPA is complete and re-evaluated after implementation.

STANDARD:

C4.8.4 The results of Collection Facility audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement CAPAs when necessary, and follow up on the effectiveness of these actions in a timely manner.

Evidence:

The Collection Facility audit process and example audits must demonstrate that this is an ongoing process and that the QM records demonstrate CAPAs that are based on audit findings. Additionally, when audit results identify a corrective action or process improvement, there should be a date designated as the expected date of completion of the corrective action and a planned time to re-audit the process to verify that the corrective actions were effective.

Example(s):

For example, product yields may be expected to fall within a certain range based on national or international data. Although the yields continue to fall within that range, a trend downward to the lower end of the expected range may indicate a need to investigate the cause (e.g., new staff, a new piece of equipment, a reagent unexpectedly received from a different supplier).

STANDARD:

C4.8.5 Collection Facility audits shall be performed annually at a minimum and shall include at least the following:

Explanation:

The Collection Facility must have an audit calendar that shows at least these required audits annually. Other processes should be chosen for audits at the discretion of each individual program or identified by risk assessment. Audits that continuously fail to identify potential problems or opportunities for improvement should be replaced on the schedule by a new audit topic.

STANDARD:

C4.8.5.1 Documentation of donor suitability and eligibility determination prior to the start of the collection procedure.

C4.8.5.2 Documentation of daily assessment of donor suitability as required in [C9.5](#).

Explanation:

These audits should confirm that donor suitability and eligibility determinations were completed and documented appropriately, in accordance with SOPs and Applicable Law, prior to the start of the procedure. They should also verify that donor suitability assessments were performed and documented prior to the start of each subsequent collection procedure.

STANDARD:

C4.8.5.3 Management of cellular therapy products with positive microbial culture results.

Explanation:

The intent of this Standard is to only audit what is applicable to the Collection Facility's defined responsibilities.

STANDARD:

C4.8.5.4 Documentation that each external facility performing critical contracted services has met the requirements of the written agreement.

Explanation:

It is essential that audits include a review of external facilities performing critical contracted services to confirm that the requirements of the agreements have been met. Such reviews should be performed on a regular basis and should also be performed after there has been a change in the agreement or in Applicable Law that pertain to the agreement.

Example(s):

Audits of external facilities may be accomplished by reviewing the facilities' internal and external audit reports, performing on-site inspections for compliance, receiving periodic performance reports from the facility, or the Collection Facility can audit its experience with the contracted facility using data that it defines and collects. There may be other alternatives, but the contracting facility must establish that their contracted services are meeting requirements.

Collection Facilities completing audits of external facilities can include the following:

- Verification of accurate donor identity.
- Timely receipt of complete collection prescription and medical information to ensure donor safety.
- Critical supplies inventory control.
- Equipment maintenance.
- Environmental monitoring to include temperature, humidity, facility cleaning, and prevention of contamination and cross-contamination.
- Staff training and competency.

STANDARD:

C4.8.5.5 Environmental monitoring as defined in the facility assessment to include environmental parameters, including storage areas, that may affect cellular therapy product viability, integrity, contamination, or cross-contamination during collection.

Explanation:

Facility requirements differ based on Applicable Law (e.g., Publications Office of the EU, FDA, Therapeutic Goods Administration). The Collection Facility must identify the parameters that should be qualified, controlled, and monitored based on their potential effect on the cellular therapy product (see [C2.4](#)). Environmental considerations include temperature and humidity control, ventilation and air filtration, and sanitation of the Collection Facility and storage area(s) at appropriate times. There must be ongoing monitoring of any parameters that have been determined to be critical; these should be defined by an SOP, and compliance should be evident through quality records.

Evidence:

Each facility should assess the risk of environmental conditions on the safety of the cellular therapy product. The assessment should be documented, including those instances where an environmental condition included in the list contained within the Standard has been deemed not applicable to a particular facility. Records of environmental conditions such as temperature and humidity and their review should be available for review by the inspector.

STANDARD:

C4.8.6 Additional audits shall be performed as part of a risk-based approach to the follow-up of occurrences.

Explanation:

This Standard ensures that programs implement a proactive and systematic method to monitor and improve quality and patient safety in response to occurrences. The decision to perform additional audits is guided by an evaluation of the potential severity, frequency, and impact of the occurrence. Additional audits are not routine inspections but are focused and issue-specific evaluations designed to identify root causes and contributing factors, assess whether the existing quality system controls were adequate, evaluate the effectiveness of any CAPAs, and prevent recurrence by addressing systemic issues.

By tailoring audit activities to the level of risk, the Collection Facility can allocate resources effectively, maintain quality assurance, and protect outcomes.

STANDARD:

C4.9 The QM Plan shall include, or summarize and reference, policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency.

Explanation:

This Standard ensures that Collection Facilities are prepared to manage external audits in a consistent, organized, and compliant manner. External audits may be initiated by commercial manufacturers (e.g., sponsors of IEC therapies or gene-modified products) or by applicable regulatory agencies (e.g., FDA, European Medicines Agency, Health Canada) as part of their oversight responsibilities.

The QM Plan must either directly describe or reference policies or SOPs that outline how external audits are managed. The QM Plan detailing the management of external audits supports regulatory compliance and sponsor confidence in the reliability and integrity of the cellular therapy program.

STANDARD:

C4.10 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results that address at a minimum:

C4.10.1 Notification of the recipient's physician, Processing Facility, and any other facility in receipt of the cellular therapy product.

C4.10.2 Donor follow-up, if relevant.

C4.10.3 Documentation and investigation of cause.

C4.10.4 Reporting to regulatory agencies as required by Applicable Law.

Explanation:

The Collection Facility, whether operating independently or as part of an integrated cellular therapy program, must have an approach to the management of cellular therapy products with positive microbial culture results that are identified before or after the products have been administered. Policies or SOPs are required to manage the aspects for which the Collection Facility is responsible. This requirement may be satisfied with a single policy or SOP or there may be separate documents. The policies and SOPs should cover investigation of the cause of the positive microbial culture, detail what action is to be taken, including reporting to regulatory authorities if applicable, identify who is responsible for taking the action, and state the expected timeframe of the actions. In many cases, the actual responsibilities for these activities may belong to the Processing Facility. For this reason, different approaches to management may be acceptable as long as they are consistently followed and meet regulatory requirements.

The Processing Facility is usually first to be notified of a positive culture result. The Collection Facility must have an agreement with the Processing Facility for timely notification of culture results. Notification to the Collection Facility should in turn initiate investigation of all records related to that collection to determine if anything in the collection process could have contributed to the positive culture result. Collection Facility personnel are responsible for investigation of the relevant collection events.

The Collection Facility should carefully review the collection(s) and look for evidence of breach of sterility, determination of whether the donor had any evidence of sepsis at the time of collection, investigation of laboratory culture procedures to rule out a false positive result, contamination of the sample in the microbiology laboratory, or other causes that do not indicate compromise of the product.

Policies and SOPs must also be in place for the timely notification of clinical staff of the positive culture result so that appropriate care can be delivered to the donor, and, if the product has already been administered, to the recipient.

Evidence:

The inspector may ask to see the collection record of a cellular therapy product that was found to have a positive microbial culture and review how the Collection Facility managed the process.

Example(s):

Each area in a cellular therapy program may have responsibilities that do not apply to other areas. In this case, an overarching document for the management of cellular therapy products with positive cultures is recommended.

Examples of evidence of compliance with this requirement may include:

- Policies or SOPs on management of products with positive microbial culture results.
- QM meeting minutes containing a report on products with positive microbial results.
- Non-conformance reports for products with positive microbial results.

Examples of investigation and follow-up into a positive culture result may include:

- Documentation of proper equipment cleaning.
- Review of staff competency for possible trends.
- Review of findings for possible breach in aseptic technique, donor sepsis, or other issues.

Evidence of investigation of cause, outcome analysis, and any preventive or corrective action taken as a result of the investigation should be communicated to all areas of the program (clinical, collection and processing) and be evident in QM meeting minutes.

An example of donor follow-up is a situation in which the investigation found that the donor was infected at the time of collection. The Clinical Program is responsible for following up with that donor to notify them of the infection and provide recommendations for care.

In the U.S., reporting regulations are detailed in [21 CFR Part 1271](#). A cellular therapy product with a positive microbial result must be reported to the FDA only if the product is administered, whether the result was known prior to or after administration. Marrow derived products with positive microbial results do not need to be reported to the FDA. In the EU, all adverse events shall be reported to the relevant Competent Authority.

STANDARD:

C4.11 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for occurrences (errors, accidents, deviations, adverse events, adverse reactions, and complaints). The following activities shall be included at a minimum:

Explanation:

One of a QM Program's goals is to continuously improve processes. Monitoring occurrences and trends facilitates recognition of improvement opportunities and reduces the negative impact of an occurrence on the program. There must be policies, processes, and procedures to detect, evaluate, take corrective action, document, and report a summary of the factual details of the occurrence report in a timely fashion to key individuals, including the Collection Facility Director, Medical Director, Quality Manager, and governmental agencies and other entities as appropriate. The Collection Facility should define errors, accidents, deviations, adverse events, adverse reactions, and complaints in SOPs and describe when, how, by whom, and to whom each is reported. Facilities may use the definitions stated by applicable regulatory agencies; however, the definitions should meet the intent of these Standards. See [A4: Definitions](#). Management of each of these types of occurrences is slightly different; however, the same steps (detection, evaluation/investigation, documentation, determination of CAPA, and reporting) apply to all types.

Evidence:

The inspector should expect to find a process for documenting occurrences including detection, investigation, documentation, corrective action, preventive action, and follow-up. This should be reviewed by the Collection Facility Director and Quality Manager. The process shall include, as appropriate, reporting to the Clinical Program Director, the Processing Facility, appropriate governmental agencies, and other third parties involved in the manufacture of the cellular therapy product.

STANDARD:

C4.11.1 Detection.

Explanation:

Detection involves the means by which an occurrence is discovered. For example, occurrences may be discovered by audits, analysis of process improvement data, patient surveys and complaints. Immediate action must be taken and documented to mitigate further risk to product quality or patient safety.

STANDARD:*C4.11.2 Investigation.*

C4.11.2.1 A thorough and timely investigation shall be conducted by the collection staff in collaboration with all entities involved in the collection, manufacture, testing, or administration of the cellular therapy product, as appropriate.

C4.11.2.2 Investigations shall identify the root cause and a plan for short- and long-term CAPAs as warranted.

C4.11.2.3 Occurrences shall be tracked and trended.

Explanation:

Cellular therapy products affected by deviation(s) are released by the Collection Facility for use by the Clinical Program only when the benefit outweighs the risk to the patient and no alternative is available; although in some cases, the information is not known until after the administration of the cellular therapy product has occurred. The most common deviations encountered involve products with a positive microbial culture or products from ineligible donors.

It is critical to identify the cause(s) of events that pose significant risk or severity and to establish and determine what CAPA will most likely be effective. Often "systems" play a role in causation. Collection Facilities should be encouraged to stratify occurrences according to risk or severity and invest more time and energy into management of the more critical issues. Only an understanding of cause allows creation and implementation of new or revised systems or controlled documents that will correct the issue and may prevent recurrence.

STANDARD:*C4.11.3 Documentation.*

C4.11.3.1 Documentation shall include a description of the occurrence, the date and time of the occurrence, the involved individuals and cellular therapy product(s) including the unique identifier for the product involved as applicable, when and to whom the occurrence was reported, and the immediate actions taken.

Explanation:

As in the investigation, documentation of the involved individuals in any adverse event or other deviation should not be punitive. This information should be used for investigation and trending purposes to identify potential corrective and preventive measures, such as the need for additional training and staff resources.

STANDARD:

C4.11.3.2 All investigative reports shall be reviewed in a timely manner by the Collection Facility Director, Medical Director, and Quality Manager.

Explanation:

Timing of investigative reports may vary based upon the nature of the investigation, program or institutional policy, or regulatory requirements. Facilities must define the schedule of investigative reports.

STANDARD:

C4.11.3.3 Cumulative files of occurrences shall be maintained and include written investigative reports containing conclusions, root cause analysis, follow-up, CAPAs, and a link to the records of the involved cellular therapy products, donors, and recipients, if applicable.

Explanation:

Documentation should be done as close as possible to the time of detection and concurrently to ensure all critical information including description, personnel involved, date and time, and actions are captured. Sufficient information, such as unique identifiers, should be provided to link the investigative report to the records of the involved cellular therapy products, donors, and recipients, if applicable.

Complaints of cellular therapy product performance, delivery of service, or transmission of disease must be investigated and resolved. In this context, a complaint should be considered as information that implies the product or service did not meet quality specifications, failed to function as expected, or resulted in an adverse event or reactions for the recipient.

The FDA definition of a complaint is more restrictive and deals primarily with the transmission of a communicable disease, likely due to the cellular therapy product or to a failure to comply with practices that might increase the risk of transmission of a communicable disease. Corrective action or process improvement must be implemented to prevent recurrence as defined by an SOP.

Evidence:

The Collection Facility should be prepared to show examples of the cumulative files of occurrences and how they have been managed according to this process. If any occurrences have been reported to a governmental agency or other entity, the report(s) should be available for inspector review.

A tracking and filing system must be evident to show that all occurrences are logged, tracked and maintained to facilitate review and trending. Trending data should be presented at the quality meeting to ensure the effectiveness of the system is meeting requirements.

The inspector should review the complaint file and determine if corrective, preventive, or process improvement actions have been identified, implemented, and are adequate to prevent future occurrences and that regulatory agencies have been notified where that is required.

Example(s):

Communication of occurrences, investigations, and conclusions may occur in many formats, such as reporting during a regularly scheduled QM meeting with inclusion in the meeting minutes. Alternatively, a separate report may be generated, distributed, and signed by the appropriate individuals, including the Collection Facility Director, Collection Facility Medical Director, and potentially the Clinical Program Director. As appropriate, some documentation should be included in specific donor records related to specific incidents, reactions, or products.

STANDARD:

C4.11.4 Reporting.

C4.11.4.1 When it is determined that a cellular therapy product has resulted in an adverse event or reaction, the Occurrence Report and results of the investigation shall be reported to the donor's and recipient's physician(s), as applicable, to other facilities participating in the manufacturing of the cellular therapy product, registries, grant agencies, sponsors, IBCs, IRBs, Ethics Committees, accrediting bodies, and governmental agencies as required by Applicable Law.

C4.11.4.2 Occurrences shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product.

Explanation:

The FDA defines an adverse reaction as an adverse event involving the transmission of a communicable disease, cellular therapy product contamination, or failure of the product's function and integrity if the adverse reaction a) is fatal, b) is life-threatening, c) results in permanent impairment of a body function or permanent damage to body structure, or d) necessitates medical or surgical intervention.

Adverse reactions may also include unexpected reactions to the graft that are designated as possibly, probably, or definitely related. For suspected adverse reactions to administration of cellular therapy products, the results of investigation and any follow-up activities must be documented.

Adverse reactions meeting the FDA definition of products regulated under GTP or GMP (products produced under IND or IDE) must be reported to FDA within their specified guidelines. Reporting to other oversight organizations may also be necessary (e.g., accrediting agencies, registries, grant agencies, IRBs or Ethics Committees).

European [Directive 2004/23/EC](#) distinguishes between serious adverse events, which are incidents, errors, etc. that have potential consequences, and serious adverse reactions, which are actual reactions in a donor or recipient. Both must be documented and reported to the competent authorities.

- “Serious adverse event” is defined as any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life threatening, disabling, or incapacitating conditions for patients, or which might result in or prolong hospitalization or morbidity.
- “Serious adverse reaction” means an unintended response, including a communicable disease in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life threatening, disabling, incapacitating, or which results in or prolongs hospitalization or morbidity.

EU Commission Directives [2006/17/EC](#) and [2006/86/EC](#) include equivalent requirements for non-conforming products.

If an unexpected or serious adverse reaction occurs due to cellular therapy product collection or administration, for which there is a reasonable possibility that the response may have been caused by that product, the report of the adverse reaction and its outcome and investigation should be communicated to all facilities associated with collection, processing, and/or administration of infusing that product. This includes graft failure. Usually, the Clinical Program is responsible for making the initial report; however, each involved facility must participate in the investigation and evaluation of the potential cause, particularly related to its own SOPs that were involved.

Example(s):

The following are examples of adverse events that may need to be reported based on the requirements of the relevant competent authority:

- Adverse events involving the transmission of communicable disease.
- Product contamination.
- Adverse reactions that are fatal, life threatening, result in permanent impairment of a body function or permanent damage to body structure, or necessitate medical or surgical intervention.

For clinical trials, it may be appropriate to report adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) criteria. In the U.S., reporting to MedWatch may also be acceptable. After a cellular therapy product has been licensed by the applicable regulatory authority and is available for commercial use, the manufacturer will specify the reporting mechanism. Some may have a pharmacovigilance plan. The U.S. FDA provides guidance for such plans in [E2E Pharmacovigilance Planning](#) and [Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment](#) (both issued in 2005).

STANDARD:

C4.11.5 Corrective and preventive action.

C4.11.5.1 Appropriate 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.

Explanation:

All events may not require immediate corrective action. Follow-up after implementation of CAPA plans is critical to ensure effectiveness. Lack of effectiveness would indicate the need to continue further investigation of cause or other contributing circumstances and additional actions. Clinical Programs should define in their policies or SOPs when events warrant preventive plans, along with their plan to audit the effectiveness of the changes.

Immediate actions are those actions taken for each non-conformity detected in order to minimize and mitigate the impact of the non-conformity. Preventive actions are actions taken to eliminate the cause(s) of the nonconformity in order to reduce the likelihood of recurrence or occurrence elsewhere.

Investigations and corrective actions should, at a minimum, address:

- Identification of the involved individuals or cellular therapy product affected and a description of its disposition, where relevant.
- The date and time of the event.
- The nature of the problem requiring CAPA.
- To whom the event was reported.
- A description of the immediate corrective action taken.
- The date(s) of implementation of the corrective action.
- Follow-up of the effectiveness of the corrective action, where relevant.

STANDARD:

C4.11.5.2 Follow-up audits of the effectiveness of CAPAs shall be performed in a timeframe as indicated in the investigative report.

Explanation:

Short term corrective (immediate) actions are those actions taken immediately upon discovery of the occurrence or shortly thereafter to contain the problem and prevent it from causing further harm. These actions typically address the symptoms of the problem rather than the root causes. Long term corrective (preventive) actions are taken to address the root causes of the problem and are intended to be a permanent solution to the problem, preventing recurrence.

STANDARD:

C4.12 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for cellular therapy product Chain of Identity and Chain of Custody that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

Explanation:

The Collection Facility must have a policy or SOP for Chain of Identity and Chain of Custody to allow tracking and traceability of each cellular therapy product through all steps from collection to administration or final disposition. Documentation in the medical record should include the proper product name, unique product identifier(s), ISBT 128 DIN and product code, EU SEC or equivalent, content of the cellular therapy product, identification of the donor including medical record numbers, unrelated donor registry identifiers including Global Registration Identifier for Donors (GRID), allogeneic donor eligibility status, and the unique identity of the intended recipient including registry identifiers, where appropriate. There must be a process, including the use of the ISBT 128 barcode or other barcode or unique numbering system, to track and trace specimens removed from a cellular therapy product for testing at an external facility such as an HLA testing facility, transfusion service, or microbiology laboratory. This process must ensure linkage between the results of testing and the original product. There should also be a means, direct or indirect, that will allow outcome information to be related back to any other facilities involved in collection, processing, and distribution of the product. The final disposition of the product must be documented, whether the product was administered, destroyed, released, or used for research, remains in storage, or other disposition. The tracking and tracing system must comply with the Standards and Applicable Law.

Evidence:

The inspection team will review examples of collection records, including worksheets and reports and final cellular therapy product labels, to determine if tracing and tracking from donor selection through final product disposition and recipient identification is possible. All critical steps should identify who performed the procedure and when it was completed. The Marrow Collection Facility must have a system in place to request information, if not initially provided, to identify manufacturing procedures performed by external facilities (e.g., genetically modified cellular therapy product).

Review of the following documents may show evidence of product trackability and traceability:

- Collection orders showing recipient and donor information, including unique identification.
- Cellular therapy product receipt and distribution records showing donor identity, recipient identity, and unique product identifier.

Example(s):

Full implementation of ISBT 128 labeling ensures tracking and traceability of the cellular therapy product and associated pilot vials and segments in a facility. However, if a Collection Facility

removes specimens from a cellular therapy product and sends these to an external laboratory such as an HLA testing laboratory or a transfusion service for testing, the laboratory information system at the testing laboratory might not be compatible with ISBT 128 barcodes. If the testing laboratory assigns a new laboratory or barcode number to these specimens, there must be a system to link the reports generated following testing to the original cellular therapy product.

STANDARD:

C4.13 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event that Collection Facility operations are interrupted.

Explanation:

Collection Facilities should be prepared for situations that may interrupt typical operations so that such interruptions do not adversely affect recipients, donors, or cellular therapy products. While a policy or SOP is required that addresses emergencies and disasters, the facility must also have a plan for the management of interruptions that do not rise to the disaster level. It is difficult to anticipate every possible situation that may occur. Therefore, the Standards do not require the facility to outline actions for specific events; rather, the facility is required to describe actions to take when an interruption presents, including who needs to be contacted, how to prioritize cases, key personnel to be involved in identifying alternative steps to continue functions, and notification of staff.

A contingency plan specific to the Collection Facility would convey evidence that risk has been assessed for program-defined potential events of varying impact, such as a failure of the scheduling system, a water supply interruption, or shortage of a reagent. The plan should reflect differences between specific Collection Facility needs and general institutional needs and complement the institutional plan.

As more and more of the Collection Facility's documents exist on an electronic platform, there is increasing risk of temporary or permanent document loss. The institutional Information Technology Department generally confirms that software in use is validated for its function and that there is a regular schedule of backups to allow for retrieval of information when necessary. Freestanding facilities, as well as programs utilizing desktop storage, must have a plan to create a similar level of security. In either case, the program also needs a method to produce current versions of critical documents, such as preprinted orders, consent forms, and SOPs, when the electronic format is not available.

Policies, SOPs and associated worksheets and forms must be available to Collection Facility staff at all times. Arrangements must be made so that these documents are available in the event that the computer system goes down. Staff should have periodic training and review of alternate systems so they will be competent in the use of these systems should the need arise.

The Collection Facility should confirm that any electronic records in use meet other standards for validation and regularly scheduled backup of data. This may be in cooperation with the institutional Information Technology Department if available. This Standard covers the processes in place to obtain quality collections when the electronic records are unavailable. This should include a mechanism to determine and document donor suitability and eligibility (allogeneic donors) prior to collection, including retrieval of critical laboratory values, consents, adequacy of line placement, or other procedural specifics. These records may be hard copies of reports from the system that are periodically produced to be used as a manual record. There may also be forms to be completed that mimic entry screens.

Evidence:

The inspector should review policies and forms to be used in case the electronic record system is unavailable.

Example(s):

It is recommended that a Collection Facility has a contingency plan in the event that it is unable to provide services as intended (e.g., significant personnel change, natural disaster). The contingency plan may require a written agreement with an external facility (e.g., memorandums of understanding, purchasing arrangements, service level agreements, contracts and preventive maintenance arrangements, or written agreements with donor registries and external facilities) used for the storage of cryopreserved cellular therapy products.

Examples of interruptions include malfunctioning electronic records systems, drug shortages, power outages, equipment failures, and supply shortages. A contingency procedure would identify alternative sources of supplies, alternative supplies, or alternative preparative regimens.

STANDARD:

C4.14 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services.

Explanation:

Quality can be maintained only if there is control over critical manufacturers (including CAR-T manufactures), vendors, equipment, supplies, reagents, facilities, and services. The QM Plan must include a process to qualify these elements to safeguard their consistent function in validated procedures. This process must include the establishment of minimal standards for the acceptance of critical supplies and reagents and must document that those standards are met before they are made available for use.

Where purchasing is beyond the direct control of the Collection Facility, steps should be taken to verify supplier and vendor qualification have been performed by the parent organization.

Evidence:

The inspector should find evidence of qualification of manufacturers, vendors, supplies, equipment, facilities, services, and critical reagents. Qualification procedures should include instructions for requalification and under which circumstances qualification is required. Accredited facilities should participate in external inspections as required by Applicable Law.

Example(s):

It is not the intent of this Standard for the Collection Facility to qualify licensed pharmaceutical products, but rather a risk-based approach should be taken to identify items which require qualification. For example:

- Critical documents include a document that is directly related to and could impact donor welfare, recipient care, or cellular therapy product integrity.
- Updated software versions have the potential to materially affect performance of equipment.

For further definitions and examples of validation, see the [FACT Quality Handbook](#) and [The JACIE Guide](#).

STANDARD:

C4.14.1 Critical equipment, software, supplies, reagents, and facilities used for cellular therapy product collection procedures shall be qualified.

C4.14.1.1 Qualification shall be required following any significant changes to these items.

Explanation:

Clinical Programs may choose to delegate review of qualification studies to the Collection Facility. Clinical Programs may also utilize the assistance of Processing Facilities or institutional quality departments to assist with this task.

This Standard requires qualification of materials used for the collection procedure, but it is not intended to require Clinical Programs or Collection Facilities to qualify materials for the delivery of anesthesia or other materials outside of those directly used in the collection.

Example(s):

If there is a software change or upgrade, the Collection Facility must assess the need to qualify or requalify the software. Requalification would typically be necessary when the software version changes, but smaller upgrades may also critically affect donor safety or cellular therapy product efficacy.

STANDARD:

C4.14.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

C4.14.3 Qualification plans shall include minimum acceptance criteria for performance.

Explanation:

The Collection Facility must have a system in place that confirms that vendors provide materials in a timely and consistent manner that meets their acceptance criteria. Supplier qualification must also confirm that there is a system in place that is consistent with the Standards, can demonstrate process control, and that vendors are compliant with Applicable Law. Suppliers of infectious disease testing must also be qualified.

Critical reagents and supplies that come into contact with donors, recipients, or cellular therapy products shall be sterile and approved for human use (appropriate grade for intended use).

Qualification of a readily used reagent in the field (e.g., acid citrate dextrose [ACD], NaCl, Plasma-Lyte) may consist of documented evidence of inspection of the reagent for discoloration or damage, use before the expiration date, and review of COA prior to use.

Equipment qualification is performed to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. An example might be the qualification of a new blood warmer or heat-sealing device.

Facility qualification is based on the level of manufacturing in the facility and may range from a risk assessment to a full facility GMP qualification based on SOP and regulatory requirements.

Example(s):

An example might be the qualification of a new administration pump or marrow collection set.

STANDARD:

C4.14.4 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Collection Facility Director.

Explanation:

A plan for qualification must be reviewed and approved prior to performing a qualification.

Qualification of critical items should include:

- Design Qualification (DQ).
- Installation Qualification (IQ).

- Operation Qualification (OQ).
- Performance Qualification (PQ).

The qualification plan should be reviewed after the qualification to determine if all acceptance criteria were met. This process must include the establishment of minimal standards for acceptance and must document that those criteria are met before use.

Example(s):

There are several ways to qualify a vendor of supplies, reagents, and services. The most effective is to perform an audit of the provider. Other, often more practical methods may include one or more of the following:

- A review of third-party assessments by accrediting organizations such as FACT, JACIE, AABB, CAP or others.
- Remote audits by questionnaire.
- An ongoing dialog of resolution of service complaints or suggested process improvements.
- The sharing of internal audit findings and implemented corrective action plans from the provider back to the facility as evidence that deficiencies have been recognized and corrected.
- A documented review of the supplier's past performance history.

Suppliers with pre-existing service agreements preceding the implementation of this Standard can be qualified as meeting expectations by a retrospective review of the quality of service provided.

Documentation, in the form of a brief written statement, that the service provider has met the Collection Facility's requirements, worked with the facility to identify the cause of service failures, and taken corrective actions in the past may serve as documentation of service provider qualification.

General medical equipment qualification is performed to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. This qualification may be delegated to other institutional departments.

STANDARD:

C4.15 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

Explanation:

Validation is confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process (or SOP) is validated by establishing objective

evidence that the process consistently produces an expected endpoint or result that meets predetermined acceptance criteria. Validations can be performed prospectively, concurrently, or retrospectively.

Verification is the confirmation of the accuracy of something or that specified requirements have been fulfilled. Verification differs from validation in that validation determines that the process performs as expected, whereas one verifies that the products of a process meet the required conditions.

Example(s):

For further definitions and examples of validation, see the [FACT Quality Handbook](#) and [The JACIE Guide](#).

STANDARD:

C4.15.1 Critical procedures to be validated shall include collection procedures, testing, labeling, storage, and distribution, as applicable.

Explanation:

In the Collection Facility, the following should be validated at a minimum:

- The apheresis device for the intended use. Each type of apheresis machine should be validated for the process and SOPs to be performed, including cellular therapy product and/or concurrent plasma. Subsequent machines of the same type may be qualified to document performance according to expected parameters and a more limited validation of processes.
- The collection process. This validation should include all the variables used in the collection of each product, such as donor variables (e.g., white blood cell or CD34 cell count at initiation of collection, blood volume, weight) and procedural variables (e.g., machine program chosen, blood volume processed, duration of collection). The validation study should demonstrate that the process reproducibly results in a product that is sterile and is of a predetermined volume and nucleated cell content.
- Testing, if applicable.
- Labels and labeling. The validation of the label would demonstrate that the labels in use were checked against an approved template, were approved for use, maintain integrity during use, remain affixed or attached as required, are readable, do not contain any blank data points, and do include all of the required elements listed in [Appendix II](#) of the Standards. Validation of the labeling process should demonstrate completeness and correctness of each data point and the accuracy of data as shown by traceability and trackability of the product from donor to recipient or final disposition.

- Reagents, supplies, and disposables for intended use. Most Collection Facility reagents, supplies, and disposables are approved for human use. A manufacturer's COA for each type of reagent should be available. If unapproved reagents are required for collection, these should be validated to work as expected, cause no harm to the product, and be sterile.
- Storage of the product prior to distribution.
- Distribution of the product. This may include packaging, temperature, and monitoring for products transported or shipped within or between facilities.
- Electronic records system, if applicable.

It is not the intent of the Standards to include hospital-based systems and clinical medical records. For further guidance see Standard [C12.6](#).

Evidence:

The inspector should ask to see the SOPs for conducting validation studies and review a sample of validation studies. The inspector should note whether studies are properly designed, objectively collect the required data, that outcome and intended actions are summarized, and that both the finalized plan and report are reviewed and approved by the Apheresis Collection Facility Director and Quality Manager.

Example(s):

A change of equipment used for collection would need to be validated to verify product nucleated cell recovery, viability, sterility and potency are maintained at acceptable limits. The potential for adverse reactions and comparison of times to engraftment should also be examined.

In the case of collection of cells for a third-party manufacturer, the manufacturer may have data to validate the procedure. This is acceptable, though the collection procedure should at least be verified at the collection site to confirm it produces the expected results.

If there is a requirement from a manufacturer outside of what is established in a programs SOP, this could be managed by a separate SOP applicable to manufacturer requirements.

STANDARD:

C4.15.2 Each validation or verification shall include at a minimum:

Explanation:

Validation studies should be performed according to a validation SOP, utilizing a consistent format for approval of the validation plan, conducting of the studies, collection and documentation of results, data analysis, conclusions, and approval of the studies. A validation study performed because of a proposed change in a process or SOP shall include a documented assessment of the

risk involved in the change to donor and recipient health and safety and the quality and safety of cellular therapy products.

The design of the validation study should be adequate to determine if the process reproducibly achieves the purpose for which it is intended. The validation plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. Any change in the planned study that occurs during the study requires explanation. There should be an explanation, follow-up, and/or repeat of any test that fails to meet the expected outcome.

Validation should confirm acceptable endpoints can be achieved while maintaining purity, potency, and safety of the cellular therapy product. Examples of acceptable endpoints may include volume; collection efficiency; and contamination with RBCs, granulocytes, and platelets.

STANDARD:

C4.15.2.1 An approved plan, including conditions to be assessed.

C4.15.2.2 Acceptance criteria.

Explanation:

Validation of the collection procedure should confirm that acceptable criteria can be achieved while maintaining the purity, potency, and safety of the cellular therapy product. Examples of acceptable criteria may include, but are not limited to, nucleated cell recovery, viability, sterility, and hematocrit of the product.

STANDARD:

C4.15.2.3 Data collection.

C4.15.2.4 Evaluation of data.

C4.15.2.5 Summary of results.

C4.15.2.6 References, if applicable.

C4.15.2.7 Review and approval of the plan, report, and conclusion by the Collection Facility Director and the Quality Manager.

Explanation:

Review and approval need to be completed by a minimum of two individuals. One must be the Quality Manager, and the second must be the Collection Facility Director. A Quality Manager designee may need to be utilized when the Quality Manager is unavailable (e.g., on vacation, in the

process of hiring for that position, on parental leave). In this situation, the Quality Manager designee must be a qualified member of the QM team to complete the review and approval process.

STANDARD:

C4.15.3 Significant changes to critical procedures shall be validated and verified as appropriate.

Example(s):

Use of a new system for collection would require validation to confirm the system performed as expected with no compromise of the purity, potency, or safety of the collected product.

STANDARD:

C4.16 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for evaluating the risk of changes to critical procedures to assess the effect(s) elsewhere in the operation.

Explanation:

Evaluation of risk is a process to assess and document the risks involved in a change in a practice, process, SOP, or environment that has the potential to affect a critical procedure; direct patient care; and/or the cellular therapy product integrity, sterility, viability, or recovery. Critical procedures requiring risk assessment should be defined by the facility. Examples include donor management, collection, labeling, and storage.

Evaluation of risk may be documented in the SOP, in a validation plan, or as a separate document. Documentation may include:

- Identification of a risk.
- Context.
- Evaluation.
- Impact.
- Management response.

Evidence:

The inspector should ask to see the SOP for evaluation of risk for changes to a practice, process, SOP, or environment and preferably an example of how it has been applied.

Example(s):

Identification of a risk can be made by providing a description of a potential or known risk. Establishing the context or scope means all the possible risks are identified and the possible ramifications or impact in all areas are analyzed thoroughly. Once the context or scope has been

established, the next step is identification and evaluation of potential risks as either source or effect. During source analysis, the source of risks is analyzed, and appropriate mitigation measures are put in place. This risk source could be either internal or external to the system. During problem analysis, the effect rather than the cause of the risk is analyzed.

A general description of the issue and identification of the specific risk(s) should be included. After the risk has been identified, it must be assessed on the potential of criticality or on its likelihood of occurrence and potential impact, including quantitative and qualitative evaluation. Risk prioritization is when the 'likelihood of occurrence × impact' is equal to risk.

There are many different approaches to calculating risk, and there are tools that can help assist in defining the probability of the effect occurring, the root cause, and the effects and magnitude of risk under different scenarios. Examples of tools that a program might use include The Five Whys technique for root cause analysis, FMEA (Failure Mode and Effects Analysis), an Ishikawa or fishbone diagram, or SWOT (strengths, weakness, opportunity, and threats).

Once the risk assessment is established, then a risk management plan can be developed and implemented. Risk Management includes justification and rationale for accepting the risk and how to manage the impact, if applicable. This can often be established in a simple one-page document for change with low impact and risk. An example might be a change in a reagent or supply of acceptable grade.

Below is an example of a risk assessment matrix that combines the concept of likelihood and severity:

		Probability (Likelihood of occurrence)			
		Occasional (Possible to occur in time, if not corrected)	Likely (Will probably occur in most circumstances)	Frequent (Expected to occur in most circumstances)	
Risk Matrix	Severity of Incidence	Minor (low risk to the product or patient)	Low (1)	Low (1)	Medium (2)
		Moderate (Probable risk to product or patient)	Medium (2)	Medium (2)	High (3)
		Major (High risk to product or patient)	High (3)	High (3)	High (3)

STANDARD:

C4.17 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining and reviewing feedback and taking action when appropriate.

C4.17.1 Feedback shall be obtained from associated Clinical Programs and Processing Facilities.

C4.17.2 Feedback shall be obtained from donors or legally authorized representatives.

Explanation:

The QM Plan must describe how the Collection Facility obtains feedback from the Clinical Program and Processing Facility. This Standard is not intended to be prescriptive. While casual comments may be included, the intent is to have an active process for soliciting feedback.

Feedback (including complaints) must also be obtained from donors, recipients, and legally authorized representatives. It may be obtained directly by the Collection Facility; however, it is also acceptable to use a hospital-wide system, such as patient satisfaction surveys, as long as the cellular therapy program is included and relevant issues can be readily identified.

Evidence:

Evidence to show compliance may be:

- Minutes of QM meetings where issues are discussed.
- Mutual resolutions of non-compliances.
- Records of compliments and complaints.
- A survey of resolution of complaints.

STANDARD:

C4.18 The Collection Facility Director shall review the quality management activities with representatives in key positions in all areas of the cellular therapy program at a minimum quarterly.

C4.18.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

C4.18.2 Performance data and review findings shall be reported to key positions and staff.

Explanation:

QM activities, including the results of audits, shall be reported quarterly at a minimum to review the performance of the QM Program and its objectives. This is to determine whether the elements in the QM Plan are relevant and effective and necessary actions are taken in a timely manner.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported with each audit, while others may be retrospectively analyzed and reported at defined intervals. The data should be analyzed, assessed, and trended over time to identify improvement opportunities on a regular basis, such as at each QM meeting. Strategies for improvement should be identified and implemented. The results of these implemented strategies should be measured and the improvement strategies either continued or new alternatives developed, depending on the results.

Minimally, quarterly meetings are required. The minutes and attendance list of regularly scheduled QM meetings are effective ways to document QM activities and communication of quality assessments to key individuals within participating facilities in the cellular therapy program. Having multidisciplinary meetings that involve several academic disciplines or key personnel is an acceptable approach to develop recommendations for performance improvement.

Evidence:

The inspector should ask to see evidence that, at a minimum, a summary of key performance data and review findings have been reported to staff (although all findings can be shared) within all participating entities in the cellular therapy program. The inspector should ask to see the minutes of the QM meetings, which should document who was in attendance and what topics were covered. At a renewal inspection, it is particularly important to ask for QM meeting minutes that represent the time since the previous accreditation in order to determine that the QM Program is and has been ongoing. Minutes should summarize activities such as training performed, documents reviewed, audits performed, and SOPs introduced or revised, and outcome parameters reviewed.

STANDARD:

C4.18.3 The Collection Facility Director shall not have oversight of their own work if this person also performs other tasks in the Collection Facility.

Explanation:

Any person responsible for overseeing QM activities should not be directly responsible for review of work solely performed by that person. It is important that the final review be unbiased and that there has been sufficient time away from the work for the review to be objective. Alternatively, in small Collection Facilities where there may be only one person responsible for most of the collection activity, the Collection Facility Director, Collection Facility Medical Director, or a person from the Processing Facility may be designated to review these activities. It may be acceptable, however, for an individual to review their own work at a time and place removed from the actual performance of the work.

Evidence:

The inspector should assess if the person documented as performing the task is also the person reviewing or approving the work. For example, the Collection Facility Director should not be the sole approver of a planned deviation for a collection that they are responsible for performing.

STANDARD:

C4.19 The Collection Facility Director shall review the effectiveness of the QM Program annually.

C4.19.1 The annual report and documentation of the review findings shall be made available to key personnel, the Clinical Program Director, the Processing Facility Director, and staff of the program.

Explanation:

The ultimate responsibility for performance and monitoring of the QM Program, including internal or contracted components, belongs to the Collection Facility Director. If the Collection Facility is part of an integrated cellular therapy program, a single annual report is sufficient.

The overall effectiveness of the QM Program must be reviewed and reported to staff on an annual basis. The annual report will provide a year-long view of the overall function of the QM Program, its effect on and interactions with the Clinical Program and Processing Facility and provide clues on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated.

The annual report should also contain trending information related to key indicators that are monitored, patient outcomes, patient satisfaction, adverse events, and other important elements utilizing data from prior years and goals for the coming year.

Example(s):

Collection Facility Directors may wish to report on the effectiveness of the QM Program more frequently than once a year. If so, the report should utilize some data from the previous 12 months to provide a longitudinal perspective of how the QM Program is functioning over time.

Examples of sections to include in the report on the performance of the QM Program are:

- Overall programmatic indicators (e.g., accreditation achieved, new faculty, relocations and renovations, data updates).
- Collection efficiencies.
- Donor adverse events.
- Other events such as complaints or deviations.
- Audits.
- Validations.
- Risk assessments.
- Service-level agreements.
- Process improvements.
- Goals for the coming year.

C5: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

C5.1 The Collection Facility shall establish and maintain policies or Standard Operating 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:

Explanation:

Each Collection Facility must have written policies or SOPs that comprehensively address all aspects of the facility. The policies and SOPs required in C5 are operational in nature, whereas those required in [C4](#) pertain to the QM Program. A policy describes a course of action or mission statement in general terms. An SOP gives specific step-by-step instructions on how to perform a particular task. The policies and SOPs must be detailed, unambiguous, and adequately define all operational aspects of the Collection Facility. The Standards allow the facility to create its document hierarchy based on its own internal requirements and policies. The facility is not required to have both a policy and SOP for each item, nor is a dedicated policy or SOP required for each item on the list as long as each item is addressed somewhere within the appropriate document. The items listed in C5.1 include the minimum requirements; a facility may exceed these requirements but not omit any of them.

The Collection Facility can utilize institutional policies and SOP but retain the responsibility for verifying that those policies and SOPs meet the requirement of the Standards. In those circumstances where program or institution standards vary from these minimal requirements, the program will be held to the higher standards.

It is recognized that the practice of medicine requires some flexibility, and the Collection Facility may choose to designate policies for some clinical care related to the collection procedure as practice guidelines. Policies and SOPs must comply with the document control requirements listed in [C4](#). Review and approval of all policies and SOPs shall be performed at the time of document creation, at each revision, and every two years thereafter.

Evidence:

Prior to the on-site inspection, the inspector will have a list of all SOPs or a table of contents from the Collection Facility's SOP Manual that includes the title and version for all controlled documents along with the other pre-inspection materials. The list should be examined for evidence of the existence of SOPs addressing each item listed in the Standards before arriving at the inspection site. Prior confirmation that a specific SOP has been generated will reserve limited on-site inspection time for evidence of implementation of written SOPs and other activities that can only be verified in person at the inspection site. Implementation may be verified by direct observation, by a mock-up scenario, or verbal conveyance of the SOPs.

When multiple topics are covered by a single SOP, it will aid the inspection process if the Collection Facility prepares a crosswalk between the list of required SOPs in C5.1 and the facility's own SOP Manual.

The inspector should verify that the procedure for development and review for all policies and SOPs is being followed and that the policies and SOPs are comprehensive and define all aspects of the Collection Facility's operations.

If a Collection Facility is operated out of a transfusion service and shares certain SOPs or policies with the transfusion service, then an index of the shared policies and SOPs should also be submitted.

Example(s):

The policies and SOPs can be generated within the Collection Facility or in collaboration with other entities within the institutional infrastructure. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and emergency response to disasters. In cases where general institutional policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the facility, the facility must develop its own policies and SOPs to supplement those of the institution. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for initial review and approval and approval of revisions every two years by the facility to ensure the most current version is in use and applicable to all functions of the Collection Facility.

Some Collection Facilities may collect cells for cellular therapy products that are manufactured by a third party. These manufacturers may require processes different than what is outlined in the facility's SOPs for its usual activities. When this occurs, the facility may handle different manufacturer requirements via the planned deviation process (acceptable for infrequent situations), additions within existing SOPs, or separate SOPs for those processes. The facility is responsible for verifying that the different process achieves the intended results.

Both FACT and JACIE have published Quality Handbooks (the [FACT Quality Handbook](#) and [The JACIE Guide](#)) to provide additional explanation of quality principles. These handbooks can be used as additional resources to develop policies and SOPs in compliance with the Standards.

STANDARD:

C5.1.1 Donor and recipient confidentiality.

Explanation:

Confidentiality is a critical aspect of care management, and it is applicable in every case. How programs manage confidentiality will look different based on the type of program (e.g., autologous, related allogeneic, unrelated allogeneic).

Example(s):

Donor and recipient confidentiality includes confidentiality of records.

STANDARD:

C5.1.2 Donor informed consent for cellular therapy product collection.

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

Explanation:

Determination of eligibility refers to the allogeneic cellular therapy product donor for whom all the donor screening and testing have been completed in accordance with Applicable Law and who has been determined to be free of risk factor(s) for relevant communicable diseases.

Evidence:

The inspector will look for information in the policy or SOP for consents that detail how the donor or recipient is informed on treatments, collection practices, storage, and what happens to the product including administration, release for research, use for quality assurance activities, or stability testing.

STANDARD:

C5.1.4 Donor-specific issues related to age, sex, height, and weight.

Explanation:

Depending on the age range of donors, Collection Facilities should be able to demonstrate how processes are adjusted for age-specific issues. Age and size-specific considerations for support during the peri-donation period must be addressed in clinical care SOPs.

Collection of cells from pediatric donors requires specific policies and SOPs that address issues of age and size of the donor. Any Collection Facility that collects a cellular therapy product from a minor donor must have appropriate SOPs that address at least issues of informed consent, donor size, and venous access.

Collection of cells from small donors by apheresis requires several considerations, including at least extracorporeal volume, RBC reduction, and citrate toxicity. These issues are particularly important in donors under approximately 25 kg. Procedures should describe at least the priming of the extracorporeal circuit with irradiated RBCs if the donor's blood volume or oxygen carrying capacity will be compromised during the procedure and prophylactic calcium supplementation to prevent citrate toxicity. Alternative anticoagulants could also be considered.

Young children and other small donors may have inadequate peripheral vein size to accommodate apheresis needles. In these cases, there must be policies and SOPs for central venous access or provisions to collect with alternative methods that include details of risk, consent, access to a competent physician to secure central venous access, documentation of adequate line placement, and other procedural details. There may be limitations based on Applicable Law. Young children and small donors may be restricted from CVCs. In addition, collection of cellular therapy products from obese donors may present challenges, including dosing of mobilization agents, and should be addressed in SOPs.

Small and obese donors undergoing marrow collection also have unique needs and challenges which should be addressed in SOPs. Allogeneic blood may be needed if the recipient is significantly larger than the donor. Technical aspects of the collection require attention because of the size of the iliac crests.

STANDARD:

C5.1.5 *Management of donors who require central venous access.*

C5.1.6 *Cellular therapy product collection.*

Example(s):

During final cellular therapy product collection, the Collection Facility must ensure that requirements for further manufacturing are achieved. For example, for genetically modified cells, the final collected product often requires low hematocrit and low platelet counts (Fesnak, Lin, Siegel, Maus. [CAR-T Cell Therapies From the Transfusion Medicine Perspective](#). *Transfus Med Rev.* 2016;30(3):139-45).

STANDARD:

C5.1.7 *Administration of blood products.*

C5.1.8 *Prevention of mix-ups and cross-contamination.*

C5.1.9 *Labeling including associated forms and samples.*

C5.1.10 *Cellular therapy product expiration dates.*

Evidence:

The inspector will review the SOP(s) describing the expiration dates and storage conditions for the cellular therapy products collected and the process for its performance.

STANDARD:

C5.1.11 Cellular therapy product storage, including alternative storage.

Explanation:

The Collection Facility must define the expiration dates and storage conditions (e.g., container, temperature) of all of its collected cellular therapy products, including those released to a Clinical Program, Processing Facility, or another facility.

STANDARD:

C5.1.12 Release and exceptional release.

Explanation:

Release is defined as the removal of a cellular therapy product from in-process status when it meets specified criteria. Collection Facilities must have release criteria for when a cellular therapy product can be distributed to the Processing Facility, Clinical Program, or outside facility. Release criteria are not only applicable to directly releasing a cellular therapy product for administration, but also to releasing a cellular therapy product to another facility (e.g., to a Processing Facility for processing and storage).

Each cellular therapy product must be verified to have met release criteria before being released. SOPs must outline how this verification takes place and who approves the release. There may be times when a product does not meet release criteria. An SOP must define the process for exceptional release, outlining the steps to take for documentation and approval.

Evidence:

The inspector will review the SOP(s) describing the release criteria and the process for release of cellular therapy products that meet those criteria. The inspector will also verify existence of an SOP for exceptional release, including documentation and approval.

Example(s):

In addition to being released to a Processing Facility or Clinical Program, cellular therapy products may be released from the Collection Facility directly to outside manufacturers or unrelated donor registries.

Examples of release criteria include, but are not limited to:

- Correct labeling, including storage temperature and expiration date.
- Sealed secondary container.
- Completed allogeneic donor eligibility documentation.

STANDARD:

C5.1.13 *Packaging, transportation, and shipping, including methods and conditions within the Collection Facility and to and from external facilities.*

C5.1.14 *Cellular therapy product disposal.*

Explanation:

Disposal of a cellular therapy product in the Collection Facility is unusual but does occur occasionally. The Collection Facility must have a policy or SOP which addresses the types of circumstances for which disposal would occur, approval of the disposal, and appropriate documentation.

If a cellular therapy product is disposed of at the Collection Site, the records for disposal of the product shall indicate the Collection Site. The procedures for disposition must be available and include the unique numeric or alphanumeric identifier of the products; the reason, date, and method of disposal; the individual who disposed of the product; and the individual who authorized the disposal.

STANDARD:

C5.1.15 *Critical equipment, reagent, and supply management, including recalls and corrective actions in the event of failure.*

C5.1.16 *Equipment operation, maintenance, and monitoring including corrective actions in the event of malfunction or failure.*

C5.1.17 *Cleaning and sanitation procedures, including beds, chairs, and operating rooms as applicable, and the identification of the individuals performing the activities.*

Explanation:

Beds and chairs must be cleaned between patients. If an institutional policy is followed for the cleaning and sanitation of beds and chairs, the policy must be referenced within the Collection Facility's SOP.

STANDARD:

C5.1.18 *Environmental control, as determined in [C2.4](#), including a description of the environmental monitoring plan.*

Explanation:

The Collection Facility must have policies and SOPs defining how environmental concerns will be managed including factors which directly affect the cellular therapy product, equipment, or personnel performance.

STANDARD:

C5.1.19 *Handling and disposal of medical and biohazard waste.*

C5.1.20 *Cellular therapy emergency and disaster plan, including the Collection Facility response and product management.*

Explanation:

Contingency planning for emergency and disaster events that may critically impact donor and recipient care must be included in Collection Facility's SOPs. It is highly recommended that a facility that is part of a complete cellular therapy program have a contingency plan in place in the event the Collection Facility, Processing Facility, or Clinical Program are unable to provide services as intended (e.g., significant personnel change, disaster).

The Collection Facility must have a disaster plan that is specific to the facility. The facility may use institutional policies for the general responses. However, specific SOPs relating to the chain of command and necessary SOPs to address the safety of donors and recipients are needed to augment the institutional policies (such as actions to take in response to an emergency or disaster occurring during an apheresis collection or after a donor is prepared for an apheresis collection, or an event that prevents collection for a recipient who has already undergone myeloablation). This plan should include actions to be taken in case of a disaster (such as how to locate and use emergency power) and include specifics such as how to proceed if a donor is undergoing collection at the moment of the disaster or what to do if cellular therapy products need to be moved. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for review and approval.

Evidence:

Compliance with most of the Standards in this section can be determined before the on-site inspection by review of the document control system and SOPs submitted in the pre-inspection material. However, additional SOPs should be reviewed during the inspection for compliance.

Example(s):

Examples of disasters include fires, hurricanes, floods, earthquakes, nuclear accidents, and pandemic disasters. Specific natural disaster policies may be more pertinent dependent on geographic location. Infectious threats include failure of isolation facilities; outbreak of aspergillosis, respiratory syncytial virus (RSV), or (para) influenza; or pandemics, leading to an emergency closure or modifications to practices of the Collection Facility.

In cases where institutional policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the facility, the facility must develop its own policies and SOPs. The article [*Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program*](#) (Wingard, Leahigh, Confer, et al. *Biol Blood Marrow Transplant*. 2006;12(11):1229-38) provides a framework for disaster plans that can be customized for individual facilities.

Additionally, the FDA offers information on its webpage [*Impact of Severe Weather Conditions on Biological Products*](#) (2018).

STANDARD:

C5.1.21 ECP, if performed by the Collection Facility.

C5.1.22 Chain of Identity.

C5.1.23 Chain of Custody.

Explanation:

Chain of Custody and Chain of Identity policies and procedures in this document pertain to the cellular therapy product. The Collection Facility must have a policy or SOP for the linkage to allow tracking and traceability of each product through all steps from collection to administration or final disposition. Documentation in the medical record should include the proper product name, unique product identifier(s), ISBT 128 DIN and product code, EU SEC or equivalent. There must be a process, including the use of the ISBT 128 barcode or other barcode or unique numbering system, to track and trace specimens removed from a cellular therapy product for testing at an external facility such as an HLA testing facility, transfusion service, or microbiology laboratory. This process must ensure a linkage between the results of testing and the original product. There should also be a means, direct or indirect, that will allow outcome information to be related back to any other facilities involved in the collection, processing, and distribution of the product. The final disposition of the product must be documented, and whether the product was administered, destroyed, released, or used for research, remains in storage, or other disposition. The tracking and tracing system must comply with the Standards and Applicable Law.

While linkage must be maintained, the identity should not be readily apparent in the later stages of processing and storage. With the requirement to maintain long-term linkage with the donor, there is information collected and stored that could allow tracing of the donor by an interested third party. The Collection Facility must demonstrate processes in its record system that prevent the unnecessary display of such demographic information.

STANDARD:

C5.2 The Collection Facility shall maintain a detailed list of all controlled documents, including title and identifier.

Explanation:

Controlled documents must be maintained in an organized fashion so that all current documents can be found. Many Collection Facilities have adopted an electronic method of compiling their policies and SOPs, which is acceptable. Hard copy, bound manuals also meet the intent of the Standard. There must be a list of all SOPs to serve as a master index or table of contents from which personnel can determine which SOPs exist.

Evidence:

The detailed list should be organized in such a manner that the inspector can ascertain that the controlled documents are comprehensive and define all aspects of the Collection Facility.

Example(s):

A Collection Facility may choose to have one detailed list of controlled documents or divide policies and SOPs into several manuals by subject. A technical procedure manual in conjunction with a quality, policy, and database manual may serve to better organize information if the facility chooses this format.

STANDARD:

C5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual Standard Operating Procedure shall include:

Explanation:

Policies and SOPs must be detailed, unambiguous, and adequately define all operational aspects of the Processing Facility. Policies in general should identify an intended goal and include the elements required to meet that goal. However, policies may need one or more associated SOPs to actually describe the actions that are taken. The minimal elements must be included in all SOPs; if one of the items is not applicable, this should be indicated with N/A.

Evidence:

Compliance with most of the Standards in this section can be determined before the on-site inspection by review of the document control system and submitted SOPs contained within the pre-inspection material. However, additional SOPs should be reviewed during the inspection for compliance.

Example(s):

In some Collection Facilities, the actual "SOP" may be limited to minimal work instructions, and required elements such as a reference list may be found only in higher level documents. Such variability is acceptable if all elements are documented and readily available to staff. [*The Art of Writing and Implementing Standard Operating Procedures \(SOPs\) for Laboratories in Low-Resource Settings: Review of Guidelines and Best Practices*](#) describes suggested practices for writing SOPs (Barbé, Verdonck, Mukendi, et al. *PLoS Negl Trop Dis*. 2016;10(11):e0005053). Adherence to a uniform format is required to maintain documents.

STANDARD:

- C5.3.1 *A clearly written description of the objectives.*
- C5.3.2 *A description of equipment, reagents, and supplies used.*
- C5.3.3 *Acceptable endpoints and the range of expected results.*

Explanation:

The Collection Facility should establish a range of acceptable results, when appropriate, for each procedure. Examples include nucleated cell recovery, hematocrit, sterility, and plasma volume. The range for a given parameter can be determined within the Collection Facility by evaluating data from its own products.

STANDARD:

- C5.3.4 *A stepwise description of the procedure.*
- C5.3.5 *Reference to other policies or Standard Operating Procedures required to perform the procedure.*
- C5.3.6 *A reference section listing appropriate and current literature.*
- C5.3.7 *Documented approval of each Standard Operating Procedure by the Collection Facility Director or Medical Director, as appropriate, prior to implementation and every two (2) years thereafter.*
- C5.3.8 *Documented approval of each procedural modification by the Collection Facility Director or Medical Director, as appropriate, prior to implementation.*

Explanation:

The Standards require documented review of each SOP by the Collection Facility Director or by the Collection Facility Medical Director every two years. It is important that the documentation of review every two years clearly indicates the version of each policy or SOP that was reviewed. If a process changes, the SOP must be updated at that time and reviewed before the changes are implemented; unchanged SOPs must be reviewed at a minimum every two (2) years.

Example(s):

A review signature on the document itself or on a listing of the reviewed documents by name that includes the unique identifier and version is acceptable proof of document review. A validated electronic review system is also acceptable. A single page in the manual with a signature and a date is not sufficient since SOPs may be revised throughout the year. Approving several SOPs at once with a single signature and date is not sufficient, as it does not demonstrate that individual SOPs were actually reviewed and approved.

STANDARD:

C5.3.9 *Reference to a current version of orders, worksheets, reports, labels, and forms.*

Explanation:

Current versions of worksheets, reports, labels, and forms, where applicable, must be identified in or attached to each SOP. The purpose of this Standard is to ensure that these documents are easily accessible to a reader of the SOP and that it is clear what documents may be required for the performance of that SOP. It is acceptable to simply reference applicable worksheets, reports, labels, and forms for which a separate SOP exists describing their use.

Example(s):

Reference to relevant controlled documents within an SOP requires some flexibility. Some Collection Facilities include it in the body of the SOP at the end of that relevant step, whereas others may include it at the very end of the procedure as a separate section that lists other required SOPs where the procedure identifier (minus the version) and name are listed.

Completed forms do not necessarily need to be used as examples, but it may be prudent to attach one or more completed forms to illustrate possible real-life scenarios. For electronic systems, the use of links is acceptable.

STANDARD:

C5.4 *Controlled documents relevant to processes performed shall be readily available to the facility staff.*

Explanation:

The written copy or electronic version (with provision of hard copy as necessary) of the Collection Facility's controlled documents must be immediately available to all relevant employees in their working environment(s). There must be only one source document created from which review occurs. Any copies of policies and SOPs must be identical to the source document and must not be used to alter, modify, extend, delete, or otherwise edit any SOP.

If an electronic manual is used, there must be a mechanism to access the manual at all times, even if the network is not available. If collections are performed in the patient room, the collection SOP must be readily available.

Evidence:

The written copy or electronic version of the SOPs should be readily identifiable to the inspector. The inspector should expect to see SOPs or electronic access to SOPs in all performance areas of the Collection Facility. The SOPs should be organized in such a manner for the inspector to ascertain that the SOPs are comprehensive, defining all aspects of the Collection Facility.

Example(s):

The detailed list and master copies are usually physically located in a management team member's office. However, collection procedures are often performed outside of those locations (e.g., at the bedside). If SOPs are not physically present at locations in which the collection procedure is performed, there should be a process to get access to them in case they are needed, and the staff should be familiar with that process.

STANDARD:

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

Explanation:

Before a staff member is allowed to perform new and revised procedures, they must have reviewed or received the applicable training. Clinical Programs are not required to train all staff members before implementing a new policy or SOP, but they must document an individual's review or training before that person uses the revised policy or SOP.

Evidence:

Documentation that approved and implemented policies or SOPs are performed only after the individual staff member has reviewed and been trained on the new or revised procedure should be reviewed by the inspector.

Example(s):

Sometimes a revision to a policy or SOP is minor, such as an update to a referenced regulation or grammatical corrections. In these cases, full training may not be necessary, and review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

It is recommended that every policy and SOP and associated revisions have a specific signoff sheet to document that each staff member required to review the policy or procedural revision has done so prior to performing the task(s) described. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each procedure and to any major revision also facilitate documentation of appropriate training of staff.

STANDARD:

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

Evidence:

The inspector should observe on-site that procedures are performed according to the written SOPs.

STANDARD:

C5.7 Planned deviations shall be pre-approved by the Collection Facility Director or Medical Director and reviewed by the Quality Manager.

Explanation:

Planned deviations should be approved by the Collection Facility Director or Medical Director at a minimum. Retrospective review by the Quality Manager must be performed in compliance with processes designed for deviations. Processes set up for review of planned deviations are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately.

Example(s):

Planned deviations may be necessary in the following scenarios:

- Performance of a collection outside of a validated time window.
- Use of alternative collection equipment.
- Collection of a product exceeding protocol volume or cell count.

C6: ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

Explanation:

Standards in C6 mirror those in [B6](#), reflecting the fact that these responsibilities are usually the primary responsibility of the Clinical Program staff. Collection Facility staff are usually not responsible for donor selection. Cellular therapy program policies and SOPs must clearly define responsibility for all aspects of donor selection, evaluation, eligibility (allogeneic donors only) and suitability determination, and management.

In situations in which the Collection Facility is primarily responsible for activities related to donor selection, the applicant and inspector must complete the corresponding sections in the Clinical Program inspection checklist.

These Standards are intended to optimize the safety of the donor and recipient as well as the safety and efficacy of the cellular therapy product. For allogeneic donors, additional requirements exist to achieve appropriate histocompatibility matching and to protect the recipient from the risks of transmissible disease. For both allogeneic and autologous donors, an assessment of their acuity to include co-existing comorbidities and other challenges such as the presence of a central line, can help determine whether the Collection Facility is capable of safely performing the collection.

Donor eligibility and suitability should be differentiated as defined in [A4](#), where “eligibility” refers to a donor who meets all transmissible infectious disease screening and testing requirements, and

“suitability” refers to issues that relate to the general health of the donor and the donor’s medical fitness to undergo the collection procedure.

STANDARD:

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

Explanation:

The Collection Facility must have in place written SOPs defining all aspects of donor identification, evaluation, selection, and management, including identification of the personnel responsible for each aspect. Facilities should consider requirements of the FDA, EU Directives, NMDP, WMDA, and other regulatory authorities and accrediting agencies when creating and reviewing these SOPs. For donors of cellular and tissue-based products, Applicable Law on allogeneic donor eligibility determination usually requires that donor evaluation include risk factor screening by health history questionnaires, review of medical records, physical examination, and testing for relevant communicable disease agents and diseases.

The allogeneic donor is determined to be eligible if they:

- Are free from risk factors for and clinical evidence of relevant communicable disease agents and diseases.
- Are free from communicable disease risks associated with xenograft in the donor or in someone with whom the donor has had close contact.
- Test negative or non-reactive for relevant communicable disease agents within the specified time frame for the product.

These Standards also require that if allogeneic donors are ineligible according to Applicable Law or do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented. There must also be documentation in the recipient’s medical record by an attending physician of urgent medical need for the cellular therapy product. Urgent medical need means that no comparable product is available, and the recipient is likely to suffer death or serious morbidity without the product. The product should be accompanied by a summary of records to the Collection and Processing Facilities stating reasons the donor is ineligible, including results of health history screening, physical examination, and results of infectious disease testing.

In addition, this Standard requires that the Collection Facility identify the institutional criteria for medical suitability of donors. Written criteria should include criteria to determine the number of cellular therapy product donations permitted by a single donor. This includes criteria for both related and unrelated donors. It also requires that each aspect of this process be performed according to written SOPs and that the results of the evaluation are documented. Donor suitability

should be documented within the medical record in the Clinical Program and be provided in writing to the Collection and Processing Facilities.

Evidence:

The inspector should verify that policies and SOPs (for donor evaluation and management), including criteria to collect at certain sites if they are different from other sites in terms of medical capability, are written, clearly defined, and unambiguous. The inspector may ask to verify compliance with these SOPs by reviewing a specific donor evaluation. The inspector may also verify the rationale and informed consent for a specific donor who did not meet the institution's donor criteria, as well as make sure that there is an SOP for urgent medical need documentation and labeling for allogeneic cellular therapy products.

Example(s):

Eligibility testing is only required for allogeneic donors; however, autologous donors must be tested if required by Applicable Law. Autologous donors who are tested and have positive results for some infectious diseases (e.g., Hepatitis B or C, HIV), are not necessarily excluded as a donor. It is helpful for programs to be aware of infectious disease status but does not constitute a contraindication for autologous donation.

According to the U.S FDA guidance document [Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products](#) (2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in [21 CFR 1271.55](#). In January 2025, the FDA released additional draft guidance: [Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](#).

STANDARD:

C6.1.1 *The donor shall undergo the collection procedure at a site with the appropriate capabilities to manage the level of acuity and risks.*

Explanation:

The Standard does not require that all collection sites be equivalent. Some collection sites may be within an inpatient hospital or in an outpatient clinic; others may be free-standing collection sites. Furthermore, Collection sites may vary in capabilities, capacity, potential for donor isolation, staffing, access to transfusion services, interventional radiology, or support for pediatric patients. Some collection sites may be relatively distant from the main facility and be most appropriate for collections from healthy adult donors without CVCs.

Evidence:

The donor criteria for each collection site should be documented in the facility's QM plan, specific site description, or elsewhere.

Example(s):

The following are example statements that could indicate criteria for a collection site:

- Capable of managing co-existing comorbidities.
- Capable of managing allogeneic or autologous donors.
- Capable of managing donors with a central line.
- Capable of managing patients receiving a mobilization regimen.

STANDARD:

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:

Explanation:

Clinical Programs typically obtain informed consent to donate; similarly, Collection Facilities must obtain informed consent to perform the specific procedure. It is acceptable to include both the consent to be a donor and the consent for the collection procedure in the same process and obtain both consents at the same time. The informed consent content and process is determined by the law in the jurisdiction of the Collection Facility. The essential elements of informed consent are that the donor or recipient is told, in terms they can reasonably be expected to understand, the reasons for the proposed therapy or procedure, the risks associated with the treatment or procedure, and the potential benefits. This applies to both autologous and allogeneic donors. In addition, the donor or recipient should be given the opportunity to ask questions and to have these questions answered to their satisfaction. The discussion that ensues is the most important part of the process of obtaining informed consent; however, it is the documentation of this process that can be easily audited. Informed consent is to be documented according to institutional standards and criteria.

The information must be given by a trained person able to transmit it in an appropriate and clear manner, using terms that are easily understood. The health professional must be certain that the donor has a) understood the information provided, b) had an opportunity to ask questions and been provided with satisfactory responses, and c) confirmed that all the information they have provided is true to the best of their knowledge and documented in the medical record.

Evidence:

Inspectors will review one or more completed donor consent forms to determine if all the required elements are in place and may review the clinic note which details discussion of the protocol. The inspector may also ask to see each version of the consent form or clinic notes when a different process is used for pediatric recipients and donors.

Example(s):

It is recommended that the consent process be documented in the clinic chart by the consenting licensed healthcare professional who is familiar with the collection procedure. In addition, it is recommended that a signed copy of the informed consent, even outside of a research protocol, be provided to the donor and recipient.

This process may take place over several visits. A preprinted consent form detailing each of the required elements is an easy method of documentation; however, informed consent does not specifically require such a form. In the absence of a form, the clinical notes detailing the consent discussion must be significantly detailed.

STANDARD:

- C6.2.1.1 The risks and benefits of the procedure.*
- C6.2.1.2 The intent of the collection for treatment or research.*
- C6.2.1.3 Tests and procedures performed on the donor or donor's specimens to protect the health of the donor and the recipient.*
- C6.2.1.4 The rights of the donor or legally authorized representative to review the results of such tests according to Applicable Law.*
- C6.2.1.5 Protection of medical information and confidentiality.*
- C6.2.1.6 Alternative collection methods.*
- C6.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.*
 - C6.2.2.1 Family members and legally authorized representatives shall not serve as interpreters or translators.*

Explanation:

The intent of this Standard is for interpretation and translation related to the consent process for relevant medical care to be utilized. For family member conversations not related to care, institutional policies should be followed.

There may be instances when a translator is unavailable for a rare language or dialect. This occurrence must be documented, and an explanation must be provided in accordance with the requirements in [C4](#).

STANDARD:

C6.2.3 *The donor shall have an opportunity to ask questions.*

C6.2.4 *The donor shall have the right to refuse to donate or withdraw consent.*

C6.2.4.1 *The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal in the event that consent is withdrawn after the recipient has begun the preparative regimen.*

Explanation:

The right to refuse to donate and the right to withdraw consent are two separate concepts. Refusing to donate is prior to ever consenting to the donation, while withdrawing consent would be after the consent to the donation has already been given. This Standard is not meant to be coercive, but to require full disclosure of the effects a donor's decisions could have on a recipient. Donors shall be informed that the consequences to the recipient of the donor's refusal to donate are significantly different depending on the stage of transplant. If the potential donor declines prior to typing versus refusing after selection and the day before the administration, then the degree of risk incurred to the recipient will be very different.

STANDARD:

C6.2.5 *Donor informed consent for the cellular therapy product collection, including use, storage, and discard, shall be obtained and documented by a licensed health care professional knowledgeable in the collection procedure and the intended use of the product.*

C6.2.5.1 *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.*

Explanation:

In the allogeneic setting, to prevent conflict of interests that may exist when a physician or other health care provider cares for both the donor and the recipient, donors must be consented by a member of the team other than the primary health care professional of the intended recipient or a clinician who is not a member of the team but is knowledgeable in the collection procedures.

STANDARD:

C6.2.6 In the case of a donor who is a minor or who does not have the capacity to consent, informed consent shall be obtained from the donor's legally authorized representative in accordance with Applicable Law and shall be documented.

Explanation:

Donors must be of legal age of consent (in the jurisdiction of the collection), or the informed consent for donation must be signed by the legally authorized representative. Specific consent is required for the use of growth factor in a minor, allogeneic donor. It is appropriate to discuss the donation procedure with the pediatric donor in terms they can understand. For minor donors, although consent is obtained from legally authorized representatives in accordance with Applicable Law, assent should also be obtained in an age-appropriate manner. Institutional policy should guide providers in how to define and determine the donor's capacity to consent.

In the event that the legally authorized representative is the potential recipient, an alternative donor advocate should be appointed. There may be other Applicable Laws that apply.

Evidence:

Inspectors may ask to review one or more signed consent forms from minor donors. If the informed consent process is performed verbally, the clinic note must detail discussion of the protocol, including the documentation of required elements consistent with institutional policy and Applicable Law.

Example(s):

It may be helpful to include a child life specialist, a social worker, or another qualified individual in the consent process to make certain that the minor donor has age-appropriate understanding.

STANDARD:

C6.2.6.1 There should be a process to obtain appropriate assent from minor donors.

Explanation:

There are jurisdictions where informed consent may be obtained from minor donors; however, this Standard is the minimum expected. The Collection Facility should define the parameters for obtaining assent. Applicable Law may allow additional documentation when attaining the assent for a minor.

Collection Facilities must be compliant with institutional policy and governmental laws when addressing issues of assent of a minor who may be unwilling to donate. The age of assent and consent varies depending on the legal jurisdiction. Conferring with appropriate legal counsel is indicated in complex cases.

STANDARD:

C6.2.7 *The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient or the recipient's physician.*

Explanation:

The purpose of this Standard is to protect the donor's confidentiality regarding their health information. Donors should be aware of testing results so that they may decide whether or not to allow recipient access to information that may disclose lifestyle behaviors or prompt coercion to donate based on HLA typing results. The Collection Facility should have the consent available prior to the collection procedure. Release of health information to the recipient is only required after donor selection.

Evidence:

Documentation of donor informed consent and recorded authorization to release relevant donor health information may be used as evidence of compliance. The date informed consent was obtained in relation to the date the release of the donor's health information occurred will be compared.

Example(s):

It is acceptable to obtain informed consent and authorization to release this information after donor screening and testing as long as it is obtained prior to sharing the results and prior to the collection. If a potential donor is screened but is deemed not to be suitable for collection, donor health information related to this decision does not need to be released to the potential recipient.

STANDARD:

C6.2.8 *The donor shall be informed of the policy for cellular therapy product storage, discard, or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product.*

Explanation:

Policies may differ between institutions and donor registries as to the outcome of a donated cellular therapy product that is not or is only partially used for a cellular therapy procedure. It is important that the donor be informed of these policies at the time of donation.

Evidence:

The inspector should review the information provided to the donor regarding cellular therapy product storage and discard.

Example(s):

Many facilities consider that the donated cells become the property of the intended recipient since donation was for the recipient's use. Registries that facilitate unrelated transplants may have specific

requirements for what information must be provided to the donor regarding cellular therapy product discard.

STANDARD:

C6.2.9 *Documentation of consent shall be verified by the Collection Facility staff prior to the collection procedure.*

C6.3 *SUITABILITY DETERMINATION FOR ALLOGENEIC AND AUTOLOGOUS DONORS*

C6.3.1 *There shall be criteria and evaluation policies or Standard Operating Procedures in place to protect the safety of donors during the process of cellular therapy product collection.*

Explanation:

Donor suitability refers to issues related to the general health of the donor and protection of donor safety. The criteria and evaluation SOPs must account for the entire collection process from initial evaluation and mobilization (where applicable) to collection and post-collection care.

Example(s):

To avoid overlooking important information, especially in larger Collection Facilities, the facility could have a separate document that highlights major concerns and ensure that this document is distributed to the individuals performing the cellular therapy product collection.

Vulnerable donors (e.g., children) and donors at increased medical risk from donation (e.g., those with cardiac disease) are examples for when donor suitability assessment is crucial.

The HCT Comorbidity Index is a useful tool for determining if any comorbidities put donors at unacceptable risk. The resources below provide additional information about the HCT Comorbidity Index, followed by an example of the calculation tool itself:

- Berro M, Bittencourt H, Oliveira MP, Dulley FL, Saboya R, Arrais CA, et al. [Hematopoietic Cell Transplantation–Specific Comorbidity Index predicts morbidity and mortality in autologous stem cell transplantation](#). *Biol Blood Marrow Transplant*. 2017;23(10):1646–1650.
- Thakar MS, Broglie L, Logan B, Artz A, Bunin N, Burroughs LM, et al. [The Hematopoietic Cell Transplant Comorbidity Index predicts survival after allogeneic transplant for nonmalignant diseases](#). *Blood*. 2019;133(7):754–762.
- Sorror M. [Hematopoietic Cell Transplantation–Specific Comorbidity Index \(HCT-CI\)](#). MDCalc.

STANDARD:

C6.3.1.1 The collection staff shall confirm that clinically significant findings are reported to the donor with documentation in the donor's record of recommendations made for follow-up care.

Explanation:

Clinically significant findings in a donor, including but not limited to the testing results, may have important implications for the individual apart from their role as a donor. In certain cases, clinically relevant information may be discovered after the donation. Appropriate care of the donor requires that all clinically significant findings be communicated to the donor and that recommendations be made to that donor for follow-up care (including transfer of care, if applicable). The Collection Facility must confirm that these actions are documented in the donor's medical record.

Evidence:

The inspector should review documentation in the medical record that donors were informed of significant findings, including recommendations for work-up, treatment, and follow-up (including transfer of care, if applicable). The inspector may need to specifically request a record of a donor with abnormal findings and undergoing collection since this may not be a common occurrence.

Example(s):

For donors with abnormal test results, it is recommended that appropriate follow-up evaluations be completed or that a referral be made to an appropriate physician.

STANDARD:

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.

Explanation:

A physician or health care professional other than the recipient's primary care provider must perform the donor suitability evaluation to minimize potential bias of the recipient's health care professional(s). This individual should have knowledge of the risks of the donation procedures.

Medical literature supports the idea that having the allogeneic donor evaluated by a physician or health care professional who is not the primary health care provider of the recipient decreases the potential conflict of interest with regard to the health and safety of the recipient and the donor (van Walraven, Nicoloso-de Faveri, Axdorph-Nygell, et al. [Family donor care management: principles and recommendations](#). *Bone Marrow Transplant*. 2010;45(8):1269–1273). Furthermore, the American Academy of Pediatrics (AAP) and the ASTCT recommend this practice for related donations.

Evidence:

The Clinical Program's policy on donor evaluation and medical charts can be used to verify that an individual other than the recipient's primary licensed health care professional evaluates the donor for suitability.

Example(s):

A potential donor could be evaluated by another attending physician of the Clinical Program; however, programs are not required to have sufficient staffing to evaluate donors using their own attending physicians. Small programs may not have enough attending physicians to separately evaluate donors within their own programs. Physicians and licensed health care professionals outside of the program may perform this function, including a clinician who is a member of a different program, the donor's primary care physician (if they possess knowledge of the donation procedure), a general internal medicine clinic, or a clinic not directly associated with the program.

STANDARD:

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

Explanation:

Testing or screening of autologous donors in connection with cellular therapy product collection is not required by the Standards. However, consistent with [C1.2](#), if required by Applicable Law, autologous donors must be evaluated and tested.

Collection Facilities may choose not to test autologous donors for infectious diseases or disease agents for their safety, or they may choose to test autologous donors with diagnostic tests. Positive screening tests for autologous donors must have the appropriate warning statements on their labels. It is important for the Collection Facility to notify the Processing Facility so that the final product can be labeled in accordance with the Standards and Applicable Law.

STANDARD:

C6.3.2 The risks of collection shall be evaluated and documented, including:

C6.3.2.1 Possible need for central venous access.

Evidence:

The inspector should inquire how the program assesses the need for a central line for the donor.

STANDARD:

C6.3.2.2 Anesthesia for cell or tissue collection.

Explanation:

Collection of HPC, Marrow or other tissue requires that evaluation occur for any medical condition that would expose the donor to the risk of the procedure including the need for anesthesia. This evaluation must be documented.

Evidence:

The donor's medical records for pre-collection workup results will contain evidence of compliance.

STANDARD:

C6.3.2.3 Mobilization for cell collection.

Explanation:

Mobilization requires that evaluation occur for any medical condition that would expose the donor to increased risk due to the mobilization agents (e.g., thrombotic events). This evaluation must be documented, including the pre-collection and collection time frames specific to growth factor administration.

G-CSF is not advised for mobilization in patients with sickle cell disease or complex hemoglobinopathies. For more information, see [C6.3.6](#).

Evidence:

The donor's medical records for pre-collection workup results must contain evidence of compliance.

STANDARD:

C6.3.2.4 Other donor-specific risks.

Explanation:

The purpose of this Standard is to evaluate the donor for potential risks associated with the collection, such as anesthesia for collection of HPC, Marrow or central line placement. This evaluation is generally the responsibility of the Clinical Program, but the Collection Facility is responsible for verifying that appropriate testing and evaluation has been performed.

There should be a mechanism for independent review of suitability for vulnerable donors (e.g., children) and for donors at increased medical risk from donation (e.g., those with cardiac disease). The rationale and medical necessity should be discussed with the donor and recipient and documented within both medical records.

STANDARD:

C6.3.3 *General or regional anesthesia, if required, shall be performed or supervised by a health care provider licensed and credentialed to administer anesthesia.*

Explanation:

For patients requiring general or regional anesthesia during cellular therapy procedures, the anesthesia must be administered or supervised by a qualified healthcare provider who is both licensed and credentialed to administer anesthesia, such as an anesthesiologist or a qualified nurse anesthetist under appropriate supervision. This maintains patient safety and optimal outcomes during these complex procedures.

STANDARD:

C6.3.4 *Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in the administration of these agents and management of complications in persons receiving them.*

C6.3.4.1 *Appropriate mobilization shall be used for the disease being treated and for the donor being collected.*

Explanation:

Administration of hematopoietic mobilization agents is not free from side effects. There are reports of serious morbidity and mortality among recipients of hematopoietic growth factors. A licensed health care professional who is trained in dealing with complications of G-CSF must supervise its administration. Supervision can be exercised either directly, especially during the first injection, or indirectly (e.g., via phone contact with nursing personnel) for the subsequent injections, especially if self-administration is considered. The interim assessment of donor symptoms related mobilization agents and relevant laboratory tests should be performed, and dose adjustments made accordingly. When parameters have been set by the Clinical Program as to when not to administer mobilizing agents, the Collection Facility should have a mechanism in place to confirm all relevant personnel administering mobilizing agents should be clearly defined in relevant SOPs and have processes to ensure all relevant personnel receive and follow these parameters.

Evidence:

The inspector should verify that the licensed health care professional supervising administration of mobilizing agents is experienced in recognizing adverse reactions due to mobilization agents. When appropriate, donor side effects potentially attributable to mobilization agents should be reviewed by the inspector.

Example(s):

The patient record should show the doses of the mobilization agents to be administered and the person administering the agent.

G-CSF is not advised for mobilization in patients with sickle cell disease or complex hemoglobinopathies.

STANDARD:

C6.3.5 A pregnancy test shall be performed for all donors with childbearing potential:

C6.3.5.1 For collections with mobilization, within seven (7) days prior to starting the donor mobilization regimen or undergoing anesthesia and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.

C6.3.5.2 For collections without mobilization, within seven (7) days prior to cellular therapy collection and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.

Explanation:

Pregnancy testing is required since the donation of cells from marrow or peripheral blood and anesthesia may pose a risk to the fetus. The intent is to confirm the donor is not pregnant before the initiation of the mobilization agent or administration of anesthesia and before the recipient starts the conditioning regimen. Childbearing potential is meant to include all donors ages, puberty through menopause, unless there is some definite medical indication that pregnancy is impossible (e.g., a past hysterectomy). The Collection Facility will define its policies for continuing with the collection when consent for the pregnancy test is refused.

The purpose of the required time frame is to prevent donor mobilization and recipient conditioning from occurring before finding out that the donor is pregnant. There are some obvious situations in which pregnancy testing would not occur within seven days prior to recipient conditioning. For example, if a cellular therapy product is collected from the donor and subsequently cryopreserved for administration weeks later, the donor does not have to be retested for pregnancy. However, if a recipient is on a 21-day conditioning regimen, a pregnancy test must be performed within seven days prior to beginning that regimen. The Collection Facility must be aware of situations where donor pregnancy screening may need to occur more than seven days in advance.

Evidence:

The inspector may look for the process or documentation of pregnancy testing of the donor.

Example(s):

In women determined to have potential for becoming pregnant (post/peri-pubertal, pre-menopausal females who have not undergone hysterectomy), a pregnancy test is required; serologic assays for human chorionic gonadotropin (HCG) or urine pregnancy tests should be used.

If a cellular therapy product is collected from the donor and subsequently cryopreserved for administration weeks later, the donor does not have to be retested for pregnancy.

If the recipient undergoes a preparative regimen for a long duration, a pregnancy test must be performed within seven days prior to beginning the regimen. The donor must be retested prior to collection to confirm there is no change in pregnancy status.

STANDARD:

C6.3.6 *The donor shall be evaluated for the risk of hemoglobinopathy and, if indicated, tested.*

C6.3.6.1 *The evaluation shall be verified prior to collection or administration of the mobilization regimen, if used.*

Explanation:

Hemoglobinopathy assessment is required because administration of mobilization agents such as G-CSF may pose a risk to the donor as it has been associated with morbidity (e.g., vaso-occlusive crisis) and mortality in donors with sickle cell disease (HbSS), (HbSC), and also with compound hemoglobinopathies such as sickle beta-thalassemia (S/β thal). Testing is not required; however, if testing is not performed, the inspector should look for a thorough family history to evaluate the risk. The Clinical Program is to define how donor risk is evaluated.

Of note, medical literature reports that donors with sickle traits have been safely mobilized and collected. Although donors with the sickle trait did have higher symptom scores than control donors, there were no symptoms suggestive of sickle crisis. Thus, in this group, the risk is limited.

References include:

- Fitzhugh CD, Hsieh MM, Bolan CD, Saenz C, Tisdale JF. [Granulocyte colony-stimulating factor \(G-CSF\) administration in individuals with sickle cell disease: time for a moratorium?](#) *Cytotherapy*. 2009;11(4):464-471.
- Rosenbaum C, Peace D, Rich E, Van Besien K. [Granulocyte colony-stimulating factor-based stem cell mobilization in patients with sickle cell disease](#). *Biol Blood Marrow Transplant*. 2008;14(6):719-723.
- Kang EM, Areman EM, David-Ocampo V, Fitzhugh C, Link ME, Read EJ, et al. [Mobilization, collection, and processing of peripheral blood stem cells in individuals with sickle cell trait](#). *Blood*. 2002;99(3):850-855.

Evidence:

The inspector may look for the process or documentation of risk evaluation in the donor. For example, hemoglobinopathy risk evaluation might include a relevant question in the Donor History Questionnaire.

Example(s):

Hemoglobinopathy risk assessment may include testing for the detection of Hemoglobin S by solubility testing (e.g., SICKLEDEX®) or an Hb-electrophoresis test, but a test is not required. An assessment may be performed by thorough review of the donor's medical history.

STANDARD:

C6.3.7 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, certified, or licensed in accordance with Applicable Law.

Explanation:

All laboratory tests must be performed by a laboratory accredited for the relevant tests. Testing may be performed at any time prior to the initiation of the recipient's preparative regimen except for infectious disease tests. These must be done within 30 days prior to collection of HPC and within seven days prior to or after collection of other cell products as required by the FDA in the U.S. or non-U.S. equivalent regulations.

Evidence:

The inspector may look for infectious disease markers testing results and verify they were performed according to Applicable Law.

Example(s):

Some governmental authorities, such as the U.S. FDA, allow for testing up to seven (7) days after collection of HPC products; however, this is intended only for rare occasions. To be compliant with the Standards, HPC products for which infectious disease testing is not performed within 30 days prior to collection must be approved, investigated, and evaluated per the requirements for deviations in [C4](#).

Examples of relevant accreditation organizations include CLIA, CAP, ASHI, AABB, Joint Commission, CMS, EFI, United Kingdom Accreditation Service, and Royal College of Pathologists of Australasia.

STANDARD:

C6.3.8 *The Collection Facility shall verify that appropriate donor suitability has been determined.*

Explanation:

Donor suitability assessment is an important function which promotes safe and effective treatment. It is not expected that the Collection Facility requests donor suitability assessment records; however, it is important for collection staff to document that the donor has been determined suitable by a provider who has been defined as qualified to make the assessment by the Clinical Program.

STANDARD:

C6.3.9 *Collection from a donor who does not meet collection suitability criteria shall require documentation of the rationale for selection by the donor's physician and approval by the Collection Facility Medical Director. Collection staff shall document review of these donor suitability issues.*

Explanation:

The decision to use a donor who does not meet donor safety criteria must be made by the donor's physician. The Collection Facility must review this information on donor safety. These Standards also require that if allogeneic donors selected for transplant do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented.

Evidence:

The inspector may ask for charts of nonconforming donors and documentation of selection rationale, safety issues, and communication.

STANDARD:

C6.3.10 *If central venous access is required, the rationale shall be documented in the donor's records.*

Explanation:

Appropriate care should be taken to protect donor safety when a CVC is inserted solely for a collection procedure and that collection extends over more than one day. Donors need to be assessed for the risks of CVCs, including significant complications such as hematomas, pneumothorax, hemothorax, and bacterial infections.

Example(s):

The WMDA Serious (Product) Events and Adverse Reactions (S[P]EAR) Committee has provided recommendations for policies in response to reported adverse events ([Document Reference: 0110824-CLWG-SEAR-August 2011, Version: 2](#)):

- Stem cell donor registries should review their policies concerning the placement of CVCs.
- If a stem cell donor registry does not have a policy concerning CVC placement, one should be written.
- Insertion of a CVC for PBSC collection should only be used in exceptional circumstances (i.e., only when peripheral venous access is not deemed feasible after skilled assessment or cannot be obtained or has failed).
- The policy should cover, at a minimum, the need for the following:
 - Requirement for careful peripheral venous assessment at the time of donor medical evaluation.
 - Evidence that alternative methods of donation have been discussed if appropriate.
 - Written justification for placement of a CVC.
 - Consenting procedures (and counselling) for CVC insertion, including who should obtain informed consent.
 - Qualifications and expertise of the person(s) permitted to insert the CVC.
 - Permissible sites for CVC insertion.
 - The requirement for radiological guidance for all CVCs inserted above the umbilicus, if locally available.
 - The need for care for all patients with CVCs, cared for by appropriately trained personnel.
 - The requirement for reporting adverse events or serious adverse events.

STANDARD:

C6.3.11 Adequacy of central line placement shall be verified and documented by the Collection Facility staff prior to initiating each collection procedure.

Explanation:

Prior to collection and use of a CVC, the Collection Facility staff must receive documentation of placement and its appropriateness for use. This step will provide the Collection Facility staff the assurance to use the CVC and include documentation of satisfactory venous access in the donor record.

The appropriate and safe positioning and function of CVCs is critical to the performance of cellular therapy product collection by apheresis. A licensed, trained, and qualified health care provider (such

as a physician or a nurse) is responsible for obtaining central venous access. Credentialing of health care providers for this activity is the responsibility of the individual institution.

Confirmation that the line is satisfactorily positioned and functioning prior to collection must be provided. The methods should be appropriate for the site of placement (i.e., subclavian/jugular access – fluoroscopy, ultrasound) while femoral line placement could be confirmed by ultrasonography. Imaging should be used for central venous line placements due to known risks (e.g., death due to hemothorax). The records describing the rationale for placement of the CVC, the position and function of the catheter, and that both are appropriate to proceed with the collection must be available to the collection team.

Evidence:

The inspector may look at the documentation of central line placement verification by the Collection Facility, including documentation of imaging used to confirm line position and function prior to collection.

Example(s):

The National Institute for Health and Care Excellence (NICE) provides guidelines regarding the placement of CVCs ([Guidance on the use of ultrasound locating devices for placing central venous catheters](#), 2002). Another resource with published guidelines is [Practice Guidelines for Central Venous Access 2020: An Updated Report by the American Society of Anesthesiologists Task Force on Central Venous Access](#) (*Anesthesiology*. 2020;132(1):8–43).

A S(P)EAR Alert was submitted to the WMDA dated August 2011 informing the committee of a donor death due to a tension haemo/pneumothorax related to the insertion of a CVC. The event is noted in this guidance as a warning to transplant programs of the critical importance of compliance with this Standard ([Document Reference: 0110824-CLWG-SEAR-August 2011, Version: 2](#)).

STANDARD:

C6.3.12 There shall be policies or Standard Operating Procedures for the management of collection-associated adverse events and follow-up of donors.

C6.3.12.1 There shall be a process to track and trend collection-associated adverse events.

Explanation:

There should be a policy that provides guidelines for the post-collection care of donors. All donors should be monitored closely following the collection procedure.

Donor follow-up following the collection procedure can help to ensure donor safety and address collection-associated adverse events. These events should be assessed via a collaborative approach

between the Clinical Program and Collection Facility and be addressed in accordance with the Clinical Program's QM Plan and shared with key stakeholders.

It is recommended that related donors are registered (e.g., Data Collection Forms of the EBMT or WMDA registry) and adverse events are recorded.

Example(s):

The guidelines for post-collection care of donors may include the following short- and long-term measures:

- Upon completion of the collection, the donor should have a complete blood count and ionized calcium drawn, and the physician caring for the donor should be notified of the results.
- If a temporary apheresis catheter was placed for the collection procedure, there should be a clear guideline for catheter removal prior to discharge. This may include minimum platelet count prior to removal of the catheter.
- Discharge instructions should be given.
- The donor should remain at the Collection Facility for an adequate time. A follow-up appointment in the facility or an appropriate facility post donation should be performed.
- The donor should be contacted in 1–4 weeks for follow-up post donation.
- Long-term follow-up guidelines beyond a few weeks after collection may be defined by the Collection Facility based on transplant type and medical need on a case-by-case basis.
- There should be a defined minimum duration of observation and clear guidelines for discharge.
- There should be orders for donor monitoring during observation that may include frequency of vital sign monitoring, lab draws, frequency of clinical evaluations for adverse events, intravenous hydration, dressing of marrow harvest sites, pain medications, and iron supplementation.
- There should be discharge instructions that include a phone number to call if the donor experiences and symptoms of adverse events such as prolonged fatigue, high fever, and wound infection.
- The donor should remain at the collection facility for an adequate time.

The World Health Organization *Guiding Principles of Human Cell, Tissue and Organ Transplantation* ([Guiding Principle 10](#)) recommends long-term follow-up of donors.

STANDARD:**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 do not have the capacity to consent, as those terms are defined by Applicable Law.*

Explanation:

A donor advocate is an individual distinct from the transplant recipient's primary treating physician who confirms the donor is fully informed of the collection procedure and promotes the interests, well-being, and safety of the donor. The role of the advocate is to help ensure that the consent is made without time pressure and with full information, to enhance the personal attention given to the donor during all procedures, to help prevent unnecessary inefficiencies and discomfort, to mobilize official expressions of gratitude after the donation, and to aid in the resolution of subsequent problems.

Donor advocates do not need to be routinely appointed for all donors who are not capable of full consent (such as donors who are minors or who are mentally incapacitated). However, a donor advocate process must be available at the center, and donor advocates must be utilized with minor donors when the conditions necessary for minors to participate as donors are at risk of not being met (see circumstances below). In these circumstances, the donor advocacy role should be documented and should not be fulfilled by an individual involved in the recipient's care.

Evidence:

For Clinical Programs using minor or mentally incapacitated donors, there must be documentation that a donor advocate was involved in the donor assessment process in circumstances when the conditions necessary for minors to participate as donors are at risk of not being met. Circumstances in which a donor advocate should be considered during the minor donor assessment process include (but are not limited to) when:

- A potential donor is deemed to be at increased risk for physical injury due to the collection process.
- A potential donor may not experience psychological benefit from donating, such as might occur when the potential donor does not have an established relationship with the recipient, is not in the same household as the recipient, or is estranged from the family or recipient. Specific examples that illustrate this circumstance might include a donor who is emotionally distant from the recipient (e.g., a stepbrother who has never met the recipient) or when a possibly abusive relationship exists between the recipient and donor.
- A potential donor expresses in words or actions opposition to participation.
- A request is made for a donor advocate by the family or healthcare team.

Example(s):

Examples of donor advocates include chaplains, patient advocates, and social workers. The article [Family Donor Care Management: Principles and recommendations](#) provides recommendations for donor advocacy in the related transplant setting (van Walraven, Nicoloso-de Faveri, Axdorph-Nygell, et al. *Bone Marrow Transplant*. 2010;45(8):1269-1273). The ASTCT is also a source of information.

In the UK, the HTA provides guidance on third-party patient advocates in [Code G: Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation](#). This Code provides supplementary guidance to clinicians working in the field of allogeneic bone marrow and PBSC transplantation and HTA Accredited Assessors.

When Applicable Law defines donor advocate and specific requirements, those must be followed.

STANDARD:

C6.4.2 *Allogeneic donor infectious disease testing shall be performed using donor screening tests licensed, approved, or cleared by the governmental authority.*

Explanation:

Donors are often asymptomatic, and infectious disease tests must be sensitive enough to produce a positive result when a disease has not yet manifested in the donor. In some countries, the relevant governmental authorities may require use of approved or cleared tests for any tests performed in their jurisdiction, even if the recipient is in a different country. If such tests are not used, the donor eligibility is considered incomplete, but the donor may be used provided that all requirements for urgent medical need in the recipient's country are met. There may be countries where this requirement is not applicable.

Evidence:

The inspector will look for infectious disease markers testing results and verify they were performed according to Applicable Law. There may be regions where this requirement is not applicable.

STANDARD:

C6.4.2.1 *Hemodilution in the donor prior to collection of blood samples for infectious disease testing should be assessed, and acceptance criteria should be defined.*

Explanation:

The scope of the FACT-JACIE Standards includes living, beating heart, and cadaveric donors. The 2025 FDA Draft Guidance for Industry: [Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](#) states that transfusion or infusion might dilute plasma from a donor blood specimen, making test results unreliable. A

specimen taken before the transfusion or infusion may be tested, or if an adequate pretransfusion/infusion specimen is not available, an appropriate algorithm to determine whether plasma dilution is or is not sufficient to affect test results may be used. In the absence of an appropriate specimen to test under either of these options, the donor must be determined to be ineligible per [21 CFR 1271.80\(d\)\(2\)](#). The UK's Department of Health & Social Care has provided Guidance ([Chapter 7: haemodilution, transfusion and donor testing](#)) that describes clinical situations impacting hemodilution in the context of infectious disease testing.

Example(s):

For example, the guidance states that for donors over 12 years of age, infusion of more than 2,000 milliliters of crystalloids within one hour immediately preceding the collection of samples is sufficient to affect the results of communicable disease agent testing. The Collection Facility should specify within SOPs the acceptance criteria for samples undergoing infectious disease testing. The Collection Facility may include test manufacturer's instructions within the SOP.

STANDARD:

C6.4.3 Collection staff shall comply with [B6.4.8](#) through [B6.4.8.8](#) when primarily responsible for donor screening for transmissible disease.

Explanation:

The Standards and the FDA require that all donors be screened by medical history and risk factors for human transmissible spongiform encephalopathy, CJD, and potential transmissible infectious disease agents through xenotransplantation, as there are no screening tests for these agents. Travel history is essential for these screenings. Information about areas of the world where CJD is a risk factor should be established using trusted sources (e.g., national or international health agencies' websites or publications).

Other risks may be associated with unlicensed vaccines, receipt of human-derived growth hormone or clotting factor concentrates, or hepatitis B immune globulin. Prospective donors should be questioned about these issues.

In some donors, other tests may be necessary based on their medical history. In the case of child donors born of mothers with HIV, hepatitis C, hepatitis B, or HTLV infection, the evaluation of risk of transmitting infection should include consideration of the age of the child, history of breastfeeding, and results of infectious disease marker testing; eligibility criteria must be in accordance with Applicable Law.

There are standard deferral times after immunization for allogeneic blood donation that can be used to determine the potential risk that may exist. Blood donors are typically deferred for four weeks after attenuated live virus vaccines such as oral polio, herpes zoster, and measles. In those cases for which a potential donor has recently been vaccinated, both the reason for the vaccination and the time interval should be evaluated to estimate the potential risk to a recipient. There should

be specific SOPs for dealing with donors who have received smallpox vaccination. Donors must be screened for traveling to areas that would put them at risk for malaria, human transmissible spongiform encephalopathy, severe acute respiratory syndrome (SARS) during periods of world-wide prevalence, or rare strains of HIV, which may not be detected by current screening tests.

CMV is not a relevant communicable agent or disease. However, allogeneic donors must be tested for evidence of infection with CMV. The time frame for this testing is not restricted. A prospective donor who was previously positive for anti-CMV should be considered to be a seropositive donor. Use of CMV-seropositive donors is permissible; however, the Collection Facility (or Clinical Program, if applicable) should have a clearly defined policy or SOP that addresses the use of CMV-seropositive donors. Cellular therapy product labels from CMV-positive donors do not require any special labeling (e.g., statements, biohazard labels). However, there must be an SOP for communicating test results of donors who are positive or reactive for CMV antibodies.

STANDARD:

C6.4.4 Collection staff shall comply with [B6.4.9](#) through [B6.4.13](#) when primarily responsible for infectious and non-infectious disease testing of donors.

Evidence:

Infectious disease testing is usually conducted by the Clinical Program during the donor selection process. However, if a Collection Facility conducts such testing for a program, this Standard applies, and the facility is responsible for completing the applicant portion of the inspection checklist for the referenced Standards. For information regarding these Standards, see the corresponding guidance sections.

STANDARD:

C6.4.5 Collection staff shall comply with [B6.4.4](#), [B6.4.5](#), and [B6.4.14](#) through [B6.4.14.4](#) when primarily responsible for testing for the selection of allogeneic donors.

Evidence:

C6.4.5 only applies to Collection Facilities that are primarily responsible for testing allogeneic donors during the donor selection process. This testing is usually conducted by the Clinical Program. However, if a facility conducts such testing for a clinical program, this Standard applies, and the facility is responsible for completing the applicant portion of the inspection checklist for the Standard.

STANDARD:

C6.4.6 Collection staff shall confirm that allogeneic donor eligibility determination was performed prior to collection, starting the donor mobilization regimen, or initiation of the recipient's preparative regimen.

Explanation:

The responsibility for eligibility determination belongs to the Clinical Program, but the Collection Facility staff must verify that this determination was completed and documented.

STANDARD:

C6.4.7 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 their selection and documentation of the informed consent of the donor and the recipient.

Explanation:

These Standards require that if allogeneic donors are ineligible according to Applicable Law or non-U.S. equivalents, or if they do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented. There must also be documentation in the medical record by the transplant physician of urgent medical need for the cellular therapy product. Urgent medical need means that no comparable product is available, and the recipient is likely to suffer death or serious morbidity without the cellular products.

The risk(s) for use of an ineligible donor are obvious for the recipient; however, there are risks to the donor which necessitates informed consent. The donor is exposed to psychological trauma if discovered that the donation contributed to the transfer of a communicable disease to the recipient or had a negative effect on recipient's outcome. Additionally, the donor must consent to sharing confidential health information with the recipient.

The cellular therapy product should be accompanied by a summary of records to the Collection and Processing Facilities stating reasons the donor is ineligible, including the results of health history screening, physical examination, and infectious disease testing.

Evidence:

The inspector should examine the summary of records accompanying the cellular therapy product provided to the Collection and Processing Facilities stating reasons the donor is ineligible. This summary should include results of health history screening, physical examination, and infectious disease testing. The rationale and informed consent for a specific donor who did not meet the institution's donor criteria should be available to the inspector for verifying the appropriate urgent medical need documentation and labeling.

Example:

In the setting of resistant disease or relapse/progressive disease, it may be medically necessary to administer donor lymphocytes or other cellular therapy products before availability of repeat transmissible disease testing. The recipient must be informed of this deviation, and the discussion of urgent medical need must be documented in the medical record.

According to the U.S FDA guidance document [*Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products*](#) (2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in [21 CFR 1271.55](#). In January 2025, the FDA released additional draft guidance: [*Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)*](#).

STANDARD:

C6.4.8 *Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.*

Example(s):

For cellular therapy products that are manufactured in or distributed for use in the U.S., the FDA requires that an accompanying statement of authenticity be present for records translated into English.

STANDARD:

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

C6.4.10 *Allogeneic blood products administered to the donor during apheresis collection or used during priming procedures shall be CMV-appropriate and irradiated or equivalent prior to transfusion.*

Explanation:

Donors may require a blood transfusion during the collection procedure. Collection Facilities need to be prepared to provide appropriate blood products for donors during priming procedure. Autologous units may be collected prior to apheresis or marrow collection, or allogeneic CMV-appropriate and irradiated units may be used. The decision to use autologous or allogeneic blood depends on the benefits and risks to the donors, especially in the case of pediatric donors.

A special concern for the allogeneic donor is the fact that transfused allogeneic blood contains lymphocytes that can become part of the collected cellular therapy product. Therefore, these transfusions must undergo irradiation (or equivalent technology such as pathogen reduction) to prevent engraftment of third-party lymphocytes in the transplant recipient. The use of irradiated or equivalent blood products during the immediate post apheresis donation or post-operative period

following marrow collection may be necessary if there is any consideration that the donor may need to donate a second cellular therapy product in that immediate timeframe. This scenario would happen, for example, if a child needs to be harvested twice or if the target yield in the cellular therapy product was not achieved.

The Collection Facility should follow the institutional practice determining whether adult marrow donors will donate autologous blood prior to the collection procedure. In the situation of small marrow donors and large recipients, transfusion is expected. Many places have difficulty collecting autologous blood from donors <40 kg.

Evidence:

The inspector should verify the availability of irradiated, leukoreduced, and CMV-seronegative or CMV-appropriate cellular blood products and other blood components in case they are needed. A review of the process by which such products are ordered should provide adequate evidence.

Example(s):

An example of this would be a 25 kg donor and an adult-sized recipient (common in sibling transplants). In this case, transfusion is expected, frequently occurs during the collection, and the blood products must be irradiated or equivalent.

STANDARD:

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

- C6.5.1 *Allogeneic donor eligibility and suitability determination, including the name of the responsible person who made the determination and the date of the determination.*
- C6.5.2 *Donor identification including at least name and date of birth.*
- C6.5.3 *Age, sex at birth, medical history, and, for allogeneic donors, behavioral history.*
- C6.5.4 *Consent to donate.*
- C6.5.5 *Results of laboratory testing.*

Explanation:

There should be a written SOP covering the creation and retention of donor records. The policy should address the following:

- For each donor, there should be a record containing:
 - Identification of the donor (first name, family name, and date of birth).

- Age, sex, and medical and behavioral history (the information collected must be sufficient to allow application of the exclusion criteria, where required), including donor eligibility information for allogeneic donors. If behavioral history is not performed (i.e., for autologous donors), it does not need to be included in the donor records.
- Consent and authorization form(s), where applicable.
- Clinical data, laboratory test results, and the results of other tests performed.
- The donor's suitability must be documented, including the rationale for selecting the donor when they do not meet donor safety criteria. For unrelated donations, when the organization responsible for procurement has limited access to recipient data, the transplanting organization must be provided with relevant donor data.
- All the records should be clear and readable, protected from unauthorized amendment, and retained and readily retrieved in this condition throughout their specified retention period in compliance with data protection legislation.
- Donor records required for full traceability must be kept for a minimum duration as dictated by institutional practice and governmental regulatory requirements.

The health care professional responsible for obtaining the health history must make certain that the donor has confirmed that all the information provided is true to the best of their knowledge.

C7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

STANDARD:

C7.1 *ISBT 128 AND EUROCODE CODING AND LABELING*

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

Explanation:

ISBT 128 is the international information standard for transfusion and transplantation. Initially, ISBT 128 was developed for blood and blood component transfusion but has now been extended to include cellular therapy products and tissues. International Council for Commonality in Blood Banking Automation (ICCBBA) is the not-for-profit organization (<https://iccbba.org/>) that is responsible for the development and maintenance of the ISBT 128 standard. ICCBBA maintains the databases for facility identification and product coding, assigns new product codes, and provides technical support.

Several volunteer technical advisory groups support and inform ICCBBA. The Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) comprises representatives from major cellular therapy professional organizations. Its purpose is to advise ICCBBA of the needs of cellular therapy organizations for coding and labeling.

The two main pieces of the standard terminology used to unambiguously describe a cellular therapy product are class and attributes. Classes are broad descriptions of products (such as HPC, Apheresis) and attributes are additional characteristics that uniquely define the product. A group of attributes, called Core Conditions, are required; these conditions include anticoagulant or additive, nominal collection volume, and storage temperature. There are also other characteristics called groups and variables that can be used to provide more information about the product. The intent is to capture relevant characteristics about the product from the donor and collection through the final processing. It is not intended that products would be relabeled at the bedside, so attributes such as “thawed” would only be applied if that process occurred in the laboratory.

Cellular therapy products must be labeled using the ISBT 128 standard terminology. The labels must contain both machine-readable electronically stored information (e.g., bar codes) and eye-readable text. The text may be in the native language of the country in which the product is collected. The machine-readable technology must be universally understood such that international transport and exchange will be facilitated.

The standard terminology is structured in a manner that allows revisions, additions, and deletions as necessary on a continuous basis. In this edition of Standards, under “Definitions” then “Products,” the common major classes of cellular therapy products have been defined as was current at the time of publication. Attributes were not included because of their sheer number and complexity. As the body responsible for the development and maintenance of the databases for product coding, ICCBBA is the appropriate authority for maintaining publications on current terminology. To prevent use of obsolete terminology, the Collection Facility is instructed to refer to Chapter Three, Cellular Therapy, of the [*ISBT 128 Standard Terminology for Medical Products of Human Origin*](#) for current terms and definitions related to cellular therapy. The website also includes resources and tools for identifying and assigning standardized codes for cellular therapy products or requesting a code for a new unique product. Additional information and assistance can be obtained by contacting ICCBBA directly.

To utilize ISBT 128 and obtain a unique facility identification code that becomes part of each product’s unique alphanumeric identifier, facilities must register with ICCBBA. Facilities in or affiliated with hospitals may find that their blood bank has already registered and a unique facility code already exists. Stand-alone facilities can register individually.

Eurocode International Blood Labeling Systems (Eurocode-IBLS) provides an international non-profit standard for labeling blood products and tissues to enhance security in blood transfusion and tissue transplantation.

The main benefits of Eurocode-IBLS are:

- One bag - one number (unique product bag number worldwide).
- Unique coding of product properties.
- Country codes following [ISO 3166](#).
- Center codes according to national agreements.
- Matching enhanced space-saving barcode systems.
- Charge-free access to all information via Internet.

Eurocode-IBLS assigns, publishes and maintains the databases for Eurocode facility identification (Center Codes) and product coding.

Centers using Eurocode require a Eurocode membership. All resources, such as Eurocode's technical specification, guidelines, and the databases including all product and center codes, can be accessed on <https://www.eurocode.org/>.

Eurocode product codes characterize each product by the product group it belongs to, supplemented by a set of properties laid out in up to 18 predefined categories, such as anticoagulant used, storage temperature, donor/recipient relationship, and intended use. These property categories are called "qualifiers."

Both ISBT 128 and Eurocode product codes are compliant with the EU SEC.

Evidence:

Inspectors will inspect Collection Facilities according to the current ISBT 128 or Eurocode terminology and definitions, as applicable.

Example(s):

The appropriate product name for HPCs collected by apheresis is HPC, Apheresis. The acronym HPC(A) would be an acceptable abbreviation in documents and on partial labels. However, the U.S. FDA does not allow abbreviations on final product labels for licensed products.

STANDARD:

C7.1.2 Coding and labeling technologies shall be implemented using ISBT 128 or Eurocode.

Explanation:

The use of ISBT 128 or Eurocode for all cellular therapy products provides a uniform coding and labeling system worldwide that is supported by FACT, JACIE and numerous other cellular therapy organizations. Such standardization is beneficial for, and thus required for, autologous as well as allogeneic products. The most recent version of the [ISBT 128 Standard Terminology](#) is published on

the [ICCBBA website](#), as well as resources to help centers implement ISBT 128. The [Eurocode website](#) features guidelines, product codes, and other resources.

Implementation of ISBT 128 or Eurocode is required for FACT accreditation, although as stated above, FACT does recognize that not all cellular therapy products previously collected will use this coding system.

STANDARD:

C7.1.3 Cellular therapy collections for further manufacturing should be labeled with the standardized ISBT 128/manufacture label specified in [ICCBBA ST-018](#).

Explanation:

This Standard applies to cellular therapy products collected for further manufacturing. Using the ISBT 128/manufacture label specified in [ICCBBA ST-018](#) for cellular therapy products intended for further manufacturing is crucial for Standardization & Traceability, Regulatory Compliance, and Minimized Risk of Errors. Further manufacturing refers to the processing, modification, or expansion of collected cellular products to create a final therapeutic product. Unlike cellular therapy products intended for direct infusion into a patient, those designated for further manufacturing serve as raw material for advanced therapies.

Example(s)

An example of a product collected for further manufacturing is an MNC product collected for the manufacturing of CAR T cells.

STANDARD:

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.

Explanation:

The labeling SOPs should encompass each of the following areas, as applicable:

- Version control.
- Ordering: initial orders and reorders.
- Receipt, quarantine and reconciliation.
- Verification of accuracy.
- Proper storage.

- Inventory control.
- Documented destruction of obsolete or unusable labels.

STANDARD:

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

Explanation:

Labels must be stored in a designated area where access is limited to authorized personnel. Stocks of unused labels representing different cellular therapy products must be stored separately to prevent errors. Labels should be organized physically or electronically so staff can readily identify the labels and be able to distinguish labels of different products from one another (e.g., by color-coding, size, location). It is not acceptable to have labels of different types and representing different products stored together with no separation. The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors.

Evidence:

The inspector should observe that there is an organized storage area for the labels and that the labels are arranged in a manner to prevent mislabeling.

Example(s):

Printed labels can be in containers to provide separation of each label type. Electronic labels can be in separate file folders for each label type.

STANDARD:

C7.2.1.2 Obsolete labels shall be restricted from use.

Evidence:

The inspector should verify that the destruction process is documented and that there are no obsolete labels in the collection or storage area.

STANDARD:

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

Explanation:

New labels must be placed in a quarantine area upon receipt. The new labels must be inspected for:

- Manufacturing or printing defects.

- Form or version number, if applicable.
- Legible and correct eye-readable information.
- Conformity to source (original) label that has been approved for use by the Collection Facility Director.

The inspection of labels at receipt from the manufacturer or after printing must be performed by one person and independently verified by a second person. The process and outcome must be documented prior to release of the labels from the quarantine area. Labels from an IND holder or a commercial manufacturer should be approved as part of the acceptance protocol established by the Collection Facility.

Evidence:

The inspector should review all relevant labeling SOPs. The inspector should also review documentation of verification of accuracy.

Example(s):

A form where superseded labels and new labels are attached to show the changes in the label content may be helpful. Approval of the Apheresis Collection Facility Director can be documented on this form. The same form can be used to document acceptability of the new label and inspection of content by two staff members.

This Standard applies to pre-printed labels produced by the Processing Facility as well as those produced by a commercial manufacturer.

STANDARD:

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

Explanation:

The final fate of all labels must be documented to ensure that a label allocated to a particular donor cannot be associated with the cellular therapy product, concurrent plasma, or related samples of another donor. The purpose of reconciliation is to ensure that all labels have been accounted for and no mix-up occurred. A system for label reconciliation shall be used that documents the number and type of labels for a particular collection, the number and type of labels used, the number and type of labels passed to another unit such as the Processing Facility, and the number and type destroyed.

Evidence:

The inspector shall review the relevant SOPs that detail the label reconciliation process in use and shall review examples of documentation of labels received, used, passed to another unit, or destroyed. The method of destruction of unused labels should be verified.

Example(s):

A form detailing the number of labels received, used, passed to another unit, or destroyed may be captured on the collection worksheet, on another form associated with the collection, or on a separate label reconciliation form. Unused labels may be affixed to the label reconciliation form or relevant collection-related form, crossed through and annotated to explicitly state that they are no longer in use.

STANDARD:

C7.2.4 Label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Collection Facility Director.

Explanation:

"On demand" means that the labels are printed just prior to the labeling process. Print-on-demand label systems must be validated against approved label templates. Each on-demand label does not need to be validated so long as the system by which they are printed has been validated to confirm accuracy regarding identity, content, and conformity to the templates. The Processing Facility may have validated the print-on-demand system against approved label templates. If so, the Collection Facility can provide evidence of the relevant validation document. However, Collection Facility personnel do need to confirm that the correct label was printed before the label is used.

If the Collection Facility is responsible for validation of the print-on-demand system, it should develop a validation protocol for implementation of "on-demand" computer software that confirms and documents that labels printed meet the criteria of acceptability.

Evidence:

Validation studies of the print-on-demand labels must be evident for the inspector's review. Personnel confirmation that the correct label was printed must also be documented.

STANDARD:

C7.2.5 A system for label version control shall be employed.

Explanation:

The document control system used for elements and data structures of the label and what constitutes a label version must be defined by the Collection Facility. Any change in the label or a label element that would change the interpretation of the label would constitute a version change. Only the current version of each label should be available for use in the collection area.

Evidence:

The inspector should verify that the versions of labels in the labeling or storages area are the current version.

Example(s):

A checklist where changes to a label's content are described is an example of how to document labeling changes. This could also include documentation of label content accuracy and destruction of obsolete labels. A master list of labels in use with version numbers helps with document control.

STANDARD:

C7.2.5.1 Representative obsolete labels with inclusive dates of use shall be archived for a minimum of ten (10) years after the last cellular therapy product was distributed or as defined by Applicable Law, whichever is longer.

Explanation:

Obsolete or unusable label stock should be defaced immediately to prevent its accidental use and then destroyed. However, as a controlled document, representative obsolete labels (or label templates) and their inclusive dates of service must be archived minimally for ten years after the last cellular therapy product was distributed, or as defined by Applicable Law, whichever is longer.

Evidence:

The inspector should verify that the destruction process is documented by reviewing documentation of obsolete labels that have been destroyed. There should be no obsolete version of labels available to staff or in the collection labeling or storage areas. Labels in use must be the same as the approved labels.

The inspector should review examples of archived obsolete labels and inclusive dates of service within the document control system.

STANDARD:

C7.2.6 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

C7.2.6.1 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process or two (2) qualified staff members.

Explanation:

At least two people must confirm that manually entered information on the label is accurate. One person may verify information if a validated process is used. Verification of the information must be documented in the collection records. It is important for the collection staff to verify the accuracy of the donor or patient information and to confirm that all parts of the collection (cellular therapy product labels, tie tags, sample tubes, and associated forms) are labeled completely and legibly before removing them from the proximity of the donor and prior to distribution to the Processing Facility.

In addition to confirming correct content, the label verification process should also ensure that:

- The label is correctly affixed to the product or tie tag.
- The correct label is positioned appropriately.
- The label is identical to the one specified in the SOP.
- Handwritten information is written with blue or black indelible ink.
- All information is legible and accurate.
- The unique identifier is firmly affixed to the product bag and identical to the identifier on associated forms and accompanying records and documents.
- The label is not damaged or defaced.

Evidence:

The inspector must verify the documentation in the collection records. Initials or signatures of staff as defined by the labeling process should be present in the collection records. The inspector should examine labeled cellular therapy products on-site to verify that labels are firmly attached or affixed and that a sufficient area of the product remains uncovered to allow examination of contents.

STANDARD:

C7.2.6.2 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.

Explanation:

This Standard requires facilities to have a careful process for electronically transmitting information (e.g., a bar code) and to double check that the information transmitted is correct.

STANDARD:

C7.2.6.3 Cellular therapy products that are subsequently repackaged into new containers shall be labeled with new labels before they are detached from the original container.

Explanation:

Labels for re-packaged cellular therapy products must conform to the proper label content as described in Appendices [II](#) and [III](#) as applicable. The criteria for repackaging of products and tracking mechanism shall be included in SOPs.

Evidence:

If cellular therapy products are repackaged, the inspector should examine the labels on a repackaged product to ascertain whether there are mechanisms in place (either on the label itself or via accompanying paperwork) to track the product from its origin to the final disposition.

STANDARD:

C7.2.7 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

Explanation:

The cellular therapy product container should not be covered such that the contents cannot be viewed. Inspection of the content is essential in determining abnormal color of plasma that could be due to hemolysis, bacterial contamination that could affect the safety of the product, and clots that could reduce the efficacy of the product.

Evidence:

The inspector should examine labeled cellular therapy products on-site to verify that labels are firmly attached or affixed and that sufficient areas of the products remain uncovered to allow examination of contents.

STANDARD:

C7.2.8 Labeling elements required by Applicable Law shall be present.

Explanation:

Label elements that are required by Applicable Law must be clearly visible. The Collection Facility should review FDA, EU, Health Canada, and other applicable governmental requirements for labeling and format labels accordingly.

STANDARD:

C7.2.9 All data fields on labels shall be completed.

Explanation:

All data fields on a label must be complete; fields for which information is not required must be filled as "N/A" or "none."

Evidence:

The inspector should examine labeled cellular therapy products on-site to verify the presence of appropriate information on the labels.

Example(s):

In some cases, a base label is used, with stickers applied containing specific elements based on the cellular therapy product type or the modification that was performed. Also, many facilities apply biohazard labels and warning statements, if applicable, using tie tags.

STANDARD:

C7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

Explanation:

Indelible ink must be used to record any information entered manually on the label. Inks and labels must be resistant to alcohol wipes or sprays if they are likely to be subjected to such liquids at collection, in the Processing Facility, or on the ward. Validation of the labels should include the properties of the ink used.

Evidence:

Documentation of evidence that the inks and labels were demonstrated to be resistant to alcohol wipes or sprays should be available to the inspector. The inspector should always verify that all labels are completed clearly and legibly.

Example(s):

Some Collection Facilities use post-collection cellular therapy product labels that are stuck over pre-collection labels and have all of the required label data printed on them. Others use labels in which as many fields as possible have preprinted data on them. Often the only hand-written data are the post-collection data (including time collection ends, approximate collection volume, or quantity of anticoagulant used). Staff can complete representative labels using a variety of pens and then wipe the labels using agents that may be applied to them in the Collection and Processing Facilities (such as alcohol wipes or sprays) to determine the smear resistance of each pen's ink. The Collection Facility can then determine the type of pen to be used in a formal validation of the indelibility of the preferred pen's ink.

STANDARD:

C7.2.11 Labels affixed directly to a cellular therapy product bag or container shall be applied using appropriate materials as defined by the applicable regulatory authority.

Explanation:

Adhesives that are applied directly to the cellular therapy product bag have the potential to leach through the plastic into the product itself. Collection Facilities must use materials that meet criteria, if any, established by applicable regulatory authorities.

This Standard does not apply to labels applied to a base label of a bag used for blood products. Those labels have been approved by the FDA.

Example(s):

Collection Facilities in the U.S. should contact the FDA regarding any labels affixed directly to the cellular therapy product bag to determine what data are needed to demonstrate that the labels meet FDA requirements. For further information, see the FDA guidance document [Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels](#) (2024).

STANDARD:

C7.2.12 The label shall be validated as reliable for storage under the conditions in use.

Explanation:

Adhesive labels affixed either directly to a cellular therapy product bag or to the base label of a product bag must remain affixed to the product bag (or base label) for as long as the product remains in the bag. The product's exposure to alcohol wipes or sprays or periods of cold storage, whether while still in the control of the Collection Facility or once in the Processing Facility's control, must be considered. For example, the Processing Facility may transfer the product into a storage bag after applying alcohol wipe or spray to the bag's surface, or the product may remain in the collection bag (with its label[s] affixed) through cold storage, thawing, and infusion. It is critical that the label(s) affixed to the product bag remain affixed throughout the bag's use so that product tracking and tracing are not compromised.

Evidence:

Documentation of evidence that the label(s) applied to the cellular therapy product bag remained affixed to the bag under all relevant storage conditions should be available to the inspector.

Example(s):

A validation of the adhesiveness of the labels applied to the cellular therapy product bag in the Collection Facility under all relevant product bag storage conditions can be completed either by the Collection Facility or the Processing Facility, or jointly. The extent of each facility's responsibility in carrying out the validation must be detailed in the validation document.

STANDARD:**C7.3 PRODUCT IDENTIFICATION**

- C7.3.1 Each cellular therapy product collection shall be assigned a unique numeric or alphanumeric donation 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 donor samples shall be labeled with the same identifier.*
- C7.3.1.2 If a single cellular therapy product is stored in more than one (1) 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.*

Explanation:

The cellular therapy product identifier must be unique. Unique is defined as not being used for any other purpose. Thus, it is not acceptable to use only patient information (such as medical record number or social security number) or only donor information (such as name, medical record number, or registry identifier) to identify the product. Products collected from a single donor at different times must be distinguished from each other by different unique product identifiers. If, however, more than one donation may need to be collected to deliver a given therapy, the donations should be linked by a Chain of Identity Identifier, which does not replace the unique product identifier but is the same on all donations associated with a patient's given therapy.

The essential point is that Chain of Identity of each cellular therapy product must be unambiguously traceable from donor to recipient and through all transport steps, processing steps, and storage locations. The label must clearly indicate the identity of the facility that assigned the product identifier with the exception of products shipped by registries, where the source facility must remain confidential. In such cases, the records that accompany the product must allow tracing to the donor.

Third-party manufacturing organizations may not want patient-identifiable data visible on the product label or accompanying documentation at the point of product distribution from the Collection Facility into their control. At a minimum, however, a unique identifier must remain on the product bag and accompanying documentation on distribution from the facility into the responsibility of the third-party organization. This will ensure that the unique identifier can be associated with the product during its passage through the third-party organization and must accompany the final product when it is distributed from the third-party organization for clinical use. For autologous products, this will allow confirmation that the product assigned to the patient originated from that patient, and, for allogeneic products, this will allow vein-to-vein tracking and traceability.

There must be an SOP indicating how a unique identifier is assigned and tracked and the acceptable modifications that can be made to the cellular therapy product label or identifier. When a product from a single donor is divided into multiple containers, each container must be uniquely labeled. If products are being pooled, the pool number must allow tracing to the original products. Note that only products from a single donor may be pooled unless specifically allowed for a given protocol by the appropriate regulatory authority.

Product and donor samples collected at the time of cellular therapy product collection should be labeled so as to prevent misidentification. At a minimum, this must include the donor's name (except for the case of unrelated donors), identifier, and date of sample collection.

Evidence:

The inspector must review the SOP for labeling the cellular therapy product with the unique identifier and how the identifier is assigned. There should be evidence that the product identifier is not duplicated, such as the use of a product identifier log. The inspector should perform a review to determine that the product identifier can be traced to the records used from collection to distribution of the product. The SOP for collection shall be sufficiently detailed to permit the inspector to match the collection records to a uniquely identified final collected product and to the donor and recipient.

Example(s):

The donor or recipient registry number can be used by the local site as the sole or additional identifier if it is combined with other information that makes it unique, such as the collection date, so that each cellular therapy product can be uniquely identified.

Identification of cellular therapy products with multiple containers may occur by modifying the unique identifier on each container with a suffix (either letter or number) or by modifying the product label on each bag (such as bag 1 of 2).

Marrow may be initially collected, filtered, and/or transported to the processing laboratory or clinical unit in two or more bags. All bags resulting from a single collection procedure should be linked to the collection by a unique identifier.

STANDARD:

C7.3.2 An ISBT 128 Chain of Identity Identifier should be assigned before or at the time of collection to each product or donation intended for further manufacturing.

C7.3.2.1 If more than one (1) donation is needed to deliver a given therapy, the Chain of Identity Identifier shall link all donations.

Explanation:

The purpose of the ISBT 128 Chain of Identity Identifier is to link all collections that may go into a final product. This Standard applies to cellular therapy products collected for further manufacturing.

Additional information regarding the Chain of Identity Identifier can be found on the ICCBBA website ([ST-018](#)) and in the FACT "[ISBT 128 Hybrid \(Split\) Label Webinar](#)."

Example(s):

An example of a product collected for further manufacturing is an MNC product collected for the manufacturing of CAR T cells.

STANDARD:

C7.3.3 Supplementary identifiers shall not obscure the original identifier.

Explanation:

The Collection Facility may assign additional identifiers to a cellular therapy product; however, it is recommended that no more than two unique product identifiers be affixed to a product container. The original identifier may not be obscured, and subsequent labels are not to be placed over the original label. If a supplemental unique identifier is replaced with another identifier, records must link the current unique identifier to the previous one.

Evidence:

The inspector should observe label procedures if this function is being performed by the Collection Facility; if not, the inspector should verify that the supplemental labeling procedure is described in the relevant supplemental labeling SOP and that the content of the label is appropriate.

Example(s):

To prevent obscuring the original product identifier and other label information, the Collection Facility may record the supplemental identifier on a tie tag.

STANDARD:

C7.3.4 *The facility associated with each identifier shall be named in the documents to accompany the cellular therapy product.*

C7.3.5 *If the original donation identifier is replaced, documentation shall link the new identifier to the original.*

C7.4 LABEL CONTENT**Explanation:**

Requirements for labeling cellular therapy products are detailed in ISBT 128 and can be found at [ST-004 ISBT 128 Standard Labeling of Cellular Therapy Products](#).

STANDARD:

C7.4.1 *The cellular therapy product shall be labeled with the proper name of the product and the unique numeric or alphanumeric identifier, at a minimum.*

C7.4.1.1 *For Apheresis collections, the proper name of the product and the unique numeric or alphanumeric identifier shall be applied to the collection container prior to the collection procedure.*

C7.4.2 *Labeling at the end of collection shall occur before the cellular therapy product is removed from the proximity of or disconnected from the donor.*

C7.4.2.1 *The content of the label shall be verified prior to removing the cellular therapy product from the proximity of the donor.*

Explanation:

Cellular therapy product labels, tie tags, sample tubes and associated forms must be labeled completely and legibly before the product is removed from the proximity of or disconnected from the donor, as appropriate.

Handwriting the end-of-collection data on the cellular therapy product label before the product is disconnected from the donor can result in illegible data and carries with it a risk of puncturing the product container. The Collection Facility may choose to add final data to the label after disconnecting the product. Any change to the required process (i.e., label completion after the product has been disconnected from the donor but remains within the proximity of the donor) must be controlled and the risk associated with completing the label once the container has been disconnected from the donor identified and mitigated.

Labeling of the product before disconnecting it from the donor or removing it from the proximity of the donor once the container has been disconnected from the donor will prevent mix-ups when

there is more than one donor being collected. If confidentiality is a concern, partial labels may be used until the cellular therapy product is disconnected from the donor.

Evidence:

The inspector should verify that labeling at the end of collection occurs before the cellular product container is removed from the proximity of or disconnected from the donor and contains all of the information listed in [Appendix II](#). If labeling at the end of collection is carried out in the proximity of the donor after the cellular therapy product container has been disconnected, the inspector shall review the relevant documentation including the associated risk assessment.

Example(s):

The use of print-on-demand post-collection labels containing all relevant label information, including end-of-collection data, may be affixed on top of the pre-collection product label before the cellular therapy product is removed from the proximity of or disconnected from the donor.

During an apheresis collection, the device typically displays results at the end of the collection procedure. Users may be able to clamp the cellular therapy product in order to retrieve the information before disconnecting the product from the donor.

STANDARD:

C7.4.3 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](#).

Explanation:

The required label content as specified in Appendix II represents minimum requirements and must be present as indicated at the various stages of cellular therapy product collection, processing, and distribution.

While marrow and other tissue products may not be regulated by applicable health authorities, FACT and JACIE treat these products the same as HPC, Apheresis for purposes of label content. Therefore, product labels must include all label content as required by the information in Appendices [II](#), [III](#), and [IV](#).

Accompanying paperwork should be packaged in a secondary bag with the cellular therapy product for distribution to the Processing Facility, third-party manufacturing entity, or clinical infusion site. It is not acceptable to distribute multiple product bags from different donors using partial labels with all of the additional information on a single inventory sheet.

Only some or no patient-identifiable data on the cellular therapy product label may be required by a third-party entity. The Collection Facility must confirm with the third-party entity the extent of patient-identifiable data to be included on the product label, the concurrent plasma container (if

applicable), and accompanying paperwork at the point of transfer of the product out of the control of the Collection Facility and into the control of the third-party entity. Patient- and donor-identifiable data is placed on the cellular therapy product label prior to collection to ensure that the product is being collected from the correct donor and put into a correctly labelled product container. Some or all of this data may need to be obscured using an indelible marker pen or another validated method. However, a unique identifier must remain on the product label, concurrent plasma container, and accompanying paperwork to ensure full product tracking and traceability. Specifically for autologous collections, this also ensures that the product can be associated with the patient at all times as it passes through the third-party entity and then is reissued back to the clinical facility for infusion to the patient.

When labeling cellular therapy products after collection, it is important to include the time when collection of the product was completed, along with the time zone if different from the time zone of the location where the product will be distributed, in order for downstream facilities to accurately determine the age of the product and apply the appropriate expiration date and time. The Collection Facility must define and validate its process for determining a product expiration date. Organizations such as the NMDP provide education services which may assist in establishing individual facility protocols.

The Collection Facility address should be explicit enough to correctly identify the location and allow the facility to be contacted if questions arise or an emergency occurs during processing or transportation. For cellular therapy products distributed by an unrelated donor registry, a facility identifier that does not include the facility name and address should be used to protect donor privacy.

Once regulated cellular therapy products have reached the stage of licensure, the label or accompanying records must include the statement "Rx Only," indicating that the product may only be distributed by a prescription from the physician. The physician order form required by the Standards may serve as the prescription.

Evidence:

The applicant facility provides examples of all labels in use for prescreening by the FACT office or JACIE inspectors so as to correct any deficiencies prior to the on-site inspection. The inspector should review the labels prior to the on-site inspection and determine if deficiencies have been corrected. For applicant programs performing both allogeneic and autologous cellular therapies, examples of labels will include collection, processing, transport, and distribution labels for both therapy types. In addition, labels and partial labels (if used) illustrating each cellular therapy product source handled by the Collection Facility should be included. Tie tags, instructions to the infusionist, biohazard labels, and warning labels should also be included. If any expected label is not included in the pre-inspection documents, the inspector should request it from the applicant Collection Facility or the FACT or JACIE office.

When on-site, the inspector should verify that the labels currently in use are identical to those submitted prior to the on-site inspection and that they correspond to the labels in the SOP. If this is not the case, the inspector will need to resolve the discrepancies and verify that each label in use meets the requirements listed in [Appendix II](#). The inspector should further verify that labels are available for every type of cellular therapy product collected, with acceptable modifications. Examples of completed labels must not contain blank spaces. "N/A" or "none" should be used as indicated.

The inspector should ask to see the SOP that defines the conditions for using a biohazard label and determine if the facility's procedures are adequate and appropriately safe to prevent transmission of infectious disease.

Example(s):

Additional information may be attached to the cellular therapy product via a tie tag or included in accompanying documentation, as detailed in [Appendix II](#). The immediate packaging of an investigational cellular therapy product regulated under section 351 of the PHS Act in the U.S. must be labeled with the statement "Caution: New drug limited by federal law for investigational use."

The recommended storage temperature listed on the label may include ranges (e.g., 2–8° C, 20–26° C).

STANDARD:

C7.4.4 *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.*

Explanation:

A biohazard label must be attached or affixed to any cellular therapy product from a donor who has tested positive for a relevant communicable disease (as listed in [B6](#) and its subStandards except CMV) or when donor screening indicates a risk factor for a relevant communicable disease or disease agents. "Table 2. Biohazard and Warning Labels..." of the inter-organizational *Circular of Information for the Use of Cellular Therapy Products* outlines when biohazard labels must be used. Biohazard labels must not be applied indiscriminately, as they are meant to denote a greater hazard than that posed by any biological product. Biohazard labels can only be applied to products not required to be labeled biohazard when specific circumstances for their use are defined by Collection Facility or Clinical Program policy. Using biohazard labels on all products without documented rationale is considered a deficiency.

Warning labels are required to be affixed or attached to the cellular therapy product when product testing or screening is positive for infectious disease risk or is incomplete (see [Appendix II](#)). Note that residence in a country on the U.S. Department of Agriculture list as at risk for bovine spongiform encephalopathy (BSE) is considered to constitute a risk identified by donor screening. Thus,

allogeneic cellular therapy products require a biohazard label and the statement “Warning: Advise recipient of communicable disease risks.”

If any of the required allogeneic donor eligibility requirements are not completed, the statement “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” must be attached to and/or accompany the product. For example, this would apply in the following situations:

- A product not tested at all for relevant communicable disease agents and diseases.
- A product tested for only a subset of relevant communicable disease agents and diseases.
- A product screened and tested for all relevant communicable disease agents and diseases but using diagnostic tests rather than donor screening tests.
- A product screened and tested for all relevant communicable disease agents and diseases but not within the required time period (e.g., within 30 days for HPC, within 7 days for MNC products) or still pending at the time of labeling.
- A product screened and tested for all relevant communicable disease agents and diseases using approved donor screening testing, but for which no official donor eligibility determination was made.

Products for which donor testing is positive must also include the statement “Warning: Reactive test results for (name of disease agent or disease)” with the name of the disease agent or disease specified.

Communicable disease testing is not required for autologous donors in relation to cellular therapy product collection unless required by Applicable Law, nor is there a requirement for donor eligibility determination. Programs may, however, decide to carry out communicable disease testing and eligibility determination in autologous donors to help standardize processes, reduce the risk of error, and facilitate non-segregated autologous and allogeneic product storage. Relevant policies and procedures will reflect this decision and the relevant Standards within [B6.4](#) will apply. Organizations that do not perform autologous donor testing must carefully establish processes that maintain compliance with FDA regulations for labeling.

Autologous cellular therapy products must be labeled with “FOR AUTOLOGOUS USE ONLY.” If an autologous donor is missing any of the testing and screening required for an allogeneic donor, the cellular therapy product label must contain the statement “NOT EVALUATED FOR INFECTIOUS SUBSTANCES.” In addition, if the autologous donor undergoes at least some of the testing or screening prior to collection and is found to be positive or at risk for a relevant communicable disease, the product label must also bear a biohazard label and the statement “WARNING: Reactive test results for (name of disease agent or disease).” Since autologous recipients are not at risk of contracting a communicable disease from themselves (i.e., they already have the disease), the statement “Warning: Advise recipient of communicable disease risks” is not required on autologous

product labels even if donor testing results are positive. In this situation, a biohazard label is required.

The immediate packaging of an investigational cellular therapy product regulated under section 351 of the PHS Act in the U.S. must be labeled with the statement "Caution: New drug limited by federal law for investigational use." Currently HPC, Apheresis products and some HPC, Cord Blood collected from unrelated donors for NMDP are regulated under an IND held by NMDP and thus have labeling with this statement.

Evidence:

The inspector should confirm that biohazard labels and warning statements are utilized as described in Table 2 of the [Circular of Information for the Use of Cellular Therapy Products](#). Autologous cellular therapy product labels should be examined to confirm that the statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" is used when any of the testing and screening required for an allogeneic donor is missing.

STANDARD:

C7.4.5 A cellular therapy product collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documentation table in [Appendix IV](#) at the time it leaves the control of the Collection Facility.

Explanation:

Requirements for accompanying documentation for products from allogeneic donors are listed in Appendix IV. The FDA GTP regulations have specific requirements regarding the information that must accompany a cellular therapy product at all times after the determination of allogeneic donor eligibility has been documented (see [21 CFR 1271.55](#)). A statement is required attesting to donor eligibility (or ineligibility) based on the screening and testing that was performed, a summary of the records used to make the donor eligibility determination, and the identity and address of the facility that made the determination. The summary must include a listing and interpretation of the results of all communicable disease tests performed, a statement confirming that communicable disease testing was performed by a laboratory with the required qualifications, and in the case of an ineligible donor, a statement noting the reason(s) for their ineligibility. Accompanying records must not contain the donor's name or other personal information that might identify the donor.

If the Collection Facility is responsible for allogeneic donor eligibility determination, that facility is responsible for distributing this documentation to the Clinical Program and Processing Facility. If the Clinical Program determines allogeneic donor eligibility, the Collection Facility must obtain the documentation from the program so that it may accompany the product.

For products that are distributed for administration, the product administration form containing these elements can be used for this purpose. According to the U.S FDA guidance document [Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products](#)

(2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in [21 CFR 1271.55](#). In January 2025, the FDA released additional draft guidance: [Recommendations for Determining Eligibility of Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](#).

Example(s):

It is permissible to have hard copies of each item physically accompany the cellular therapy product. In some cases, that may be most appropriate, such as when a product leaves the Collection Facility and is transported to another institution for processing, storage, or administration.

STANDARD:

C7.4.6 Any container bearing a partial label at the time of distribution shall be accompanied by the information required by the Cellular Therapy Product Labeling table in [Appendix 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.

Explanation:

If the Collection Facility utilizes a partial label at the time of distribution to a Clinical Program, Processing Facility, or other entity, the inspector must confirm that the SOP describes the use of the partial label, provides an example of the partial label, and includes the mechanism for providing the additional information that is not included on the partial label.

Accompanying paperwork should be packaged in a secondary bag with non-frozen cellular therapy products for shipment or transport to the external facility or infusion site. The paperwork may be placed in the canister of a frozen product. When shipping or transporting multiple product bags from different donors using partial labels, it is not acceptable to include all the additional information on a single inventory sheet, but rather each product and its associated paperwork should be segregated in a way to prevent mix-ups.

Evidence:

Inspectors should verify that partial labels at the time of distribution meet requirements as defined in these Standards and the Collection Facility's SOPs.

STANDARD:

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

Explanation:

If the Collection Facility participates in allogeneic donor eligibility determination, there must be a contingency arrangement in place to allow collection and distribution from a donor before completion of their eligibility determination. This occurrence is likely to be uncommon and in response to a recipient's urgent medical need, but a controlled process must be described and comprehensive documentation of the process completed when the process is used, including documented completion of eligibility determination in the recipient's and donor's records and notification of the recipient's physician.

Evidence:

The inspector should review that the completion of determination documentation is achieved within the timeframes outlined in the Collection Facility's SOPs.

Example(s):

Related documentation that allogeneic donor eligibility was completed during or after the use of the cellular therapy product should be in the donor's and recipient's records. Documentation of urgent medical need to release the product should also be present.

STANDARD:

C7.4.8 Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "For Nonclinical Use Only."

Explanation:

The Collection Facility may carry out cellular collections from donors whose cells will be used for nonclinical use, such as manufacturing process validation or process development. The cellular therapy product label shall contain the relevant labeling requirements (see [Appendix II](#)) and state that the product is not for clinical use.

According to ICCBBA, if the cellular therapy product is not intended for administration, the upper right quadrant should reflect this. Instead of a standard ABO/Rh code, the code "Mr" (for research use only) should be selected. The words "For Nonclinical Use Only" (in the local language) should appear.

C8: EQUIPMENT, SUPPLIES, AND REAGENTS

STANDARD:

C8.1 Equipment, supplies, and reagents used to collect cellular therapy products shall be qualified and used in a manner that maintains product function and integrity and minimizes risks of product mix-ups, contamination, and cross-contamination.

C8.2 There shall be adequate equipment and materials for the procedures performed.

Explanation:

The amount of relevant equipment in the Collection Facility should be appropriate for the type of collection performed, proportionate to the volume of work done, and conveniently located.

The Collection Facility should have policies and SOPs that address interruption in collection due to equipment failure, such as for the handling and labeling of cellular therapy products, as well as policies and SOPs that prevent subsequent delay in collections, such as an additional machine for back up or arrangements with other collection agencies or centers.

Evidence:

The inspector will evaluate whether there is adequate equipment available in the facility, if the equipment is being used appropriately, and if there is a backup plan in the event of equipment failure.

The inspector should review documentation that adequate materials are present, and have been present, for the level of activity conducted by the Collection Facility. A well-stocked supply cabinet or supply area would indicate adequate materials are in inventory. The center should have an inventory list that defines critical supplies and their quantity based on the scope and the activity of the center. A policy or SOP outlining material management, including how availability and adequacy are ensured, must be verified.

Example(s):

Frequent “emergency” orders might suggest that an inadequate supply of material is being kept in inventory.

Just-in-time is a materials management system of centralized inventory control where necessary materials, supplies, and reagents are delivered at the time of need. Documentation of “just-in-time” policies and SOPs for management of materials needed for cellular therapy product processing is acceptable so long as this practice can be confirmed by the inspector as having the desired result.

STANDARD:

C8.3 *There shall be a process for inventory control that encompasses equipment, containers for transport and shipping, supplies, reagents, and labels.*

C8.3.1 *There shall be a system to uniquely identify and track and trace all critical equipment, supplies, reagents, and labels used in the collection of cellular therapy products.*

C8.3.2 *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.*

C8.3.2.1 *Supplies and reagents shall be quarantined prior to use until verified to have met acceptance criteria.*

Explanation:

Cellular therapy product quality, as measured by adequate viability, integrity, lack of microbial contamination, and lack of cross-contamination, may be affected by the supplies, reagents, and equipment (including transport containers) used for collection. Therefore, these items used in collection that might affect product quality must be identified and tracked. For this purpose, there must be a system by which the critical equipment supplies, and reagents, including those which come in contact with cellular products, can be uniquely identified.

The identification and the tracking of supplies, reagents, and equipment used to collect cellular therapy products must be described in an SOP. Critical materials must be defined by the Collection Facility and tracked and traced. Supplies and reagents must be examined for contamination, breakage, discoloration, etc., at receipt. Records must be kept of the receipt and qualification of each supply or reagent and must include the type, manufacturer, lot number, dates of receipt, and expiration date. There must be a mechanism to link the supplies and reagents, lot numbers, and expiration dates to each product manufactured and, conversely, each product collection record must include the identity of the supplies and reagents that were used. The reagents and supplies must also be visually inspected for contamination, breakage, and discoloration, immediately prior to use and procedure initiation; findings must be documented. Equipment such as marrow harvest kits may be received outside of the Collection Facility. Responsibility for this type of equipment begins when it is received by collection staff.

Generally, the cellular therapy product inventory and reagent and supply inventory are separately managed. Each product must be assigned a unique alphanumeric identifier that is part of the control system. Equipment, supplies, and reagents should be connected to the product through the unique identifier or through an alternative system so that a link to the product can be made. Testing laboratories may require that other identifiers be used. Any blood sample or tissue for testing must be accurately labeled to confirm identification of the donor and must include a record of the time and place the specimen was taken. The system must include documentation that materials under the inventory control system meet predefined facility requirements.

Evidence:

The inspector should confirm that there is a process in place to determine acceptability of all critical reagents and supplies (including labels, cellular therapy products, and product samples) before they are accepted into inventory and prior to use.

Description of acceptable criteria for reagents and supplies to be checked against prior to use may be found in logs or relevant SOPs.

The inspector should review the inventory control process and documentation of supply and reagent examinations at receipt and prior to use to verify that the Collection Facility takes steps to confirm there is no obvious evidence of damage (e.g., leakage, damaged box).

Example(s):

The system in use may utilize an electronic system or a logbook to enter all incoming supplies and reagents.

Equipment identification can be achieved by using a pre-existing serial number but may also be achieved by assigning a unique identifier that is visible on the piece of equipment. A more casual designation, such as "Brand X centrifuge," is less desirable since over the course of time more than one centrifuge might fit that description. It is possible to accomplish this by the use of serial numbers and records of dates of use; however, over time, this is more difficult to track reliably.

Specific acceptance criteria for supplies and reagents may include visual checks (e.g., visual water damage, evidence of tampering or contamination) and verification that it is the item actually ordered.

STANDARD:

C8.3.3 Records of receipt shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.

C8.3.4 Materials shall be stored under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix-up or unintended use.

Explanation:

Once received, supplies and reagents used during collection must be stored in a manner that preserves their function and sterility. Evaluation of the storage during transport should also be included. For items requiring storage at defined specifications such as temperature and humidity, the conditions of the storage area must be monitored and documented.

Evidence:

The inspector should observe storage areas and confirm that supplies and reagents are stored under the conditions specified by the manufacturer. The inspector should confirm that the storage area is

clean and sanitary and that acceptability for use of supplies and reagents is not compromised during storage.

When refrigerators and freezers are used to store cellular therapy products, supplies, or reagents, the inspector should look for evidence that each is appropriately labeled and adequately separated so as not to cause confusion or compromise the integrity or sterility of the contents.

Example(s):

This can be accomplished by storing cellular therapy products on a designated shelf that is appropriately labeled for that purpose, utilizing designated labeled compartments, or by other procedures. It is recommended that outdated supplies and reagents and those not intended for clinical use be stored in a separate unit from those designated for patient care if possible. When this is not possible, outdated and research material must be clearly distinguished from clinical material and appropriately labeled.

STANDARD:

C8.3.5 Supplies and reagents coming into contact with cellular therapy products during collection shall be qualified, sterile, and meet predetermined specifications for the intended use.

Explanation:

Supplies and reagents that come into contact with cellular therapy products must be clinical or pharmaceutical grade, as appropriate, and free of microbial contamination.

A COA should be obtained if available from the manufacturer. Upon receipt of reagents and supplies, personnel should document review of package inserts to confirm that there are no changes in the intended use and should retain the most current package insert for reference.

Evidence:

The inspector should request COAs of the reagents that are approved for human use or of pharmaceutical grade. Package inserts of reagents and supplies provide information regarding their intended use.

Example(s):

Examples include a COA or the manufacturer's certification of sterility.

STANDARD:

C8.3.6 *Non-disposable supplies or instruments shall be cleaned and sterilized using a procedure verified to remove infectious agents and other contaminants.*

Explanation:

For some specialized procedures, equipment or instruments that come into contact with the cellular therapy product may require cleaning and sterilization between uses. When this is the case, the Collection Facility must verify that the cleaning and sterilization methods used remove infectious agents.

Evidence:

The inspector should review the records of this verification process.

Example(s):

Surgical equipment for tissue manipulation such as scissors, forceps, and scalpel handles are examples of non-disposable supplies or instruments that may be included in collection procedures.

Examples of equipment used for marrow collection include, at a minimum, reusable harvest needles and reusable stands for collections kits. An example of improper cleaning is an instance when a reusable needle is not properly cleaned before it is sterilized. When the needle is sterilized, the remaining blood inside the needle turns to black ash. When prepped for use, the black ash comes out of the needle.

STANDARD:

C8.3.7 *Supplies and reagents shall be used in a manner consistent with manufacturer instructions.*

Explanation:

It is recognized that reagents typically utilized may be used for indications that are not specifically indicated on the manufacturer's instructions. In these cases, "consistent with manufacturer's instructions" would include considerations such as sterility and final mode of administration and could be compliant with this requirement.

Evidence:

The inspector should request and review product package inserts and supply and reagent information that describes the supply or reagent and its intended use.

Example(s):

Package inserts from supplies and reagents such as packaging supplies would meet this requirement.

STANDARD:

C8.3.8 *There shall be a process to prevent the use of expired reagents and supplies.*

Explanation:

There should be a mechanism to monitor the flow of supplies and reagents within the Collection Facility to prevent the use of outdated supplies and reagents. This system should also be able to identify the location of a given lot of a supply or reagent in the event that there is a manufacturing recall.

Evidence:

The inspector should evaluate the inventory control system to determine if it is adequate to prevent the use of outdated or damaged supplies and reagents.

Example(s):

A first expired, first out system is one that is most commonly encountered. This mechanism can be tracked on paper or via a computer program.

STANDARD:

C8.3.9 *Equipment, supplies, and reagents for the collection procedure shall conform to Applicable Law.*

Explanation:

European [Directive 2006/17/EC](https://eur-lex.europa.eu/eli/dir/2006/17/ec/oj) Annex IV 1.3.10 specifies that where possible, equipment that is compliant with the CE (*Conformité Européenne* or European Conformity) Marking Directive must be used for cellular therapy product collection. CE marking is a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation implementing certain directives. Staff using such equipment must have appropriate training. For additional guidelines regarding this requirement, see https://commission.europa.eu/index_en.

Evidence:

The inspector should review the COA or CE of commercially available disposable sets used by the Marrow Collection Facility.

STANDARD:

C8.4 There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration.

C8.4.1 Equipment used in the collection of cellular therapy products shall be maintained in a clean and orderly manner. Equipment shall be located to facilitate cleaning, calibration, and maintenance according to established schedules, as described in Standard Operating Procedures, and in accordance with the manufacturer's recommendations.

C8.4.1.1 The equipment shall be inspected for cleanliness and verified to be in compliance with the maintenance schedule prior to use.

Explanation:

There must be a schedule for equipment cleaning and maintenance. Schedules may vary based on frequency of use, performance stability, or recommendations from the manufacturer. The Collection Facility must inspect equipment for cleanliness prior to each use. It may be useful for the facility to have a check box on a form to indicate that equipment was inspected and was found to be clean or cleaned if needed.

Evidence:

The inspector should confirm by visual inspection that equipment can be easily accessed for cleaning and maintenance.

Example(s):

It is recommended that recent records of regularly scheduled maintenance, cleaning, and calibration be readily available for each piece of equipment including blood warmers.

STANDARD:

C8.4.2 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.

Explanation:

Equipment SOPs must also describe how the equipment is operated or refer to relevant operations manuals that are available within the Collection Facility. Maintenance and calibration are required to detect malfunctions and defects and to safeguard that the critical parameters are maintained within acceptable limits at all times. There must be a schedule for equipment maintenance and quality control. Calibration and maintenance may be contracted with another entity, such as a biomedical department or manufacturer. The Collection Facility is responsible for maintaining a record that calibration and maintenance were performed appropriately.

Logs should be available near the equipment, or tags or stickers should be visible on the equipment, indicating that calibration parameters have been met, the date preventive maintenance and calibration were performed, and when such testing is next due. Where applicable, calibration procedures should include limits for accuracy and precision.

Evidence:

On-site, the inspector should see a sampling of calibration records and confirm that traceable standards have been used. The inspector should look for SOP(s) describing the corrective action to be taken when precision and accuracy limits are not met and written instructions to be followed if the equipment fails. Records to document these activities, including investigation of potential adverse events caused by cellular therapy products, should be available to the inspector.

Example(s):

Schedules may vary among Collection Facilities, based on frequency of use, performance stability, or recommendations from the manufacturer. It is recommended that recent records of regularly scheduled maintenance and quality control be readily available for each piece of equipment.

STANDARD:

C8.4.2.1 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.

Explanation:

Equipment identified by the Collection Facility to have a critical measuring function, such as thermometers, timers, and scales, must be calibrated against a traceable standard. A traceable standard is one that can be directly linked to a provider that has documented the accuracy of the measuring device.

Example(s):

Examples of traceable standards include National Institute of Standards and Technology (NIST) for the U.S., CE label or DIN Norm (*Deutsches Institut für Normung* or German Institute for Standardization) for the EU, reference thermometers, stop watches, and tachometers. Other vendors may provide similar products, but they must have a direct link to records indicating accuracy to a known standard. An alternative to using the actual traceable standard is to calibrate a similar device against the traceable standard and use the newly qualified device for routine measurements. If a traceable standard cannot be obtained, then the Collection Facility must document how they determined the measurement reading to be accurate.

STANDARD:

C8.4.2.2 Calibration shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.4.2.3 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.

Explanation:

Equipment used for collection must be maintained, calibrated, cleaned, and, if applicable, sterilized. Equipment SOPs must also describe how the equipment is operated or refer to relevant operations manuals that are available within the Collection Facility. The SOPs should also provide instruction in the event of failure of any device. Maintenance and calibration are required to detect malfunctions and defects and to safeguard that the critical parameters are maintained within acceptable limits at all times.

Specified critical equipment must be calibrated by a qualified technician on a regular basis as defined by the Collection Facility. A calibration report from the qualified technician must be provided to the Collection Facility and be available during the inspection. Critical equipment with the condition of calibration solely by the manufacturer must be identified in the facility SOP.

Mobile donor centers must have SOPs that demonstrate compliance with the Standards. A description of critical equipment movement shall be included in the SOP in accordance with industry guidance.

Tags or stickers should be visible on the equipment indicating that quality control parameters have been met, the date quality control testing was performed, and when such testing is next due. Where applicable, calibration SOPs should include limits for accuracy and precision. Equipment with a critical measuring function (e.g., time, temperature, speed) should be calibrated against a traceable standard, if available.

Note that if critical equipment used in collection is located outside of the Collection Facility, such as sterilization equipment, it is the facility's responsibility to verify that equipment is properly assembled for function, maintained, and calibrated. Such records should be available to the inspector.

It is also important to maintain a schedule of equipment cleaning, sterilization, sanitation, and disinfection that is described by an SOP, and documented. This is important to prevent microbial contamination of products, as well as to prevent transmission of infectious disease and cross-contamination.

Evidence:

On-site, the inspector should see a sampling of such records. The inspector should look for SOP(s) describing the corrective action to be taken when precision and accuracy limits are not met, and written instructions to be followed if the equipment fails. This should include an investigation of potential adverse effects on manufactured cellular therapy products using the equipment tracking system.

Example(s):

It is recommended that recent records of regularly scheduled maintenance and quality control be readily available for each piece of equipment including blood warmers. Calibration on at least an annual basis is also recommended.

For U.S. programs, [21 CFR 1271.200](#) provides additional details on calibration. GMP regulations also provide details (note that these are only required for 351 products; however, they may still be helpful for any Collection Facility). See also [21 CFR Part 211 Subpart D](#).

STANDARD:

C8.5 *Lot numbers, expiration dates, manufacturers of critical reagents and supplies, and key equipment used in each procedure shall be documented.*

Explanation:

There must also be a complete record of lot numbers and expiration dates for reagents and disposables used in each collection procedure. Likewise, the identity of the key equipment used during collection must also be documented. It is critical to be able to link reagents, supplies, and equipment to the collection of each cellular therapy product in the case of an adverse event or recall of reagents, supplies, or equipment. Implementation of a carefully planned inventory control system helps to facilitate documentation of lot numbers; prevention of the use of outdated or quarantined supplies; and linkage of products collected to reagents, supplies, and equipment in a timely manner.

Evidence:

Collection chart records are required to contain a listing of the required reagent and supply lots and the equipment used. Those records should be available for inspector review.

C9: PROCESS CONTROLS

STANDARD:

C9.1 Collection of cellular therapy products shall be performed according to written Standard Operating Procedures.

Explanation:

Collection of cellular therapy products must be performed according to the Collection Facility written SOPs.

Evidence:

The inspector should observe critical portions of a collection procedure to determine whether or not the personnel follow applicable SOPs, if a collection procedure is scheduled for the day of an onsite inspection. It is rarely possible to observe a marrow collection procedure on inspection day(s). Inspectors should interview collection staff and review collection records to verify that specific elements of the procedure were carried out according to the SOP. Deviations from the SOP may indicate inadequate training or out-of-date SOPs.

Questions may be asked to determine:

- Are cellular therapy products from different donors stored in the Collection Facility at the same time?
- Are products labeled at the donor's side prior to disconnecting from the apheresis line or removed from the proximity of the donor to avoid misidentification?
- Are reagents identified as dedicated to a single collection procedure?
- Is there a record of the lot numbers and expiration dates for all reagents and critical supplies used in collection?
- Is the specific apheresis machine used in each collection identified?
- How are cleaning and disinfection performed between collection procedures?

Example(s):

The Collection Facility may develop a document to record data that are captured according to the collection SOP. These data may include the items in the Evidence section. The document should also identify the staff performing each step in the SOP.

STANDARD:

C9.2 *Autologous or CMV-appropriate and irradiated (or equivalent) blood products shall be available during the collection procedure for all donors.*

Explanation:

This Standard is applicable to all donors and requires availability of CMV-appropriate and irradiated (or equivalent) blood products but does not dictate clinical practice. The Collection Facility is responsible for defining the type of blood products required for each donor.

Donors may require a blood transfusion during the apheresis collection procedure. Cellular therapy programs, especially their apheresis collection facilities, need to be prepared to provide appropriate blood products. Autologous units may be collected prior to apheresis, or allogeneic CMV-appropriate and irradiated units may be used. Many places have difficulty collecting autologous blood from donors <40 kg. The decision to use autologous or allogeneic blood depends on the benefits and risks to the donors, especially in the case of pediatric donors.

Similarly, in preparation for a bone marrow harvest, pre-collection and storage of autologous blood for later transfusion may be clinically indicated, particularly if significant blood loss is anticipated. This provision allows reduced exposure to allogeneic blood products, which is particularly relevant in pediatric or rare donor scenarios. Thus, it is expected that normal-sized, adult marrow donors would donate autologous blood and therefore not require allogeneic blood. However, in the situation of small-sized marrow donors and large-sized recipients, transfusion is expected. An example of this would be a 25 kg donor and an adult-sized recipient. In this case, transfusion is expected and frequently occurs during the collection.

A special concern for allogeneic donors is the fact that transfused allogeneic blood contains lymphocytes that can become part of the collected cellular therapy product. Since under most circumstances the need for blood products occurs during collection, these transfusions must be irradiated (or equivalent technology such as pathogen reduction) to prevent engraftment of third-party lymphocytes in the transplant recipient. Because of the occasional need for a second cellular therapy product collection, it is advisable to continue irradiating blood transfused to the donor in the immediate post-collection period (Cancelas, Bandarenko, eds. [*Cellular Therapy: A Handbook*](#). 2nd ed. AABB. 2023).

The goal is to ensure the safety and clinical appropriateness of support for all donors undergoing cellular therapy collection procedures. Ensuring CMV-appropriate components are available (e.g., universal leukoreduction policy, use of CMV-seronegative blood components) permits rapid clinical response in the event of blood loss, hemodynamic instability, or other complications during collection.

Irradiation of blood products or equivalent prevents transfusion-associated graft-versus-host disease, a rare but often fatal complication of blood transfusion, especially in immunocompromised individuals. Additional information can be found in Chapter 14 "Transfusion Therapy in

Hematopoietic Stem Cell Transplantation” (Marques, Schwartz, Wu, eds. [Transfusion Therapy: Clinical Principles and Practice. 5th ed.](#) AABB. 2025).

Example(s):

If leukocyte-reduction is used to meet this Standard and is performed at a transfusion service (e.g., blood bank), there must be a validated method in place to adequately and consistently reduce the leukocytes in the blood components. Most transfusion services procure pre-stored leukocyte-reduced blood products from their blood supplier(s).

STANDARD:

C9.3 *There shall be a written order from a physician specifying, at a minimum, the anticipated date and goals of collection.*

Explanation:

The physician who evaluates the donor and makes the decision to proceed is not always the same one who actually collects the cells. This order, either written or electronic, is required as a mechanism to safeguard that there are no misunderstandings among team members regarding the specifics of the collection. The written order should include at least:

- Identity of the donor.
- Identity of the allogeneic recipient (if applicable).
- Timing of collection.
- Date and time the cells are needed by the recipient (as applicable).
- Cell type.
- Cell dose required.
- Total blood volume to process (if apheresis) or number of collections according to standard SOPs.
- Appropriate authorized signatures.
- Blood group determination.
- Recipient weight.
- Donor weight and height.
- Pre- and post-collection laboratory results guidelines.

Orders will clarify the desired end result of a collection procedure. The information on the order will help achieve the cellular therapy product cell dose needed for the recipient. Pre- and post-collection laboratory results guidelines may include relevant hematologic and biochemical analyses. SOPs should outline how the Collection Facility will handle donors whose laboratory values are outside of the acceptable ranges. Apheresis collection timing may include a timeframe driven by CD34 analysis or specific date(s) and time(s). For collection by apheresis in children <20 kg, there should

be justification for total blood volume to be processed. Collection targets must be aligned with manufacturer specifications.

Evidence:

The inspector should confirm that the written order meets the criteria and, if there are deviations, that there is documented approval.

STANDARD:

C9.4 There shall be peripheral blood count criteria to proceed with collection including the timing of sample collection.

C9.4.1 The peripheral blood count criteria shall be met and documented prior to each collection.

Explanation:

Collection Facilities may set their own timeframes for performing testing on donors. Some registries may have specific requirements. Not only does the testing need to be performed, but facilities must have predetermined limits for when collection may or may not proceed.

The Collection Facility needs to set up pre-collection peripheral blood count criteria:

- The white blood cell count is needed to determine if the donor was mobilized and ready for the collection, thus avoiding unnecessary or unsuccessful collection procedures.
- The RBC count is a parameter used to program apheresis machines.
- The platelet count is an important donor safety measure because HPCs lie close to the platelet layer in the buffy coat, and platelets are being “scooped” during the collection procedure, potentially causing substantial loss of platelets to occur.

Collection Facilities must have procedures for actions to take when the criteria are not met. Examples include obtaining documented approval to proceed with collection as a planned deviation or planning transfusion of RBC or platelets before or after the procedure.

Not only does the testing need to be performed, but facilities must have predetermined limits for when collection may or may not proceed.

Evidence:

The inspector will review relevant SOPs to confirm that peripheral blood count criteria are defined and review documentation to confirm adherence to SOP in the event of deviations.

STANDARD:

C9.4.1.1 A complete blood count, including platelet count, shall be performed within 24 hours prior to each subsequent cellular therapy product collection.

Explanation:

The Standards require peripheral blood count criteria for proceeding with apheresis collection; however, testing within 24 hours is only required for collection procedures after the first one is completed. Healthy donors are unlikely to have sudden changes in counts; however, the apheresis procedure itself may cause changes that could put donors at increased risk during subsequent collections.

Collection Facilities may set their own timeframes for performing testing on donors in advance of the first collection. Some registries may have specific requirements.

STANDARD:

C9.5 There shall be written documentation of a daily assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

Explanation:

Day-to-day management of the donor is the responsibility of the Collection Facility. It is incumbent on the collection team to confirm the health of the donor at the time of collection. This does not require a complete history and physical examination by a physician for each apheresis collection procedure. Rather, the records from the initial evaluation (including consent for the procedure and documents regarding the goals of the collection procedure) must be immediately available to and reviewed by the collection team. A physician or registered nurse on the collection team must evaluate the donor before each collection procedure to determine if there have been changes in the health of the donor or changes in medications since the last donation.

The interim assessment should include a record of vital signs and a focused donor screening regarding changes in health, medications, or risk factors that are pertinent. Donors should also be assessed according to SOPs determined by the Collection Facility, but at a minimum should include vital signs. The results of interim laboratory tests must be obtained to determine if the donor meets the minimal blood count criteria to proceed with the collection.

This evaluation must be documented as part of the permanent record of the donor. The evaluation must be performed by a qualified member of the Collection Facility team competent in assessing the health status of the donor. Competency shall be defined in the facility SOP manual. The facility shall have a system in place to confirm donor identity so that all samples, labels, and records are appropriately and consistently completed.

Evidence:

The inspector should verify in the donor records that evaluation meets the minimal criteria prior to collection. Documentation of an approved planned deviation should be found if minimum criteria are not met.

STANDARD:

C9.6 *Collection procedures shall include a process for assessing the quality of cellular therapy products to ensure product safety and integrity and to document that products meet predetermined release specifications. Results of all such assessments and procedures shall become part of the permanent record of the product collected.*

C9.6.1 *Methods for collection shall employ procedures that minimize the risk of microbial contamination and are validated to result in acceptable cell viability and collection yield.*

Explanation:

Methods of collection must be validated to result in acceptable cell viability and collection yield. This means that the methods, including reagents, anticoagulants, additives, equipment, and supplies used, and the environment of the collection, have been shown to consistently work in the past to result in a predictable and reliable cellular therapy product. The use of audits and reviews, as defined by the QM Program, are a means of continued validation of collection methods. Any new equipment or collection procedure must be validated prior to implementation and shown to be consistent with or superior to the previous method and result in acceptable cell viability and recovery.

The Collection Facility Medical Director is responsible for defining release criteria for cellular therapy products distributed by the Collection Facility, identifying the tests to be performed, and testing intervals during collection. The release criteria may differ depending on whether the products are released to a processing facility or other external facilities for further manufacturing or directly to a clinical service for administration. This information must be clearly outlined in an SOP. All test results that are available at release must be present in the collection record.

Evidence:

The inspector should verify the validation documentation prior to implementation of collection methods and periodic verification of indicators that show compliance with the predetermined release criteria.

Documentation that the cellular therapy product met release criteria prior to distribution must be present. For products that did not meet release criteria, the required documentation for exceptional release should be present.

Example(s):

Cell viability and recovery data may be routinely captured by the Processing Facility. The Collection Facility should request this information and use it for a retrospective validation of the method of collection.

Additional release criteria that may be pertinent to a cellular therapy product being released to a processing facility or other external facilities include the following: the product is sealed completely without evidence of leakage, product labeling is complete and correct according to expected data, the product has been stored appropriately, expected product or donor samples are labeled and available to accompany the product, and allogeneic donor eligibility determination documentation is available.

STANDARD:

C9.7 There shall be a process to verify the donor's identity and the intended collection procedure prior to initiating the collection procedure.

Explanation:

To ensure donor and procedure accuracy in cellular therapy collections, a process must be implemented which involves a structured review verifying the correct donor identity and the specific collection protocol intended. This process must occur immediately before initiating the collection. The concept mirrors the safety protocols used in surgical settings known as the "Time Out."

STANDARD:

C9.8 Collection methods shall employ appropriate age, sex, height, and weight adjustments to the procedures when applicable.

Explanation:

Specific adjustments to collection procedures may be required in circumstances where donor size is unique, including pediatric and obese donors.

Evidence:

The inspector should verify that the donor collection record reflects the appropriate parameters for pediatric and obese donors as described in the Collection Facility's SOP.

Example(s):

Collection SOPs may reference methods applicable for pediatric donors, such as the use of blood prime with irradiated, CMV-appropriate, or equivalent RBC components and diluent.

The written order for the apheresis or marrow collection volume or cell dose of the HPC or MNC from peripheral blood should be appropriate for the age and size of the donor.

STANDARD:

C9.9 *Cellular therapy products shall be collected in sterile containers appropriate for the product.*

C9.9.1 *Containers shall be securely closed to prevent leakage or contamination prior to distribution.*

Explanation:

Sterile transfer bags designed for cellular blood products are required for the collection of cells from bone marrow. Commercially available disposable sets are available and should be used for collection. Ideally, the tubing connected to the bag should be heat-sealed or sealed with a grommet at the end of the collection prior to transport.

Evidence:

The inspector should observe the end of the collection procedure and verify that the collection container is sealed. The inspector should also verify the presence of heat sealers or grommets in the unit, if applicable, as indicated in the SOP.

STANDARD:

C9.10 *Records shall be made concurrently with each step of the collection of each cellular therapy product in such a way that all steps may be accurately traced.*

C9.10.1 *Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.*

Explanation:

Records must be used during cellular therapy product collection and must be completed in real time as the procedure is performed. For collection procedures, it is acceptable to record the major steps of the collection in groups, such as sets of aspirations rather than every aspiration. Records must be accurate, indelible if in written format, and legible, and must identify the person performing the work and the dates of the various entries. Records of identification codes of personnel including methods to link the name and/or signature to the initials or other identification codes used in other documents and records must be maintained. These records should include dates of employment of the personnel.

In the event that an error or adverse event results during or as a consequence of collection, it is important to perform an investigation in a timely manner. From the appropriate record it must be possible to investigate each critical step, including identification of the individual responsible and the reagents and equipment utilized.

Evidence:

The inspector should review collection records to determine if they were completed in real time and are sufficiently detailed to trace all steps in the collection procedure. The inspector should verify that records of collection have the date of performance of the procedure and staff identification for the steps performed.

Example(s):

The Collection Facility may develop a collection record that will allow documentation of detailed collection steps in real time and identification of staff performing the procedure. Labeling and release of cellular therapy products may be included in such a collection record. Use of electronic records should have the concurrent documentation elements.

In the U.S., concurrent record keeping is required in [21 CFR 1271.270\(a\)](#).

STANDARD:

C9.11 There shall be policies or Standard Operating Procedures addressing safe treatment with ECP.

C9.11.1 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 treatment with ECP.

C9.11.2 A final report of the ECP treatment, including procedure details, shall be documented in the patient's medical record.

Explanation:

ECP is a leukapheresis-based immunomodulatory therapy used in the treatment of acute and chronic GVHD, along with other non-transplant indications involving the separation of leukocytes by apheresis followed by addition of a psoralen, usually 8-methoxypsoralen, and exposure to ultraviolet A light. It is probable that inspectors will increasingly encounter the use of ECP within and associated with transplant programs undergoing inspection, both within and outside of clinical trials.

There are different methodologies for ECP that include both closed and open circuits. In the former, which is the most common, collected leukocytes remain integral to the circuit of the cell separator, while the minority of ECP procedures, the leukapheresis product is detached at some point (e.g., for addition of psoralen and/or UV irradiation). It is possible for patients requiring ECP to attend another hospital that may be at a distance from the transplant unit and have no other relationship aside from provision of ECP. No specific methodology or technology is required or recommended by the Standards.

The transplant physician will provide an order specifying at a minimum the patient's diagnosis and indication for ECP. There shall be documented agreement prior to ECP administration between the transplant physician and the physician overseeing the performance of ECP regarding the proposed regimen, timing of the procedure, and any other factors affecting safe administration. Documentation of all elements (i.e., diagnosis, indication, regimen, timing) applies in cases where the transplant physician and apheresis physician are the same individual.

If ECP is a part of therapy for GVHD or other indications for transplant recipients within a Clinical Program or Collection Facility applying for FACT or JACIE accreditation, the activities must meet the Standards as they apply. If the Collection Facility is independent from the Clinical Program, there should be a written agreement between these facilities.

Upon completion of the series of administration of ECP, a final report of the details of the treatment is provided to the Clinical Program. This may be used in the assessment of the response of the patient to the treatment.

Outcomes and adverse events can be monitored according to the Collection Facility or Clinical Program's QM Program.

Evidence:

The inspector should confirm evidence of patient consent, a therapy plan, procedure details, and a final report. The inspector should verify that there is patient education material about ECP and that consultation has occurred prior to therapy. Documentation of the administration of ECP should be available to the inspector.

Example(s):

The following publications may be used as references when establishing processes for ECP:

- Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, et al. [Consensus conference on clinical practice in chronic GVHD: second-line treatment of chronic graft-versus-host disease](#). *Biol Blood Marrow Transplant*. 2011;17(1):1–17.
- Pierelli L, Perseghin P, Marchetti M, Messina C, Perotti C, Mazzoni A, et al. [Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation \(SIdEM\) and Italian Group for Bone Marrow Transplantation \(GITMO\) consensus process](#). *Transfusion*. 2013;53(10):2340–2352.
- Das-Gupta E, Dignan F, Shaw B, Raj K, Malladi R, Gennery A, et al. [Extracorporeal photopheresis for treatment of adults and children with acute GVHD: UK consensus statement and review of published literature](#). *Bone Marrow Transplant*. 2014;49:1251–1258.
- Dignan FL, Amrolia P, Clark A, Cornish J, Jackson G, Mahendra P, et al. [Diagnosis and management of chronic graft-versus-host disease](#). *Br J Haematol*. 2012;158(1):46–61.

- Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, et al. [Diagnosis and management of acute graft-versus-host disease](#). *Br J Haematol*. 2012;158(1):30–45.
- Connelly-Smith L, Alquist CR, Aqui NA, Hofmann JC, Klingel R, Onwuemene OA, et al. [Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the Writing Committee of the American Society for Apheresis: the ninth special issue](#). *J Clin Apher*. 2023;38(2):77–278.

STANDARD:

C9.12 *Where cellular therapy products are distributed directly from the Collection Facility to the Clinical Program for administration, the Standards related to labeling, documentation, distribution, transportation, and record keeping in Sections [D7](#), [D8.4.5](#), [D10](#), [D11](#), [D13](#), and the [Appendices](#) apply.*

C9.13 *The Collection Facility shall provide the Clinical Facility, Processing Facility, or manufacturer with a summary of all cellular therapy product records relating to the collection procedure and storage procedures performed.*

C9.14 **ADDITIONAL REQUIREMENTS FOR APHERESIS COLLECTION**

C9.14.1 *There shall be a process to assess the extracorporeal blood volume and the need for blood priming.*

Explanation:

The Collection Facility shall establish and maintain a standardized process to assess whether the anticipated extracorporeal blood volume during an apheresis procedure exceeds a safe threshold for the donor. This process must be defined in a written policy or SOP and can include the following components:

- Calculation of extracorporeal blood volume.
- Threshold for Intervention.
- Assessment Process.
- Criteria for Blood Priming.
- Documentation.
- Staff Training.

This process promotes donor safety and aligns with best practices in cellular therapy collection, particularly in pediatric and small adult populations, where extracorporeal blood volume may represent a significant proportion of total blood volume.

STANDARD:

C9.14.2 There shall be a process to ensure compliance with additional requirements of applicable registries.

Explanation:

The Collection Facility shall establish a defined process to ensure that all registry-specific requirements are identified, implemented, and verified during the planning and execution of cellular therapy product collections. This process must be documented in policies or SOPs and integrated into the facility's QM and operations.

The following elements are recommended:

- Registry identification and onboarding.
- Registry requirements.
- Pre-collection planning and verification.
- Labeling and documentation compliance.
- Training and competency.
- Deviation reporting and registry communication.
- Quality oversight.

By embedding registry-specific compliance into workflows, documentation practices, and quality systems, the Collection Facility upholds international standards, protects donor and recipient safety, and supports the traceability and efficacy of cellular therapy products.

STANDARD:

C9.15 ADDITIONAL REQUIREMENTS FOR BONE MARROW COLLECTION

C9.15.1 There shall be a process to determine that the red cell volume and marrow volume to be collected are appropriate for the donor.

Explanation:

The Collection Facility shall implement a process to ensure that the volume of bone marrow and associated RBCs to be collected is both appropriate for achieving the clinical product goals and safe for the donor. This process must be outlined in a written policy or SOP and must be performed under the oversight of a qualified physician experienced in donor evaluation and marrow collection. Elements which can be included in the process include:

- Pre-collection evaluation of donor.
- Volume determination criteria.
- Donor safety limits.

- Collection planning and review.
- Documentation and quality oversight.

STANDARD:

C9.15.2 There shall be a process to ensure compliance with additional requirements of applicable registries.

Explanation:

The Collection Facility shall establish a defined process to ensure that all registry-specific requirements are identified, implemented, and verified during the planning and execution of marrow product collections. This process must be documented in policies or SOPs and integrated into the facility's QM and operations.

The following elements are recommended:

- Registry identification and onboarding.
- Registry requirements.
- Pre-collection planning and verification.
- Labeling and documentation compliance.
- Training and competency.
- Deviation reporting and registry communication.
- Quality oversight.

By embedding registry-specific compliance into workflows, documentation practices, and quality systems, the Collection Facility upholds international standards, protects donor and recipient safety, and supports the traceability and efficacy of marrow products.

STANDARD:

C9.15.3 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.

Explanation:

Commercially available sets with at least in-line 500- and 200-micron filters are certified by the manufacturer, and this certification should be retained for qualification of the supply.

Evidence:

The inspector should review the COA or CE of applicable commercially disposable sets used by the Collection Service.

STANDARD:**C9.16** *ADDITIONAL REQUIREMENTS FOR OTHER TISSUE COLLECTION*

C9.16.1 When a collection kit is received by the collection staff, the staff shall review for adequate instructions and materials for collection, labeling, storage, packing, and transporting or shipping the cellular therapy collection and associated samples.

C9.16.1.1 The collection kit shall be transported or shipped under conditions validated to maintain the designated temperature range from the time it is distributed until it is received by the collection staff.

Explanation:

The validation must be performed by the entity (e.g., commercial manufacturer, Processing Facility) that assembles the kit and is responsible for arranging its transportation or shipping. The robust validation of the conditions under which a collection kit is transported or shipped must account for extremes in temperature ranges given the variable conditions in which the kits may be exposed. At a minimum, the designated temperature range is the range that the entity recommends as the storage temperature. A smaller temperature range is appropriate, but if a larger range is designated by the collection staff, a validation needs to be completed to document that it is adequate. The instructions must also include the conditions under which the collection kit is stored before use.

Evidence:

The inspector should ask to see the instructions provided by the Collection Facility for the use and storage of the collection kit, and the documentation that the kit was correctly used and stored.

Example(s):

Without adequate instructions and monitoring during shipment, collection kits may be placed in unacceptable temperatures including:

- Before delivery to the collection site.
- Before collection when stored awaiting use.
- At the time of collection.

STANDARD:

C9.16.2 Surgically collected cellular material shall be collected at an organization licensed by the appropriate regulatory agency or accredited by the Joint Commission, DNV, Accreditation Commission for Health Care, or other appropriate accrediting body.

STANDARD:

C9.16.3 There shall be a policy or Standard Operating Procedure for the management of tissue collected for further manufacturing to include at a minimum:

C9.16.3.1 A process to minimize the risk of microbial contamination.

C9.16.3.2 Chain of Identity.

C9.16.3.3 Chain of Custody.

C9.16.3.4 Labeling.

C10: CELLULAR THERAPY PRODUCT STORAGE

STANDARD:

C10.1 Collection Facilities shall control and secure storage areas in a manner to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of cellular therapy products.

Explanation:

During hours when Collection Facility staff are unavailable, other areas of the organization may receive a product. The Collection Facility shall have policies or SOPs and agreements in place to manage the safety of the product.

STANDARD:

C10.2 STORAGE DURATION

C10.2.1 Conditions and duration of storage, including temperature of all cellular therapy products, shall be defined and validated.

C10.2.2 Collection Facilities collecting, storing, or releasing cellular therapy products for administration, processing, or further manufacturing shall assign an expiration date and time.

Explanation:

The Collection Facility shall establish a process to be certain that cellular therapy products are stored in a manner that maintains their integrity and potency and that products are not released before all release criteria have been met. Standard [C10.1](#) requires that defined areas for storage be established and that these areas be controlled to prevent the possibility of mix-ups, contamination, or cross-

contamination. This process is further defined as requiring control of the storage duration and the appropriate storage temperature.

The Collection Facility should define what constitutes storage. Any duration of time between the end of the collection and distribution to a Processing Facility or to a recipient for administration constitutes storage. Particular attention shall be paid to the security of the facility and control of temperature and humidity when cellular therapy products are stored in the facility for extended periods, such as overnight to be transported with a second collection from the same donor. Storage temperature and duration shall be defined by the storing facility and shall include conditions for fresh, cryopreserved, and thawed cellular therapy products. Generally, only fresh products are stored in the facility. Products that are awaiting release testing results (e.g., CD34 cell assessment by flow cytometry, the completion of allogeneic donor eligibility determination) may be held in quarantine at one temperature (e.g., up to 4 hours at room temperature) but stored for longer periods at another temperature (e.g., 2–8°C). Temperature ranges and duration shall be determined for each type of product and should be based on the medical literature or the facility's own data. For liquid products, including thawed products, temperature ranges, storage duration, and product expiration date and time shall be established to prevent inadequate viability and to decrease the risk of contamination. Likewise, transport and shipping temperature both from the facility to the Processing Facility and at distribution shall be defined.

Evidence:

The inspector should review the Collection Facility's established storage criteria for all relevant products and inspect the storage conditions and space to confirm adequacy of separation to prevent contamination and mix-ups. Storage temperatures on labeling may also serve as evidence.

Example(s):

EU [Directive 2006/86/EC](#) requires that the expiration date shall be part of the product information for all tissues and cells.

STANDARD:

C10.3 STORAGE TEMPERATURE

C10.3.1 Storage temperatures shall be defined in Standard Operating Procedures.

C10.3.2 Cellular therapy products shall be maintained within a specific temperature range to maintain viability and function.

STANDARD:**C10.4 STORAGE MONITORING**

C10.4.1 Storage devices shall have a system to monitor the temperature continuously and to record the temperature at least every four (4) hours.

Explanation:

It is required that the storage temperature be monitored on a continuous basis and that temperatures be recorded at least every four hours. Temperature records of stored cellular therapy products, including alarm conditions, must be reviewed prior to product distribution. Failure of the device to maintain the target temperature represents a deviation that must be documented and that includes the appropriate investigation and follow-up actions required to determine the integrity and potency of the product. The Collection Facility should establish critical values that, if exceeded, require documentation in the records for those products in storage that did not maintain the target temperature.

C11: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

STANDARD:

C11.1 Standard Operating 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.

Explanation:

Cellular therapy products may be transported or shipped from the Collection Facility to a patient care unit or a Processing Facility within the same, adjacent, or remote buildings for immediate administration, processing, or storage. There shall be a prospective agreement in place between the relevant Collection Facility, Processing Facility, and Clinical Program regarding transport and shipping conditions and the responsibilities of each facility. This agreement can facilitate the maintenance of Chain of Custody and permit tracking and tracing from collection to administration or final distribution.

It is necessary that the cellular therapy product containers be securely sealed and packaged to protect them from potential harm during transit. If the containers are appropriately validated and cellular therapy products are appropriately segregated, the potential to transport multiple products in the same cooler may be acceptable.

STANDARD:

C11.2 The primary cellular therapy product container shall be placed in a secondary container and sealed to prevent leakage.

Explanation:

The cellular therapy product shall be packaged to protect it from potential harm during transit and to prevent exposure of individuals involved in its transport or shipping from potentially infectious agents. Exposure is a risk to individuals in environments where damage to a (usually) liquid product container might occur and normally would involve unanticipated spillage or splashing (e.g., dropped product, motor vehicular accident). When heat sealers are used on the tubing entering the primary container, a minimum of three seals should be applied and the tubing disconnected by cutting through the middle seal to reduce the possibility of leakage. Primary collection bags shall be placed in a secondary securely sealed container such as a zip type bag. An apheresis progenitor cell product and concurrently collected plasma with the same identifier may be placed in a single secondary container. SOPs will vary depending on the distance, whether or not the courier and cellular therapy product leave a building, and the nature of the outside container.

Multiple primary bags from the same donor may be placed into a single secondary sealed container of adequate size. Procedures will vary depending on the transport and/or shipping distance, whether or not the courier and cellular therapy product leave a building, and the nature of the outside container.

STANDARD:

C11.3 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

C11.4 Cellular therapy products transported internally shall be packaged in a closed and rigid outer container.

Explanation:

Internal transport includes the transport within an institution that does not involve crossing public roads. The distance and characteristics of the transport may vary from program to program.

For non-cryopreserved cellular therapy products, a closed outer container must be used and must be made of materials and insulation that will withstand leakage of contents.

The closed and rigged outer container must withstand transport. A tray is not a valid container. Wrapping the secondary bag (with the primary container inside) with a cloth and transporting cells is also not valid.

STANDARD:

C11.4.1 The outer container for internal transport shall be labeled as defined in [Appendix III B](#).

Explanation:

During the risk assessment the Collection Facility must determine if there is a need for additional information to be added to the label.

STANDARD:

C11.5 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.

Explanation:

For transported or shipped cellular therapy products, an appropriate shipping container should be utilized whether product distribution is internal or external. The shipping container must be validated for its intended purpose for all types of products transported (i.e., fresh never frozen products or cryopreserved) and the temperature at receipt of the product should be documented. For cryopreserved products, the container should maintain the temperature at least 48 hours beyond the expected time of arrival at the receiving facility and be “charged” for use following the manufacturer’s instructions.

STANDARD:

C11.5.1 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.

C11.5.2 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.

Explanation:

The cellular therapy product temperature during transit is dependent upon a number of variables, including the transport time, ambient temperature ranges, initial temperature, size of the product, and characteristics of the specific container system. There shall be a prospective agreement among the collecting, processing, and receiving facilities regarding transport and shipping conditions. Most products should not be transported at temperatures above 24°C. Products not previously cryopreserved should never be allowed to cool to temperatures of or below freezing. Transport between facilities shall always consist of the use of an outer container that protects the product from adverse conditions encountered during transport (e.g., air pressure and temperature changes, rough handling) and has been validated to maintain the agreed upon transport temperature. For products transported between sites of a single cellular therapy program, the distance between the Collection Facility and the Processing Facility varies widely. For situations where transport from the

Collection Facility to the Processing Facility requires only minutes, as long as the product is transported safely, a temperature-controlled environment is optional. Transport over longer distances, for more extended periods of time, or transport outside of a building may require that a controlled temperature environment be maintained using an outer container and method validated for the temperature range specified.

For non-cryopreserved cellular therapy products requiring a controlled temperature, a validated thermally insulated outer container should be used with cold packs added as necessary to maintain the required temperature.

Containers for transport of cellular therapy products that are shipped from the Collection Facility or are transported on public roads shall be made of durable material and insulation that will withstand leakage of contents, shocks, pressure changes, and temperature extremes. The containers shall be validated prior to use to achieve proper performance for all expected extremes and maintenance of desired internal temperature. Subsequently, container performance should be verified at least twice yearly, during the warmest and coldest weather periods common for the area.

STANDARD:

- C11.5.3 The outer container shall be secured to prevent unauthorized access.*
- C11.5.4 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 A](#).*
- C11.5.5 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 A](#).*
- C11.6 Cellular therapy products transported or shipped over an extended period of time shall be transported or shipped in a container within a temperature range defined in a Standard Operating Procedure or written agreement and according to manufacturer instructions.*

Explanation:

SOPs for transportation and shipping shall address issues of packaging, labeling, temperature, identification, safety, cellular therapy product integrity, and handling for all cellular therapy products over any length of transit.

Example(s):

Distribution is any transportation or shipping and delivery of the cellular therapy product intended for human administration. It is the physical act of transferring a product within or between facilities. During shipping the product leaves the control of trained personnel at the distributing or receiving

facility. For example, cryopreserved cord blood units are shipped in a vapor shipper from a cord blood bank to a tissue establishment (Processing Facility).

STANDARD:

C11.6.1 Additives to the cellular therapy product should be used for shipping or transporting over a prolonged duration of time.

Explanation:

Guidelines for shipping and transportation shall utilize validated processes. Shipping and transportation orders including the use of additives, if applicable, shall be provided by the Clinical Program or manufacturer. Additives may be combined with the product when shipping cellular therapy products over a long duration of time for further manufacturing is anticipated.

Example(s):

The Collection Facility should consider the use of acid citrate dextrose (ACD), which may be combined with heparin, for shipping cellular therapy products over a long duration of time.

STANDARD:

C11.7 There shall be a risk assessment to evaluate the need for continuous temperature monitoring during transportation or shipment of cellular therapy products.

Explanation:

Some apheresis collection facilities perform their own transports, and when working with third-party manufacturers an agreement must outline the details of the transport. One emphasis of this Standard is for the shorter instances where this may seem overly burdensome. The time and duration should be considered during the risk assessment.

STANDARD:

C11.8 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.

Explanation:

If a patient has undergone high-dose marrow ablative treatment in preparation for transplant, the cellular therapy product is essential for the patient's survival since it may not be possible to obtain additional marrow or blood from the original donor or a second donor in time to prevent complications from aplasia. For this reason, it is important that the product be entrusted to a knowledgeable individual who accompanies it from the distributing facility to the receiving facility.

STANDARD:

C11.9 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.

Explanation:

This Standard requires that communication occur so that the transportation timelines for cellular therapy products are actively managed and collaboratively defined to protect product integrity, potency, and safety for patient use.

Cellular therapy products, whether fresh or cryopreserved, are inherently time- and temperature-sensitive. Prolonged transit times may result in:

- Loss of cell viability.
- Degradation of critical product attributes.
- Increased risk of microbial contamination (especially in fresh products).
- Delays in patient treatment or missed infusion windows.

To mitigate these risks, the distributing facility (e.g., processing, collection when applicable) and the receiving facility (e.g., Clinical Program, infusion center) must jointly establish acceptable transit time limits based on product type and stability data, transport conditions, clinical urgency, and validation studies and regulatory guidelines.

This collaborative approach ensures shared responsibility and mutual understanding of logistical constraints and clinical priorities. The agreed-upon transit time should be documented, validated, and monitored as part of the QM Program. Any deviations must be investigated and assessed for potential product impact.

STANDARD:

C11.10 There shall be contingency plans for alternative means of transport or shipping in an emergency.

C11.11 The cellular therapy product shall be transported or shipped with required accompanying records as defined in Standard Operating Procedures and in compliance with [C7.4](#) as applicable.

C11.12 There shall be a record of the date and time of cellular therapy product distribution.

Explanation:

Accompanying documentation shall include all documentation of allogeneic donor eligibility as defined in [Appendix IV](#). It is not necessary that the records in their entirety accompany a cellular therapy product from the Collection Facility to the Processing Facility. Donor eligibility documents

can be summarized. However, the entire document must be readily and easily accessible when needed.

Labeling requirements are defined in Appendices [II](#) and [III](#).

STANDARD:

C11.13 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.

Explanation:

Outer containers should not be exposed to gamma irradiation or X-ray devices designed to detect metal objects to prevent potential damage that may compromise progenitor cell repopulating capacity. Circumstances may require X-ray by airport security personnel. Those situations should be avoided if possible but complied with as required.

Evidence:

SOPs should address alternative emergency transport and provide direction to request a manual inspection of cellular therapy products rather than X-ray exposure. Inspectors should review the process for qualification of couriers appropriate to the transportation and/or shipping methods provided. Suggest validating the alternative emergency transport plan.

C12: RECORDS

STANDARD:

C12.1 There shall be a records management system for cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

Explanation:

A record is defined as documented evidence that activities have been performed or results have been achieved. A record does not exist until the activity has been performed. Each Collection Facility has the flexibility to develop an individualized system of organizing and maintaining records as long as certain objectives are achieved. The record keeping system must be documented and should include at a minimum:

- Location of new and completed forms.
- Method of error correction that prevents obscuring the original entry and indicates the identity and date of the individual modifying the record.
- Method to prevent destruction or loss of the record.

- Method of documenting modifications and distribution.
- Time of retention and proper storage location.
- System to secure confidentiality of records.
- Methods for filing and transfer of records to archival storage.

Each Collection Facility has the flexibility to develop individualized systems of maintaining and organizing records as long as the objectives of the Standards are achieved. The methods for filing and transferring records to archival storage should be specified in the Quality Manual.

STANDARD:

- C12.1.1 A records management system shall be established and maintained to facilitate the review of records.*
- C12.1.2 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.*
- C12.1.3 For cellular therapy products that are to be distributed for use at another institution, the 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.*

Explanation:

The intent of this Standard is to track the identity of the product to the final recipient. The Collection Facility must inform the receiving institution of the identifiers necessary to complete the tracking.

STANDARD:

- C12.1.4 Records shall be maintained to ensure their integrity, preservation, and retrieval.*

Explanation:

Records may be maintained in more than one location, provided that the records management system is designed to safeguard prompt identification, location, and retrieval of all records. The methods for filing and transfer of records to archival storage should be specified in a policy or in the SOP manual.

Example(s):

It is recommended that recent records be kept on-site and archived records are readily accessible within a reasonable time frame.

Records may be maintained as original paper records, electronic files, photocopies, digital images, or on microfiche or microfilm. Electronic records must be backed up on a regular basis and stored to prevent their loss when records are maintained in common electronic portable formats. Examples of common formats include but are not limited to portable document format (PDF), extensible markup language (XML), or standard generalized markup language.

STANDARD:

C12.1.5 Records shall be accurate and legible.

C12.1.6 Written records shall be indelible.

C12.1.7 Safeguards to secure the confidentiality of all records and communications among the clinical, collection, and processing staff and with donors and recipients shall be established and followed in compliance with Applicable Law.

Example(s):

Breaches in policy that might compromise confidentiality include the following:

- Unsecured patient records.
- Patient charts left unattended in areas where unauthorized personnel or visitors may have access or unattended computer screens displaying patient information in such areas.
- Patient charts or records, in hard copy or electronic format, involuntarily displayed during video conference or video calls.
- Indiscriminate discussions using patient-specific identifiers in the presence of unauthorized personnel or visitors.
- Patient information posted on chalk or bulletin boards that is potentially visible to unauthorized personnel or visitors.
- Release of confidential information without appropriate consent and approval.

Confidential storage may consist of maintaining the records in a locked room with access restricted to authorized personnel or the use of locked file cabinets. The Clinical Program must have SOPs describing the maintenance of donor and recipient confidentiality.

STANDARD:

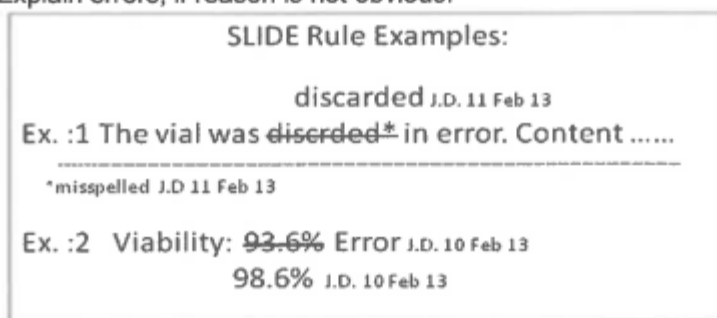
C12.2 The Collection Facility shall define and follow good documentation practices.

Explanation:

Good documentation practices are the guidelines that ensure records are created and maintained in a consistent manner, legible, indelible, accurate, and allow traceability to the person, date, and if

applicable, time, of each event and entry. Good documentation practices should be used for all controlled documents and facility records, including forms, worksheets, training records, calibration logs, cleaning logs. Examples of good documentation practices include:

- Data entry must be clear and legible.
 - Use indelible blue or black ink. Avoid gel pens, felt tip pens, or pencils.
 - Make record entries at the time the task was performed (i.e., concurrently).
 - Do not use ditto marks or continuation lines to include several data entry fields.
 - Do not use correction fluid, correction tape, or overlay of labels.
 - Use the example below as a method to correct errors:
- **Single Line** – Draw a single line through the error. The cross-out must permit the reading of the original information.
 - **Initial and Date** – Add initial of person making correction and date of correction.
 - **Errors** – Explain errors, if reason is not obvious.



Each facility should have an SOP that describes the details of the expected practices. Facility-specific SOPs may include such issues as a standardized format for date and time, expectations for attaching a label or printout to records, or other details.

STANDARD:**C12.3 RECORDS TO BE MAINTAINED**

C12.3.1 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 after the creation of the cellular therapy product record, date of the cellular therapy product's distribution, disposition, or expiration, whichever is latest, or according to Applicable Law.

Explanation:

Because QM documents provide evidence of compliance with the QM requirements, they should be maintained for as long as they are applicable to the processes, equipment, supplies, and reagents currently being used. Archived records do not need to be immediately available.

Evidence:

Collection Facilities must identify Applicable Law, and applicable regulatory authorities, in pre-inspection documentation for FACT or JACIE inspectors to reference when preparing for the inspection. Traceability records must be kept for at least 30 years per [Directive 2006/86/EC](#) and comply with General Data Protection Regulation for data protection.

The inspector should review the Collection Facility's records related to QM, including documentation of periodic personnel training and cellular therapy product characteristics, and inspect the QM documents to confirm compliance with the facility's requirements. Likewise, the inspector should examine paperwork to determine if adequate records are maintained that identify the processes, equipment, supplies, and reagents currently being used for all significant steps of collection.

STANDARD:

C12.3.2 Records of validation studies for a collection procedure shall be retained at a minimum until the procedure is no longer in use and no products remain in storage that were collected using that procedure.

Explanation:

The validation study for a current collection procedure needs to be maintained as long as the procedure is still being utilized in order to demonstrate compliance with validation requirements.

STANDARD:

C12.3.3 *Employee records shall be maintained in a confidential manner, as required by Applicable Law.*

C12.3.4 *Cleaning and sanitation records shall be retained for a minimum of three (3) years or longer in accordance with Applicable Law or by a defined program or institution policy.*

Explanation:

An exception to the 10-year requirement for retention of Collection Facility records is for the documentation of cleaning and sanitation. These records only need to be retained for at least three years after creation but should include cleaning schedules, methods, and identification of personnel responsible for cleaning. There should also be documentation for the initial training and retraining of personnel as needed.

Evidence:

If documentation of cleaning and sanitation is performed directly by the Collection Facility's institutional environmental services department, then the Clinical Program should have knowledge of this documentation and the ability to show that it is complete.

STANDARD:

C12.3.5 *Records to allow tracking and tracing of cellular therapy products shall be maintained in a confidential manner for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, or as required by Applicable Law, whichever is latest.*

Explanation:

Records related to cellular therapy products should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for collection is critical for tracing purposes in the event of a problem, recall, or adverse event.

Evidence:

The inspector should ask who is responsible for records and where these records are maintained to determine if an organized system is in place that allows timely retrieval.

This can be accomplished by selecting products from the Processing Facility and utilizing the product unique identifier to trace the records to the Collection Facility. The person responsible for records can then demonstrate where the records are maintained and how they are organized. The records related to the collection procedure should be provided in a timely fashion. The records should then be reviewed and the manufacturers and lot numbers of all reagents and supplies used in the collection should be available in the records.

Example(s):

In the U.S., NMDP requires that records pertaining to the traceability and tracking of all aspects of the manufacture of the products managed by them to be retained indefinitely, as should records of adverse reactions and post-donation complications, treatment interventions, and recovery.

Per the EU Directive, tissue establishments must keep the data necessary to ensure traceability at all stages. Data required for full traceability must be kept for a minimum of 30 years after clinical use.

STANDARD:

C12.3.5.1 These records shall include the identity of the Collection Facility, unique numeric or alphanumeric identifier, collection date and time, product code, and donor and recipient identification as found on the original container.

Explanation:

In order for the records to allow tracking and tracing of cellular therapy products, it is required that the Collection Facility keep all the required elements in the Standard as part of the record.

STANDARD:

C12.4 Recipient and donor records including, but not limited to, consents and records of care shall be maintained in a confidential manner as required by Applicable Law for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration of the product, whichever is latest.

Explanation:

Recipient and donor files (either electronic or hard copy) must be maintained with a secure system that guarantees absolute confidentiality and is in compliance with Applicable Law on confidentiality and data protection.

Evidence:

The inspector should be alert to breaches in policy that potentially compromise recipient or donor confidentiality.

Example(s):

In the U.S., NMDP requires that consent documents, screening and testing records, and records pertaining to allogeneic cellular therapy product collection, processing, labeling, packaging, storage, distribution, and final disposition be maintained indefinitely.

In EU Member States, donor records required for full traceability must be maintained for a period of 30 years. Consequently, records must be maintained for the duration of follow-up. In the U.S.,

HIPAA regulations on confidentiality and data protection apply. In the EU, the comparable law or regulation is [Regulation \(EU\) 2016/679](#).

STANDARD:

C12.5 Research records shall be maintained in a confidential manner as required by Applicable Law or for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

Explanation:

Records related to cellular therapy products collected under IRB-approved research protocols should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. If research records are stored independently of patient records, the same considerations regarding confidentiality apply. The sponsor of the research, IRB, or governmental authorities may place specific requirements for long-term maintenance of research records.

Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for collection is critical for tracing purposes in the event of a problem, recall, or adverse event.

Evidence:

The inspector should ask who is responsible for records, where these records are maintained, and determine if an organized system is in place that allows timely retrieval of research records.

STANDARD:

C12.6 ELECTRONIC RECORDS

C12.6.1 The Collection Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures. For all critical electronic record systems:

Explanation:

The definition of an electronic record is "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." This Standard requires Collection Facilities to establish and maintain a current listing of all critical electronic record systems specific to cell collection. As facilities utilize more electronic systems, it is important that they maintain a list of which ones are critical.

Electronic records are considered critical when any one of the following points occurs:

- Used as a substitute for paper.
- Used to make decisions based upon the data stored and/or created by the electronic record system (including outcome analysis).
- Used to make calculations via automated functions.
- Used to create and/or store information that are inputs into critical processes (whether the electronic record system is used during critical processes or used as source data for critical procedures).

Critical procedures include collection procedures, labeling, storage conditions, and distribution.

It is not the intent of the Standards to include hospital-based systems and clinical medical records. These systems are typically inspected by hospital-based regulatory and accrediting organizations. Furthermore, Collection Facilities may not have the authority to direct validation studies on these systems. Any data system that does exist within the scope of control of the facility is required to meet these Standards.

Each Collection Facility must determine in advance whether the staff will depend on an electronic record or a paper record to perform a regulated activity. This determination should be documented for all records created and maintained by the facility.

Evidence:

Inspectors should assess the Collection Facility's list of critical electronic record systems to confirm it includes all electronic record systems used by the facility that meet the criteria in this standard. Additionally, a list that matches critical record types to specific record systems should be provided pre-inspection (e.g., electronic laboratory record versus paper eligibility record).

The inspector should determine the scope of electronic records used by the Collection Facility and any circumstances where the electronic record is used as a substitute for a paper record.

If electronic records are used in addition to paper records, the inspector should evaluate the electronic records to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.
- The system has limited access by authorized individuals.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.

- Documentation that the individuals performing the development, maintenance, or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- There are systems and processes in place for storing and retrieving electronic records in case of failure.

Example(s):

Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

If a computerized system is used to generate SOPs, validation is not required since the quality and safety of a cellular therapy product would not be directly affected. However, if a computerized system is used to make a critical calculation (e.g., calculation of total blood volume [TBV], collection efficiency) and the electronic calculation is the only calculation performed, validation is required to ensure that the calculation is always performed correctly under any circumstances. However, if the computerized calculation is used to confirm a manual calculation, the extent of validation need not be as extensive as in the previous example.

In the U.S., for electronic records used as a substitute for paper, the inspector should refer to the FDA document [Part 11, Electronic Records; Electronic Signatures - Scope and Application](#) (2003), for guidance to assess the validation procedures, as well as the applicable requirements of HIPAA. In the EU, the inspector should refer to the Modular Requirements for Electronic Records and Document Management ([MoReq](#)).

STANDARD:

C12.6.1.1 There shall be policies, Standard Operating Procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

C12.6.1.2 There shall be a means by which access is limited to authorized individuals.

C12.6.1.3 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

Explanation:

In case of error or ambiguity, a method must exist to allow traceability of data entered into the electronic record system to the staff member who performed the entry. This may take the form of an audit trail maintained internally by software, or it may take the simple form of a login sheet on which staff members record their session with the electronic record system and identify what data was entered in that session.

Example(s):

To identify individuals responsible for record entries, several options exist. Examples include using a sign-in sheet when using the system or using a worksheet to create an audit trail of each data element. More sophisticated systems usually have an automated system that tracks record entry based upon an individual's login credentials.

STANDARD:

C12.6.1.4 There shall be written policies and Standard Operating Procedures for record entry, verification, and revision.

C12.6.1.5 A method shall be established or the system shall provide for review of data before final acceptance.

Explanation:

The final review and acceptance of entered data do not require a second individual to verify the data. Nor does the identification of individuals responsible for record entries need to be automated. The intent of the Standard is to be certain that all data is verified to be correct and to maintain documentation of who has entered pieces of information.

STANDARD:

C12.6.1.6 There shall be documented training of personnel in the system's use.

C12.6.1.7 There shall be a defined process for continued competency of personnel in the system's use.

Explanation:

Personnel must be trained to appropriately use all critical electronic record systems (including record entry, verification, and revision) and backup processes when the critical systems are not available. This training must be continuous, including initial training and ongoing training as SOPs are revised and issues with the use of critical electronic record systems are identified. As with all other cellular therapy collection activities, the staff members who utilize the electronic record system must be trained for such use. Moreover, just as SOPs are required for cell collections, SOPs must also be in place to describe how to enter, process, and retrieve data using the electronic record system. Competency of staff using the system must be documented on a regular basis (annually at a minimum) and must also be documented with changing versions of the systems in use.

STANDARD:

C12.6.1.8 There shall be a defined process for the use of electronic signatures.

Explanation:

The term "electronic signature" shall be clearly and precisely defined. The definition shall specify what constitutes a valid electronic signature and delineate how the electronic signature will be used and interpreted. The policy defining electronic signature shall include the following elements: the method of creating the signature (e.g., typing a name, using a mouse to draw, clicking an "accept" button), the elements included (e.g., first and last name, role/title, date and time stamp), a statement that the electronic signature is legally binding, and the type of records to which the signature applies (e.g., manufacturing batch records, regulatory documents, audits, validations review, contracts, agreements). The method of creating a signature and the intended use may vary among Collection Facilities.

The Collection Facility needs to define when, under what conditions, and for which programs it is appropriate to utilize electronic signatures.

STANDARD:

C12.6.1.9 Unique identifiers shall be maintained.

C12.6.1.10 There shall be the ability to generate true copies of records in both human readable and electronic format suitable for inspection and review.

C12.6.1.11 There shall be protection of records to enable their accurate and ready retrieval throughout the period of record retention.

C12.6.1.12 All system modifications shall be authorized, documented, and validated prior to implementation.

C12.6.2 For all critical electronic record systems under the control of the Collection Facility, there shall be processes for and documentation of:

Explanation:

Establishment of an electronic record keeping system that meets one or more of the criteria for a critical electronic record system requires validation. The extent of validation is somewhat dependent upon whether the computerized system was developed in-house, custom-built by an outside vendor or consultant, or developed from off-the-shelf software.

Validation procedures of critical electronic systems include, as appropriate, such elements as:

- Documentation of development requirements and function.
- Verification that calculations are performed correctly.

- Evidence that records reproducibly contain the desired information.
- Tests of system functions under “worst case” scenarios such as system overloads (e.g., too many simultaneous users, too many simultaneous processes being performed [such as too many programs open on a Windows desktop]), and power failures.
- A method for data verification before final entry.
- Internal consistency checks to verify that values are within defined ranges.
- Restricted entry of data to match predefined value limits.
- Required entry of data with field information limited with choices for data consistency.
- Source data is derived from pre-defined sources such as fixed forms. “Monitoring for data integrity” means establishing assurances that data has not been changed either by accident or by intent, and this requires access to original documents whenever possible, along with a plan for verification of the electronic system data by comparison to original data.
- Evidence of a schedule of regular backups that include storage of backup data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the backup copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include the information entered into the database, acceptable sources of the entered data, and a description of system maintenance and development history.
- Formal and documented training in system use requirements for all personnel.
- Evidence of SOPs in place for computer record-keeping systems.
- Regular quality audit trails.
- A mechanism to report deviations and to ensure that problems are reported and resolved.
- Evidence that changes to records do not obscure previously entered information.
- Documentation that deleted electronic files have been converted to non-electronic media such as microfilm, microfiche, or paper in a manner that preserves the content and meaning of the record.

Evidence:

While details of the validation system may be located in an institutional department of information services or elsewhere, the Collection Facility shall have a summary of the validation available to the inspector.

If electronic records are used in addition to paper records, the inspector should evaluate the electronic record system to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.

- The system has access limited to authorized individuals and that documentation is generated to identify which individuals have accessed the system and made record entries.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.
- Documentation that the individuals performing the development, maintenance or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- Procedures are in place to provide for record keeping in the event of failure of the electronic record system, and that the staff members who may have to follow these procedures are trained in their use.
- A process for generating backups of records maintained electronically is in place.

STANDARD:

C12.6.2.1 Prospective validation of systems, including hardware, software, and databases.

C12.6.2.2 Installation of the system.

C12.6.2.3 Numerical designation of system versions, if applicable.

C12.6.2.4 Authorization and validation of all system modifications prior to implementation.

C12.6.2.5 Systems development including the verification of calculations and algorithms.

C12.6.2.6 System maintenance and operations.

C12.6.2.7 Monitoring of data integrity.

C12.6.2.8 Backup of the electronic records system on a regular schedule.

C12.6.3 For each critical electronic record system, there shall be an alternative system to allow for continuous operation of the Collection Facility if the critical electronic record system is not available. The alternative system shall be validated, and collection staff shall be trained in its use.

STANDARD:**C12.7 RECORDS IN CASE OF DIVIDED RESPONSIBILITY**

C12.7.1 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.

Explanation:

Most, but not all, Collection Facilities will have some of the activities or services covered by the Standards performed by another entity in the same institution or in another institution. In such cases, the conditions under which the activity or service is performed must be documented through written agreements. When the facilities are within the same institution, the responsibilities may be written in a policy or other type of document.

These agreements should clearly define roles and responsibilities for critical tasks. All such agreements should be dated, reviewed and renewed on a regular basis, and include provision for the maintenance of records following termination of the agreement. How such agreements are executed is a function of the type of Collection Facility.

The agreements must clearly define the role and responsibility of the contracted facility to comply with all governmental regulations and Standards that are applicable to the performed services. The contracted facility must also adhere to critical processing, storage, and distribution standards defined by the contracting facility, although the contracted facility does not have to be accredited by FACT or JACIE. The contracting facility must have implemented a process to verify that services are performed in compliance with all applicable Standards and regulations.

The Collection Facility's records should include relevant contracts and agreements, and the Collection Facility is responsible for compliance with the Standards. The entire record of the outside facility(ies) need not be duplicated for the facility record. However, the facility record should allow tracing and tracking of relevant information to the correct source.

The facility record should indicate where the product was collected, stored, and/or administered but does not need to contain a record of the supply and reagent lot numbers used for steps performed at the Processing Facility or Clinical Program. The facility should verify that such relevant and appropriate records will be maintained by the facility that performs the work. Records of allogeneic donor eligibility screening and testing must be provided to the facility.

Maintenance of records must be specified in the SOPs, and it must be clear who is responsible for maintaining records. In general, records should be sufficiently detailed to enable tracking and tracing from a donor to a recipient or final disposition and vice versa.

Donor and recipient confidentiality must be maintained through the use of identifiers whenever the identity of the unrelated donor must remain anonymous. The location of each facility must be

known to the relevant personnel at each facility but should not be known to the recipient. To that end, the Processing Facility may not know the identification or location of the Collection Facility in the case of a product obtained through an unrelated donor registry. Facilities that participate in programs such as NMDP or other donor registries will have well-defined procedures for divided responsibility. Applicable rules and regulations regarding the sharing of confidential information must be followed.

QM Plans must include the concept of written agreements even if no agreements are currently in place at the Collection Facility. The purpose is to outline the general process for establishing agreements should the need arise. Extensive detail is not required, but the plan must minimally describe who is responsible for reviewing and approving agreements and require that agreements include the external facility's responsibility to comply with the Standards in their activities relating to the Processing Facility.

In the event the Collection Facility (or entities with which the facility has agreements) terminates its activities, it is essential that traceability data and material concerning the quality and safety of the cellular therapy products be provided to the relevant parties.

Evidence:

The inspector should review the process for establishing agreements or contracts with entities outside of the Collection Facility that participate in product processing, testing, storage, transport or other critical services that might affect the quality of the product. In the case of donor registries, they should be accredited by the WMDA. If agreements exist, examples should be reviewed by the inspector for adherence to the facility's established process. In all cases, a process must exist for the development and implementation of such agreements. The inspector should verify that there is a process in place to assess compliance with the requirements and that this process is effective. Copies of those agreements should be available to the inspector on the day of the inspection.

Example(s):

Written agreements should be reviewed every two years, similar to SOPs, although a greater or lesser time interval may be appropriate under some conditions. The effective dates of an agreement could be specified within the agreement itself. It would be helpful to have a list of written agreements to inventory whether each one is reviewed and renewed appropriately.

For services provided with the same institutions, shared policies or procedures that address expectations and performance quality can be interpreted as agreements. For Collection Facilities receiving products facilitated through donor registries, agreements may be through those registries.

Such agreements may include, but are not limited to donor qualification, determination of donor suitability and eligibility (allogeneic donors only), collection of the product, donor or product testing, and long-term storage.

Stand-alone facilities may execute agreements directly with the service providers (or institutions for which they provide services), whereas agreements involving Collection Facilities in academic institutions may be between the institution and the service provider.

Audits of external facilities may be accomplished by reviewing the Collection Facility's internal and external audit reports, performing on-site inspections for compliance, receiving period performance reports from the facility, or the Collection Facility can audit its experience with the contracted facility using data that it defines and collects. There may be other alternatives, but the contracting facility must verify that their contracted services are meeting requirements.

STANDARD:

C12.7.2 The Collection Facility shall furnish to the facility of final disposition a copy of all cellular therapy product records relating to the collection procedure.

Explanation:

The Collection Facility shall have an applicable SOP that describes the dissemination of cellular therapy product records relating to the collection procedure to Processing Facilities, Clinical Programs, and manufacturers as applicable if divided responsibility does occur. The records might include information about the quantity of the product or other relevant information of the collection procedure (e.g., need to stop the procedure and re-start, use of two product bags).

Evidence:

The inspector should determine if divided responsibility occurs regarding any aspect of the cellular therapy process and ask to review a relevant recipient file to confirm that an appropriate mechanism is in place to track and trace the process from both beginning to end and the end to the beginning.

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PART D: PROCESSING FACILITY STANDARDS

- [D1:](#) General
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PART D: PROCESSING FACILITY STANDARDS

D1: GENERAL

STANDARD:

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

Explanation:

Part D Standards apply to the processing of cellular therapy products, regardless of tissue source (e.g., bone marrow, umbilical cord blood, peripheral blood, other tissue source). The Standards cover all processing performed in the Processing Facility regardless of product destination.

Processing Facilities are not required to serve Clinical Programs or Collection Facilities that are FACT or JACIE accredited; however, the general philosophy of the Standards and accreditation programs is to encourage all organizations to become accredited in order to demonstrate that they meet minimum requirements for quality cellular therapy. It is the responsibility of the Processing Facility to have written agreements with those third parties to ensure compliance with these Standards.

Evidence:

Processing Facilities will provide information to FACT or JACIE, as appropriate, regarding the cell types and processing methods within their facilities. This confirms that an appropriate inspection team is selected, and that the on-site inspection agenda adequately covers all processes.

Example(s):

In the U.S., processing of MNCs and some HPCs will often be under IND or experimental studies approved by an IRB; however, unless otherwise stated, the Standards still apply to those cells and processing methods conducted within the Processing Facility. Separate facilities and laboratories in which cell processing takes place will be inspected and accredited separately.

In the EU, cellular therapy products to be used in clinical trials and Advanced Therapy Medicinal Products (ATMPs) must be manufactured in GMP-licensed facilities. The manufacturing of products in these facilities can be accredited by appropriate bodies, but the GMP-facility can also supply the FACT or JACIE-accredited facility with their products under a service level agreement. Find more information regarding the EU directives and regulations at:

- [Directive 2001/20/EC](#) (clinical trials).
- [Directive 2001/83/EC](#) (MPs).
- [Regulation \(EC\) No 1394/2007](#) (ATMPs).

STANDARD:

D1.2 The Processing Facility shall abide by Applicable Law.

Explanation:

FACT and JACIE are voluntary inspection and accreditation programs co-founded by ASTCT and ISCT (International Society for Cell & Gene Therapy). Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with the Standards does not guarantee compliance with all Applicable Law; regulations issued by national governments must also be followed. It is the responsibility of the individual Processing Facility to determine which laws and regulations are applicable. In many cases, regulations by governmental authorities outside the immediate jurisdiction of the facility may apply; for example, when a facility sends cellular therapy products to or receives cellular therapy products from outside of its immediate jurisdiction. This is particularly important when such products are genetically manipulated in another jurisdiction before they are returned to the Processing Facility for patient use. Requirements also vary based on the type of product, the stage of research, etc.

Compliance with other organizations' standards or governmental regulations does not ensure that the FACT-JACIE Standards have been met. Government regulations supersede any organization's standards if those regulations set a higher standard or are inconsistent with a specific standard. However, if a FACT-JACIE Standard is more rigorous than a governmental regulation, that Standard must be followed.

Evidence:

While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with Applicable Law. Evidence of compliance with the Standards will require pre-inspection information identifying prevailing governmental authorities and documentation of certificates, permits, or licenses.

Example(s):

Cellular therapy products that are cultured prior to use, such as antigen-specific T-cell lines or mesenchymal stromal cells, would be considered extensively or substantially manipulated. In such cases, the processing would be regulated through an IND or IDE (in the U.S.) or as an ATMP (in the EU). When those requirements are more stringent than the Standards, the regulatory requirements must be followed. In the U.S, there may be additional licensure requirements for cellular therapy products not defined under the [21 CFR Part 1271 Subpart D](#) GTP regulations yet are required by appropriate governing bodies to comply with Applicable Law.

In the U.S., minimally manipulated cellular therapy products from related donors are largely regulated under the [21 CFR 1271 Subpart D](#) GTP regulations (covered under Section 361 of the Public Health Service Act, and therefore are referred to as 361 products), with the exception of products collected from marrow. However, if products are from an unrelated donor or are extensively manipulated, combined with a device, or if their use is non-homologous (does not perform the same function in the recipient as in the donor), they fall under the [21 CFR Part 210–211](#)

GMP regulations. GMP products are regulated under the Public Health Service Act Section 351 and therefore are referred to as 351 products. Minimally manipulated HPC, Marrow is currently not regulated under either of these federal regulations. It is the responsibility of the Processing Facility to verify that the contracting entity for whom it performs services possesses an approved IND or BLA.

In the Member States of the EU, both HPCs and T cells fall under the European [Directive 2004/23/EC](#) of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, as well as the implementing Directives [2006/17/EC](#) and [2006/86/EC](#). Under these Directives, a tissue establishment license from the Competent Authority is required, and the tissue establishments need to notify the Competent Authority of serious adverse events and reactions of tissues and cells. Additionally, some member states require specific authorizations delivered by the Competent Authority for minimally manipulated cell products that are not classified as MPs.

[Directive 2001/83/EC](#) regulates cellular therapy products that are classified as MPs. These include somatic cellular therapy MPs and gene therapy MPs. The TMP-[Regulation \(EC\) No 1394/2007](#) entered in force on December 30, 2007 to include tissue-engineered products as well. The consequence of classification as an MP is that a GMP environment is required for the production of these cells. Furthermore, each Member State in the EU may add on additional regulations to the directives that also must be followed. Member State-specific regulations will not be detailed here. The current EU Directives will be replaced by [Regulation \(EU\) 2024/1938](#) of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application. The regulation will be fully applicable from August 7, 2027.

STANDARD:

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

Explanation:

Applicable Law may require registration or certification with the government or may require accreditation from professional organizations for the activities performed within the facility.

Evidence:

Current certificates, registrations, permits, or licenses will demonstrate which areas of a facility have been authorized by other organizations or governmental authorities.

A copy of a validated FDA registration document or EU equivalent will be sent to the FACT or JACIE office respectively with the accreditation application materials. The inspector may ask to see it on-site. The Processing Facility Director or Medical Director should know who in the institution is

responsible for the registration and where a copy may be obtained. It is not appropriate to request a faxed copy from the regulatory agency during the on-site inspection.

In the EU, the inspector would expect to see the tissue establishment license by the Competent Authority and, if applicable, a GMP-manufacturing license if ATMPs are being manufactured at the same site.

Example(s):

Any facility that is involved with the collection, procurement, screening, testing, packaging, processing, storage, labeling, or distribution of cellular therapy products in the U.S. may be required to register with the FDA annually ([21 CFR Part 207](#), [Part 807](#), and [Part 1271](#)). This registration requires a listing of the activities in which the Collection Facility engages and a listing of each applicable type of cellular therapy product that is regulated under GTP or regulated as a medical device, drug, or biological drug ([21 CFR Part 207](#) and [Part 807](#)). More information regarding the requirements and process for FDA registration can be found on the FDA webpage [Tissue Establishment Registration](#) (2021). Note that each activity performed by the institution must be registered, regardless of who performs the activity. A Collection Facility that is within a larger institution such as a hospital or medical center may combine its registration with other services related to the same regulations. Activities that may be performed by a Collection Facility include the screening of donors for infectious disease risk to determine eligibility or temporary storage of the collected material.

In the EU, the Competent Authorities in the Member States shall ensure that all tissue establishments have been accredited, designated, authorized, or licensed and that these establishments have implemented the EU Directive and other national regulations, where applicable.

Examples of verified compliance with regulations include acceptable FDA audits, hospital accreditation, (e.g., Joint Commission, DNV, HFAP) state licensure, licensing of tissue establishments by the Member State in the EU, CLIA certification, OSHA inspections, or accreditation by the AABB, ASHI, EFI, CAP, or any other applicable accreditation body.

STANDARD:

D1.3 The Processing Facility shall have a Processing Facility Director, a Processing Facility Medical Director, a Quality Manager, and a minimum of one (1) additional designated staff member. The designated team shall have been in place and actively performing cellular therapy product processing for at least twelve (12) months preceding initial accreditation.

Explanation:

Processing Facilities are required to have been in place and operating with trained staff under the direction of the Processing Facility Director and Medical Director for a minimum of one year prior to initial accreditation. It is possible that a facility will have undergone leadership changes. In that

case, as long as a director (Processing Facility Director or Medical Director) has the required credentials specified in [D3](#), the facility is eligible for accreditation.

During this 12-month period, Processing Facilities need to process enough cellular therapy products to compile an adequate amount of data to validate processes and demonstrate compliance with the Standards. Facilities should have provided service for the minimal number of autologous and allogeneic transplants required for the associated Clinical Program to be eligible for FACT or JACIE accreditation. See [Appendix I](#) for details.

Personnel competency must be maintained even if a Processing Facility's activities decline throughout an accreditation cycle. If no cellular therapy products are processed over an extended period of time, as defined by the Processing Facility, competency must be maintained and assessed using mock products similar to a cellular therapy product.

Evidence:

Current employee files and CVs should document evidence of length of employment and experience with cellular therapy product processing.

D2: PROCESSING FACILITY

STANDARD:

D2.1 There shall be secured and controlled access to designated areas appropriate for the processing procedure(s) and for storage of equipment, supplies, reagents, cellular therapy products, and records.

D2.1.1 The designated area for processing shall be in an appropriate location of adequate space and design to minimize the risk of airborne or surface microbial contamination.

D2.1.2 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.

Explanation:

There must be clearly designated areas for cellular therapy product receipt and storage that are separate from the processing area. This Standard may be interpreted differently for smaller facilities (e.g., processing less than 50 products per year) versus larger facilities. An SOP should be on-site to confirm segregation when multiple products are being processed simultaneously (e.g., three technicians working on a long bench, management of data entry into an electronic device at the point of processing).

If research activities are performed in the proximity of the Processing Facility, the facility must demonstrate adequate separation of processing and research activities. Human and non-human cells must not be in areas proximate to each other. Cellular therapy products, supplies, and reagents must be clearly segregated either by physical methods or by proper use of signs.

Evidence:

Processing Facilities must submit a floor plan of the facility prior to the on-site inspection. Inspectors use these floor plans to gain a preliminary understanding of the designated areas and how processes and products flow throughout the facility. The inspector will tour the facility during the on-site inspection, including all locations where cellular therapy products are received, processed, stored, and distributed. The areas should be designed to facilitate proper workflow and cleanliness.

In addition to processing space, there should be adequate desk space for segregation of worksheets and documents essential for processing each cellular therapy product to avoid mix-ups of documents from products that are being processed simultaneously. In the U.S., facility regulations are detailed in [21 CFR 1271.190](#).

Observation of the organization, design, location, and amount of space available in the facility can determine if it is adequate for the number and types of processing it performs and if the processing environment is adequate to minimize the risk of product contamination. The inspector should also evaluate the inventory control system to determine if it is adequate to prevent the use of outdated or damaged supplies and reagents.

A demonstration by Processing Facility staff of where each activity is typically performed and how a cellular therapy product moves through the facility can demonstrate compliance or illustrate problems. The inspector should inquire how the facility segregates products and product paperwork if more than one product is undergoing processing on a given day. Inspectors should note what safeguards are in place to prevent mislabeling, inappropriate product release, or mix-ups that could result in cross-contamination of either products or product records.

If research activities are performed in the same area, the Processing Facility should maintain evidence of cleaning of shared equipment. The facility should demonstrate segregation of cellular therapy product records, the product itself, supplies, and reagents. For shared equipment, the facility must have documentation that maintenance schedules are followed.

If there are no processing procedures occurring on the day of the on-site inspection, the inspector should ask that a mock collection be demonstrated. This allows assessment of the adequacy of the environment as well as the procedural details and staff knowledge.

Example(s):

A cluttered Processing Facility without a defined workflow is evidence that the facility does not have adequate space or is poorly designed. The inspector should be able to identify where receiving, labeling, processing, storage, and record keeping are taking place.

STANDARD:

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

Explanation:

The space used for processing and storage of cellular therapy products should be well-defined and adequate, and there should be designated space for preparation and storage of reagents and equipment.

If the location of the liquid nitrogen freezers prohibits limited access (e.g., a shared facility with other users), individual freezers containing cellular therapy products for recipients must be securely locked. Storage facilities must exist that clearly separate and distinguish tissues and cells prior to release and/or in quarantine from those that are released and from those that are rejected in order to prevent mix-up and cross-contamination between them. A process must be in place for secure quarantine of products with incomplete or unacceptable release testing results to prevent inadvertent release without proper authorization. Cryopreserved products stored in quarantine must be clearly labeled as such, although they do not have to be stored in freezers dedicated to that purpose.

The Standard also applies to cellular therapy products stored overnight as fresh samples in refrigerators (quarantine or non-quarantine) before further processing or distribution.

Example(s):

Where applicable, [21 CFR 211.42\(b\)](#) in the U.S. requires that facilities have adequate space and segregation measures for the orderly placement of equipment and materials to prevent mix-ups and contamination between different components, including cellular therapy products. Separate or defined areas, or other control systems, must be in place for operations as necessary to prevent contamination or mix-ups.

STANDARD:

D2.2 The Processing Facility shall provide adequate lighting, ventilation, access to sinks for handwashing and to toilets to prevent the introduction, transmission, or spread of communicable disease.

Explanation:

The layout and design of the Processing Facility must minimize the risk of error and permit effective cleaning and maintenance in order to avoid cross-contamination and mix-ups. The facility should be situated in an environment that presents minimal risk of contaminating materials and products and allows personnel to perform their duties safely. In the U.S., facility regulations are detailed in [21 CFR 211.52](#).

Evidence:

The inspector should observe the organization, design, location, lighting, ventilation, and amount of space to determine if the Processing Facility is adequate for the number and types of procedures it performs, and to ensure that it minimizes the risk of introduction, transmission, or spread of communicable disease.

STANDARD:

D2.3 Environmental conditions shall be controlled to protect the safety and comfort of personnel.

D2.4 There shall be a written assessment of critical Processing Facility environmental parameters that may affect cellular therapy product viability, integrity, contamination, or cross-contamination during processing, storage, or distribution.

D2.4.1 The written assessment shall include temperature, humidity, air quality, and surface contaminants at a minimum.

D2.4.2 Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.

Explanation:

The Processing Facility must identify the facility parameters that should be controlled and monitored based on their potential effect(s) on cellular therapy product quality. The facility must perform an assessment of facility conditions to determine if any parameters need to be controlled, monitored, and recorded. This includes parameters that may directly affect the product and also conditions that would diminish the integrity of supplies and equipment or the performance of personnel (such as temperature or extreme humidity). Some equipment has operating limits, but others do not.

There must be monitoring of any parameters that have been determined to be critical. These parameters should be defined by an SOP and compliance documented through quality records. Risk should be reassessed with the occurrence of any significant change.

Evidence:

The Processing Facility should have documented assessment of the risk of parameters, such as temperature, humidity, air quality, and surface contaminants, that could influence the quality of the cellular therapy product, spread contaminants in the environment, or interfere with equipment or personnel performance. The facility should have an acceptable range for control parameters necessary to maintain appropriate environmental conditions within the facility. The acceptable range of temperature, for example, may range between 20–24° Celsius, and humidity may range between 15–75%. Most importantly, the facility needs to demonstrate that their acceptable range for environmental parameters is supported by documented scientific evidence. Whether

environmental parameters are controlled by the laboratory or a central facility, there must be a mechanism to control any variations within the acceptable environmental parameters.

If no parameters are controlled, the Processing Facility must provide documentation of its reasoning prior to the inspection. It is the inspector's responsibility to determine while on-site if the facility has appropriately identified parameters that affect cellular therapy product viability, integrity, contamination, sterility, or cross-contamination. If the inspector believes a parameter that has not been identified should be controlled, this will be indicated in the inspector's report and included for discussion by the FACT or JACIE Accreditation Committee.

The Processing Facility should document if the humidity and cellular therapy product temperature went outside of the manufacturer's specifications. The inspector should evaluate the magnitude of the excursions and what corrective action was taken by the facility.

Example(s):

On-site inspections have revealed instances when humidity impacted the safety of the cellular therapy product. For example, in one particularly humid climate, liquid nitrogen freezer lids defrosted enough to prevent them from completely closing.

STANDARD:

D2.4.3 The Processing Facility shall qualify environmental control systems and validate cleaning and sanitation procedures appropriate for the environmental classification and degree of manipulation performed.

Explanation:

Methods to process cellular therapy products that expose them to greater risks of contamination or cross-contamination, such as open systems, warrant more stringent environmental controls. The requirement for surface microbial monitoring is intended to provide control where the product is handled or processed directly, rather than where product is contained and transiently stored. If a Processing Facility uses procedures that may result in contamination or cross-contamination, it must assess if air quality and surface contaminants must be controlled.

Environmental monitors for measures of air quality, such as particle counts or microbial colony counts, are recommended and should be based upon risk assessment for the identified measures.

The typical Processing Facility may not require a classified environment provided that processing steps requiring exposure to the environment are performed in a biosafety cabinet. However, a facility that extensively manipulates cellular therapy products and performs procedures with many "open" steps, such as transfer to another container without the use of a sterile connecting device or entering a product by a spiking method outside of a biological safety cabinet, requires a greater level of environmental control. Environmental monitors for controlled space should include

measures of air quality, such as particle counts and microbial colony counts, to minimize airborne contaminants.

Evidence:

The inspector should verify that the environment is acceptable for the type of manipulations carried out in the Processing Facility, and that processing steps take place in an appropriately controlled environment. There must be ongoing monitoring of any parameters that have been determined to be critical, and these parameters should be defined by an SOP with compliance documented through quality records.

Example(s):

If the Processing Facility performs more than minimally manipulated procedures or procedures with many open steps, the environmental conditions and monitoring of laminar flow cabinet and clean room shall be defined in accordance with ISO 14644 methodology.

Contaminants in the Processing Facility can be minimized through air filtration and by ensuring that the air pressure within the facility is positive to the surrounding areas (room pressure monitors should be used).

STANDARD:

D2.5 The Processing Facility shall document facility cleaning and sanitation and shall maintain order sufficient to achieve adequate conditions for operations.

Explanation:

Processing Facility cleaning and sanitation must be performed on a regular basis in order to prevent contamination and cross-contamination of cellular therapy products. The methods used must be specified by an SOP. While the benchtop, biological safety cabinet, and equipment surfaces are most often cleaned and disinfected by facility personnel, other surfaces that may be cleaned by outside vendors or institutional environmental services, such as floors, walls, and ceilings, also fall under this Standard. The facility, together with the cleaning services vendor, must establish SOPs for this activity, and these SOPs should assign responsibility for the personnel performing the sanitation procedures, the methods used, and the schedule. Facility cleaning must be documented and the records maintained for at least three years.

Frequency of cleaning and sanitation should be based on environmental monitoring, the number and nature of cellular therapy products processed, and on incidence of microbial contamination in the Processing Facility. The facility should verify that disinfectants and detergents used are adequate to reduce the risk of contamination.

A system of rotating cleaning agents and disinfectants should be in place, and environmental monitoring with swabs or contact plates should be conducted in areas where processing occurs. A

system of actions and alerts should be used when monitoring detects that contamination is present in the product or in the facility.

Evidence:

Records of cleaning and sanitation activities and concomitant microbial monitoring within the Processing Facility should be available for inspector review. SOPs that include agents to be used, frequency, responsibility, and, in the case of an outside vendor, its qualification, must be available for review.

Example(s):

Cleaning by a service vendor can be documented using a checklist completed by its staff that confirms cleaning was performed according to the method and schedule defined by the appropriate SOP.

GMPs contain more detailed requirements, and the extent to which they must be followed depends on the type and stage of the cellular therapy product. GMPs for “351” products in the U.S. (i.e., products regulated solely under section 351 of the PHS Act) can be found in [21 CFR Part 210](#), [Part 211](#), and [Part 610](#).

Cleaning agents and disinfectants used in areas where cellular therapy products are handled should be alternated, though this is not specifically required.

More than one type of disinfectant is recommended according to [EU GMP Annex 1: Manufacture of Sterile Medicinal Products](#).

STANDARD:

D2.6 *The Processing Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, visitors, and volunteers.*

D2.7 *The Processing Facility shall have a written safety manual that includes instructions for action in case of exposure to liquid nitrogen; communicable disease; and chemical, biological, radiological, electrical, or fire hazards.*

Explanation:

The Processing Facility policies and SOPs, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to governmental regulations regarding safety. Processing Facilities should post warning signs for biohazards wherever radioactive materials are in use. It is critical that the program has a safety manual and that staff members have ready access to instructions for prompt response. In case of exposure to a hazardous material. If an institution-wide manual is used, safety, infection control, or biohazard waste disposal procedures that are unique to the facility must be covered in the facility's SOPs. The use of electronic training programs that cover safety and infection control is

acceptable, but there must be evidence that the staff has completed all relevant training satisfactorily.

For patients receiving frozen HPC products, the staff members involved in identification and infusing HPC products (grafts) should be informed about the potential danger of liquid nitrogen exposure. Those facilitating the transportation of liquid nitrogen cylinders to and from the laboratory by vendors should take caution to minimize risks of exposure to visitors, patients, and staff members. Such measures may be documented following a risk assessment by the storage facility.

An adequate means of egress in areas where liquid nitrogen is stored, moved (e.g., elevators), or transported is required for the safety of personnel and potentially the public. Activities such as eating, drinking, and smoking must be prohibited in the Processing Facility.

Evidence:

The inspector will review the written safety manual (including a description of the general liquid nitrogen safety plan) to verify how personnel are prepared to handle accidents and emergencies and verify who is responsible for maintaining the emergency supplies. The inspector will also verify who is responsible for notifying and reporting events when applicable.

If a processing procedure is underway during the day of inspection, the inspector should observe personnel for use of protective clothing and other biosafety precautions and verify if this is being done according to written instructions. The inspector should examine employee files for compliance and training in biological, chemical, and radiation safety (when appropriate), in addition to reviewing safety procedures. Compliance with national and international regulations should be addressed by the Processing Facility and verified by the inspector. The presence of unnecessary or non-functioning equipment, excessive traffic from unauthorized personnel, and inappropriate storage of reagents or supplies may also contribute to an unsafe environment and should be noted by the inspector.

Example(s):

Safety training, including universal precautions ("standard" precautions per the Centers for Disease Control and Prevention) for handling cellular therapy products, is a requirement of OSHA in the U.S. Equivalent regulations apply in other countries.

The safety manual may be an institution-wide document available by hard copy or electronically. Access to the institutional safety manual solely by computer is not acceptable without a written policy describing how to access the information in the event of a computer failure or down time. An SOP that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice.

A condensed or summarized hard copy of the institutional safety manual should be kept in the facility. In this case, there must be written documentation of how the condensed version is kept updated with institutional safety manual revisions.

STANDARD:

D2.8 All waste generated by the Processing Facility's activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with Applicable Law.

Explanation:

Poor management of medical waste exposes personnel, waste holders, and potentially the community to injuries, infections, and possible toxic effects. Hazardous waste generated by the Processing Facility's activities includes a broad range of materials, including biohazard soiled or contaminated supplies, sharps, chemicals, radioactive material, viral vectors, genetically modified cells, and the cellular therapy products themselves. All medical waste must be discarded in a safe manner according to written protocols for the disposal of biohazard waste and in accordance with Applicable Law. Contaminated materials shall be placed in appropriate bags and containers marked with the international infectious substance symbol. Radioactive and chemical waste must be discarded using methods approved by appropriate governmental agencies.

Evidence:

The inspector should examine how medical waste and chemicals are handled and discarded (e.g., incinerator, waste field) and compare their observations with the written protocols.

Example(s):

Contaminated materials soiled with biohazards may typically be discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, through the use of a sanitary landfill. Sharps such as needles and blades, whether or not they are infected, should be considered highly hazardous healthcare waste and placed for disposal in puncture-proof containers. Chemicals such as cytostatic drugs, used in purging procedures, shall be discarded in accordance with Applicable Law.

STANDARD:

D2.9 There shall be a written policy for personal hygiene and the use of personal protective equipment and attire.

D2.9.1 The policy shall define the protective clothing to be worn upon entering the work area and while working within it.

STANDARD:

D2.9.2 The policy shall define personal protective equipment appropriate for the activities and classification of the environment to be worn while handling biological specimens.

D2.9.3 Such personal protective equipment shall not be worn outside the designated work area.

Explanation:

PPE is equipment worn to reduce exposure to hazards that could cause injury or illness in the workplace, and to protect the cellular therapy product from exposure to hazards that could cause injury or illness to the recipient. Personal hygiene includes hand hygiene that is undertaken to reduce disease transmission.

Processing Facilities must follow their institutional policies regarding appropriate PPE (e.g., gowns, goggles, plastic aprons, gloves) that must be worn when handling potentially hazardous substances.

All people who may come in contact with human blood or body fluids must wear appropriate PPE. This includes those exposed to cellular therapy products. To prevent the spread of hazardous substances, PPE must be removed before leaving the workspace. The use of PPE must be defined by an SOP.

Evidence:

One way to demonstrate compliance with hygiene is for the program to have a policy on handwashing.

Example(s):

The type of exposure that may be encountered will determine the appropriate protection. If aerosol exposure is likely, a mask, goggles, and gowns or aprons should be worn. Gloves must be worn whenever potential infectious exposure exists and when aseptic procedures are required to protect the personnel and product.

STANDARD:

D2.10 There shall be a biosafety plan consistent with IBC requirements that addresses genetically modified cellular therapy products in accordance with Applicable Law.

D2.11 Oxygen sensors shall be appropriately placed and utilized in areas where liquid nitrogen is present.

D2.11.1 Oxygen sensors shall have visible and audible alarms with appropriate settings to ensure safety of personnel.

STANDARD:

- D2.11.2 In areas where liquid nitrogen is present, oxygen sensors shall be placed to alert staff working in the area to evacuate and to notify any staff responding to the alarm not to enter the area.*
- D2.11.3 Instructions for staff responding to the alarm shall be posted at the entrances of areas where liquid nitrogen is present.*

Explanation:

When liquid nitrogen is used in the Processing Facility, proper ventilation and the use of oxygen sensors are required. The risk of asphyxia should be assessed wherever liquid nitrogen is used or stored. A low oxygen sensor will alert staff when there is an oxygen-deficient atmosphere in the room to prevent entry or encourage egress. Oxygen sensors and alarms must comply with Applicable Law and regulations. The use of alarms, both inside the area and external to the area where liquid nitrogen is stored, must be present to alert staff to dangerous oxygen levels. Additional guidance on alarms is provided in section [D9.6](#).

Evidence:

The inspector should confirm that oxygen sensors are located in the Processing Facility where liquid nitrogen is present. Both visible and audible alarms in the appropriate location are needed. Alarms must be detectable both inside and outside the facility where liquid nitrogen is present to prevent access while the alarm is active. Remote notification may supplement the visible and audible alarms. The facility defines the level at which the oxygen alarm should be set to allow sufficient time for evacuation to a safer location.

Example(s):

Risks to asphyxiation are real, and dangerous low levels of oxygen do occur. In December 2023, the U.S. Chemical Safety and Hazard Investigation Board released its [final report](#) on the 2021 accident which claimed the lives of six employees by asphyxiation. According to OSHA (2015, [Standard 1926.1202](#)), an oxygen concentration below 19.5% is considered a hazardous atmosphere, exposing employees to a risk of acute illness or death. The minimum safe level of atmospheric oxygen can range between 15–19%. Setting the alarm below 19.5% may allow enough time for activation of ventilation or other mitigation measures in liquid nitrogen storage areas or other affected areas. Visual or remote controls can assist staff in responding immediately to situations where there is an interruption of vapor phase nitrogen or electricity during freezing.

STANDARD:

D2.12 When a collection kit is prepared and sent to collection staff, there shall be adequate instructions and materials to collect, label, store, pack, and transport or ship the cellular therapy product and associated samples to the Processing Facility.

D2.12.1 The collection kit shall be transported or shipped under conditions validated to maintain the designated temperature range from the time it is distributed until it is received by the processing staff.

Explanation:

The validation must be performed by the entity (e.g., commercial manufacturer, Processing Facility) that assembles the kit and is responsible for arranging its transportation or shipping. The robust validation of the conditions under which a collection kit is transported or shipped must account for extremes in temperature ranges given the variable conditions in which the kits may be exposed. Temperature during shipment should be monitored. At a minimum, the designated temperature range is the range that the entity recommends as the storage temperature. The instructions must also include the conditions under which the collection kit is stored before use.

Evidence:

The inspector should ask to see the instructions provided for the use and storage of the collection kit, and the documentation that the kit was correctly used and stored.

Example(s):

The instructions should be detailed enough to cover different time points including:

- Before delivery to the collection site.
- Before collection when stored awaiting use.
- At the time of collection.
- During return to the Processing Facility.

Without adequate instructions and monitoring during shipment, collection kits may be placed in unacceptable temperatures.

D3: PERSONNEL

STANDARD:

D3.1 PROCESSING FACILITY DIRECTOR

- D3.1.1 *There shall be a Processing Facility Director with a medical or doctoral degree and a minimum of two (2) years of experience, or [an Advanced Degree as defined in these Standards](#), with a minimum of ten (10) years of experience. Experience shall be in the field of cellular therapy and in the management and oversight of the scope of activities carried out by the Processing Facility.*

Explanation:

The Processing Facility Director must be an individual with a medical degree or doctoral degree and two years of experience or an Advanced Degree and ten years of experience. Experience must be in a relevant science. An Advanced Degree is defined as a master's degree in a biological science that is enhanced by ten years of experience in cellular therapy processing, manufacturing, laboratory management, and knowledge of applicable regulations, and quality systems.

The Processing Facility Director must be qualified by training or experience (or combined training and experience) for the scope of activities carried out by the Processing Facility. The director must demonstrate competency according to the scope of their responsibilities. The director should understand the procedures, identify critical points and expected outcomes, be capable of making improvements and corrections in procedures and accompanying documents, and understand basic laboratory techniques used by the laboratory. In addition, they must have practical training, experience, and be knowledgeable for each new procedure that is introduced into the facility, even if they are not responsible for performing the procedure (e.g., DC vaccines, mesenchymal stromal cell culture, flow cytometry). Experience requirements may exceed those required by the Standards based on Applicable Law.

The Processing Facility Director may also serve as the Processing Facility Medical Director if appropriately credentialed (i.e., with a medical degree).

Evidence:

The Processing Facility Director is required to submit a CV that demonstrates combined training and experience. Alternatively, written confirmation can be a letter from each of the directors of the programs, departments, and/or institutions where this experience was obtained. The letter must include at least the types of cellular therapy products, processing methods, and job duties in the Processing Facility. If it is not possible to obtain letters from the directors where initial experience was gained, letters from directors at subsequent places of experience are acceptable.

Some regions of the world may have degrees that are equivalent to the doctoral degree. If a Processing Facility Director has such a degree, significant and compelling information regarding the degree requirements must be submitted to demonstrate equivalency. Documentation of degrees and experience should be submitted in advance so the inspector can review the documentation prior to the on-site inspection.

Example(s):

The Processing Facility Director's experience and training may include formalized fellowship in transfusion medicine or post-doctoral training in performing or supervising cell processing procedures relevant to cellular therapy.

An anatomic pathologist/dermatologist who is actually functioning day-to-day in a cell processing role for two years is an example of relevant experience.

EU regulations require the responsible person to have a minimum of two years of practical experience in the relevant fields. The Processing Facility Director can be the responsible person (according to the European [Directive 2004/23/EC](#)).

STANDARD:

D3.1.2 The Processing Facility Director shall be responsible for all Standard Operating Procedures, technical procedures, performance of the processing procedure(s), supervision of staff, administrative operations, and the QM Program, including compliance with these Standards and Applicable Law.

Explanation:

The Processing Facility Director is responsible for all SOPs and administrative operations of the Processing Facility, including compliance with the FACT-JACIE Standards and with all other Applicable Law. Specific duties of the director required by the Standards include:

- Development of and compliance with the QM Program.
 - Approval of the Quality Manager.
 - Designation and review of proficiency tests.
 - Review of adverse events and deviations.
 - Report on quality program to Clinical Program Director.
- Definition of tests and procedures for cellular therapy product assays.
- Review of processing records prior to distribution.
- Review and approval of labels.
- Review results of microbial cultures.
- Authorization of release of products.
- Authorization of return of products not meeting return requirements.

The Processing Facility Director may have other responsibilities, but they should be available to Processing Facility personnel at all times. Knowledge of day-to-day activities in addition to the specific duties listed above allows for the Processing Facility Director to be aware of overall operations in the facility. The director's responsibilities should be outlined in a job description or in the SOP Manual for the facility. Although a designee may fulfill some of the responsibilities of the director, ultimate responsibility for the above duties will rest with the director.

When a director works remotely, the Processing Facility must clearly outline how the responsibilities of the position are performed. Responsibilities for remote directors do not differ from the responsibilities of an in-person director; however, there may be more challenges in completion and documentation of these responsibilities. The following are requirements for remote directors:

- A director must be fluent in the language of the facility and must meet the minimum credentials, training, experience, competency, and continuing education requirements as defined in the current edition of Standards.
- A director is responsible for leading the facility and for providing oversight of the services, personnel, cellular therapy products, and procedures.
- A director is expected to be actively engaged in the decision-making process, policy and procedure development, and QM activities. This involvement must be documented.
- When a director is physically not present at the facility site, there must be a qualified designee named and documented to manage those responsibilities that require immediate or in-person attention. Further, all critical director functions must be covered.
- A qualified designee must meet minimum director qualifications for the delegated function and have a defined scope of authority and activity.

Specific responsibilities of each director and medical director type are defined in the Standards. Documentation of director involvement in these responsibilities must be available on-site for review.

Evidence:

The inspector should verify that the Processing Facility Director has a sufficient on-site physical presence to execute the above responsibilities. Evidence may be confirmed by examining documents, records, audits, and other documents requiring director review in order to confirm that they are available to the Processing Facility personnel when needed. Evidence should also be present to confirm that the responsibilities of the director are actually performed by the designated individual and in a timely fashion.

Documented evidence of a remote director's specific involvement in leadership and oversight of the Processing Facility, in addition to performance of designated responsibilities, must be available on-site for review by the inspector. Examples of documentation include, but are not limited to:

- Meeting minutes.
- Record review.

- Personnel review.
- SOP review and approval.
- Donor or recipient management.
- Investigative report review.
- Qualification/validation studies: plan and final report review and approval.
- Planned deviation pre-approval.
- Cellular therapy product release authorization.

STANDARD:

D3.1.3 The Processing Facility Director shall have performed or supervised a minimum of five (5) cellular therapy product processing procedures in the twelve (12) months preceding initial accreditation and a minimum average of five (5) cellular therapy product processing procedures per year within each accreditation cycle.

Explanation:

Experience and training are expected only for the type of processing for which the Processing Facility Director is responsible. The director must have performed or supervised a minimum of five processing procedures in the year preceding accreditation and shall have performed or supervised a minimum average of five processing procedures per year within each accreditation cycle.

The term “supervised” in this Standard differs from the supervision of technologists during training or directly observing processing procedures. The term refers to the director’s supervision of the procedures by ensuring the technologists are appropriately trained and have reviewed and follow the SOPs. The director is also responsible for reviewing the technologists’ worksheets and verifying procedures satisfactorily result in efficacious cellular therapy products.

Evidence:

Involvement of Processing Facility Director in cell processing or supervision of staff members performing the procedure can be evident from cell processing record review by the Director. In addition, evidence of supervision of the laboratory staff members can also be examined from cell processing-related audit and validation records, staff competency and proficiency assessments, etc.

Example(s):

Evidence of compliance may include cell processing record review or review of staff supervision of yearly competence and proficiency results with the Director’s signature or initials and date of activity.

STANDARD:

D3.1.4 The Processing Facility Director shall participate in a minimum of ten (10) hours of educational activities related to HPC transplantation, quality management, or cellular therapy annually.

Explanation:

The Processing Facility Director must participate regularly in educational activities related to the processing or use of cellular therapy products to broaden their scope of knowledge and keep up with current advancements in the field.

Evidence:

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not a Processing Facility Director meets this Standard. Recognized educational activities include both certified CME credits (preferable) and non-credit educational hours, including internal presentations and conferences.

To assess the appropriateness of the amount and type of continuing education, Processing Facilities must submit the following information for each of the completed continuing education activities within each accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, grand rounds).
- Topic of activity (e.g., cell administration).
- Date of activity.
- Approximate number of hours of activity.

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Use of a formalized CPD record such as the FACT [Educational Activities Form](#) or equivalent is recommended. Use of this form is not required, but it can be used to document compliance with continuing education requirements.

Example(s):

Evidence of compliance may include formal or informal study. Educational activities do not necessarily require large financial resources. The Processing Facility may choose to establish its own guidelines for the number of hours from each type of activity that can be counted toward the minimum requirement in this Standard. Activities for continuing education may include cell processing, cryopreservation, graft engineering, tumor purging from the graft, QM related to cellular therapy and transplantation.

Examples of appropriate continuing education activities include:

- The annual meetings of professional societies that include information directly related to the field.
- Grand Rounds, if specifically related to cellular therapy or diseases for which cellular therapy is a therapeutic option. The continuing education log must include the title, subject, and date of the presentation.
- Presentation of CME/CPD lectures.
- Presentation of a paper at a scientific meeting.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or online tutorial.
- Review of articles in the medical literature related to cellular therapy, including those where the journal offers CME credits.
- Local or regional journal club, potentially including the preparation time.
- Morbidity and Mortality conferences.

ASTCT also offers an [online Learning Center](#) that hosts recordings from its many educational events. Additional educational opportunities are provided by ESH and EBMT through their respective e-learning programs ([ESH](#) and [EBMT](#)).

STANDARD:

D3.2 PROCESSING FACILITY MEDICAL DIRECTOR

D3.2.1 There shall be a Processing Facility Medical Director who is a licensed physician with a minimum of two (2) years of postgraduate education, including training and practical and relevant experience for the scope of activities carried out in the preparation and clinical use of cellular therapy products.

Explanation:

The Processing Facility Medical Director must be a physician licensed to practice medicine in the area in which the Processing Facility is located and must have a minimum of two years combined postdoctoral training or practical relevant experience in the preparation and clinical use of cellular therapy products.

The Processing Facility Medical Director must be qualified by training or experience for the scope of activities carried out by the Processing Facility. Experience requirements may exceed those required by the Standards based on Applicable Law.

Practical relevant experience might mean day-to-day interaction in the preparation of clinically relevant attributes of cellular therapy products, attending scientific conferences with clinical and cell processing content, or clinical and cell processing regulatory activities.

Evidence:

Documentation of the medical degree is required to obtain a medical license; the license will be considered to be documentation that the director is a physician. The inspector can review these documents for evidence of experience prior to the on-site inspection.

Written confirmation can be a letter from each of the directors of the programs, departments, or institutions where practical relevant experience was obtained. The letter must include at least the following information: type of cellular therapy products, summary of role in release of products, and a description of job duties. If it is not possible to obtain letters from the directors where initial experience was gained, letters from directors at subsequent places of experience are acceptable.

The Processing Facility Medical Director is required to submit a CV that demonstrates training and experience prior to the on-site inspection. The inspector should review this information in advance and request additional information if there are questions. Evidence of experience should be apparent.

Example(s):

Experience can consist of time spent in training in another Processing Facility or on-the-job training. The Processing Facility Medical Director's experience or training may include a fellowship or post-doctoral training, but it must include at least one year of experience in performing or supervising cell processing procedures relevant to cellular therapy. EU regulations require the responsible person to have a minimum of two years of practical experience in the relevant fields (according to the European [Directive 2004/23/EC](#)).

STANDARD:

D3.2.2 The Processing Facility Medical Director shall be directly responsible for all medical aspects related to the Processing Facility.

Explanation:

The Processing Facility Medical Director is directly responsible for the medical aspects of the processing procedures. Specific responsibilities requiring documentation of director review include:

- Review of adverse events associated with cellular therapy product administration.
- Authorization for the distribution of non-conforming cellular therapy products and products released due to urgent medical need.
- Review and approval of clinically relevant SOPs.
- Approval of medically relevant planned and unplanned deviations from SOPs.

- Notification when medically relevant endpoints are not achieved.
- Authorization for cellular therapy product discard.

The Processing Facility Medical Director may have other responsibilities, but they or a designee should be available to Processing Facility personnel at all times. The director's responsibilities should be outlined in a job description.

Evidence:

The inspector should review the Processing Facility's organizational chart to verify compliance with the Standard in addition to the job description and areas of responsibilities as described in SOPs, the QM Plan, and other documents. Evidence of availability may be confirmed by examining documents, processing records, audits, and other records requiring the Facility Medical Director's review in order to confirm that the director is available to the facility personnel when needed.

Example(s):

ABO incompatibility in relation to volume is a specific topic that requires dedicated training and competency assessment, as cellular therapy product issues are different among apheresis, marrow collection, and cord blood collection.

Similarly, cord blood preparation for administration requires clinicians have dedicated training and competency in providing proper orders for washing, diluting, or reducing RBCs from the cellular therapy product.

STANDARD:

D3.2.3 The Processing Facility Medical Director shall have performed, supervised, or reviewed a minimum of five (5) cellular therapy product processing procedures in the twelve (12) months preceding initial accreditation and a minimum average of five (5) cellular therapy product processing procedures per year within each accreditation cycle.

Explanation:

Experience and training are expected only for the type of processing for which the Processing Facility Medical Director is responsible. Documentation of the medically relevant procedures performed or supervised by the Processing Facility Medical Director should be available.

The term "supervised" in this Standard differs from the supervision of technologists during training or directly observing processing procedures. The term refers to the evidence of Medical Directors' engagement in medically relevant policies and procedures, review of medically relevant cell processing records, audits, validations, etc. The records of all cellular products with exceptional release should be reviewed by the Processing Facility Medical Director. The Medical Director should be knowledgeable about cell processing, cryopreservation, and storage of HPC but does not need

to perform the procedure or supervise the technologists in the Processing Facility. Compliance with this Standard may be evident by examining cell processing record review of medically relevant items by the Medical Director. The direct supervision of laboratory staff will primarily fall under the scope of the Processing Facility Director. The purpose of this Standard is not to duplicate tasks of the Facility Director. However, for facilities where the Medical Director also serves as the Facility Director, the Medical Director must comply with [D3.1.3](#) Standards.

STANDARD:

D3.2.4 The Processing Facility Medical Director shall participate in a minimum of ten (10) hours of educational activities related to HPC transplantation or other cellular therapies annually.

Explanation:

The Processing Facility Medical Director must participate regularly in educational activities related to the processing and use of cellular therapy products to broaden their scope of knowledge and keep up with current advancements in the field.

Evidence:

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not a Clinical Program Director meets this Standard. Recognized educational activities include both certified CME credits (preferable) and non-credit educational hours, including internal presentations and conferences.

For additional Evidence and Examples related to continuing education, see the guidance following [D3.1.4](#).

STANDARD:

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 Standard Operating Procedures intended to monitor compliance with these Standards 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.

Explanation:

The Processing Facility must identify at least one person responsible for QM. The title held by this individual may differ among facilities and is not relevant as long as the duties include those

described in the Standards. The Processing Facility Quality Manager should be an individual with a minimum of an undergraduate degree in the field of health sciences or biological sciences and who has training in the field of cellular therapy product processing or QM.

The Quality Manager has responsibility for preparing, reviewing, approving, and implementing QM policies and SOPs and must confirm that they comply with the Standards and all Applicable Law before implementation. A key role of the Quality Manager is to develop systems for auditing Processing Facility activities to confirm compliance with the written SOPs. A Quality Manager may have an operational role in the Processing Facility as long as they do not audit their own work.

Formal training and certification in one or more aspects of QM is encouraged but not required. Formal training may include practical work experience in a facility, fellowship, or certification program. Additional information related to certification in quality is available from the [American Society for Quality \(ASQ\)](#) and the [National Association for Healthcare Quality \(NAHQ\)](#). Finally, resources are available on both the FACT and JACIE websites to assist Quality Managers in advancing their knowledge and skill sets.

The Processing Facility Director or other knowledgeable personnel may play a role in conducting or reviewing audits, especially audits that may include work performed by the Quality Manager. The director as specified throughout the Standards may play an active role in reviewing the work of the technologists, including QM procedures. The Processing Facility Director is ultimately responsible for the QM Plan and proper implementation of the plan for the Processing Facility. SOPs should clearly define the role(s) of the Processing Facility Director, Processing Facility Medical Director, the Quality Manager, and other QM personnel in the QM Program.

Evidence:

The inspector should look for documentation (e.g., audit reports, proficiency test reports) that a Quality Manager is in place and performs or oversees the functions covered in the QM section of the Standards. During inspection, the inspector may want to inquire about SOPs in place to avoid bias when Quality Managers must review their own work.

Example(s):

Formal training may include practical work experience in a Processing Facility, fellowship, or a certification program. Additionally, the Quality Manager's CV, job description, organizational chart, audit reports, or proficiency test reports (if applicable) are all examples of documentation that may demonstrate compliance.

For Processing Facilities that perform minimal manipulation (e.g., 361-designated products) and have a low processing volume, the Standards do not prohibit the Quality Manager from participating in facility activities, as many facilities or institutions may not be large enough to support QM staff for the Processing Facility alone. However, the Quality Manager should not review or approve technical procedures for which they are solely responsible. In such cases, that review

should be delegated. The Quality Manager may review SOPs where they have contributed to the activity following a reasonable time period to reduce the potential for bias. What constitutes a reasonable time lapse may vary based on the type of activity being reviewed. Calculations requiring a double check before proceeding to the next processing step may need to be reviewed within a few minutes or hours, whereas audits more often will be performed weeks or months after the activity that is being audited was performed. The reasonable time period for specific activities to be reviewed may be defined by the Processing Facility's policies and SOPs.

The scope of work and reporting structure should be outlined in the policy. The independence of the Quality Manager from manufacturing does not necessarily prevent them from interacting with the Processing Facility Director, but independence in approving and rejecting cell therapy quality control measures needs to be demonstrated in record. The independence from cellular therapy product manufacturing by the Quality Manager may be evident from the role of the Quality Manager in designing and approving audit validation, rejecting materials and equipment not compliant with pre-defined acceptance criteria, etc. The role of Quality Manager extends to approving and rejecting all procedures or specifications impacting product manufacturing, including identity, purity, sterility, and potency.

The Processing Facility Director or Medical Director can also assume the Quality Manager role as long as there is evidence of external review of their activities (e.g., by the institutional quality department, other supervisory individual) related to proper implementation of a QM Plan for the Processing Facility. Such a situation may occur more often in a small facility (e.g., one with two to three full-time employees), where technical responsibilities do not allow time for the activities of QM supervision, and the complexity is restricted to minimal manipulation of homologous products.

The [FACT Quality Handbook](#) and the [FACT Quality Management Series webinars](#) are resources available through the FACT website. Additionally, JACIE offers [Quality Management and Certification in Hematopoietic Stem Cell Transplantation and Cellular Therapy: The JACIE Guide](#). These are all excellent resources for Quality Managers.

STANDARD:

D3.3.3 The Processing Facility Quality Manager shall participate in a minimum of ten (10) hours of continuing education activities related to cellular therapy, cell processing, and quality management annually.

Explanation:

The amount of activity required to meet this Standard depends on the type and frequency of the educational activities. The Quality Manager must participate regularly in educational activities related to cellular therapy product processing, transplantation, and QM to broaden their scope of knowledge and keep up with current advancements in the field.

Recognized educational activities include both certified CME credits (preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are referenced in this Accreditation Manual and may include topics specific to cellular therapy and diseases in which cellular therapy is a therapeutic option.

There are many ways to meet this Standard, and the Standard is not meant to be prescriptive. A total of ten hours in combination of these topics is required. Each topic does not need to be covered in ten hours individually. The inspector should assess the documented number and content of continuing education activities and use their judgment to determine whether or not a Quality Manager meets this Standard.

For additional Evidence and Examples related to continuing education, see the guidance following [D3.1.4](#).

STANDARD:

D3.4 STAFF

D3.4.1 The number of trained and competent processing personnel shall be adequate for the number of procedures performed and shall include a minimum of one (1) designated trained individual with an identified trained and competent backup individual to maintain sufficient coverage.

Explanation:

There must be sufficient technical and other support staff for the scope and number of services provided. The Processing Facility shall have an adequate number of trained processing personnel to perform all processing activities in compliance with the FACT-JACIE Standards and Applicable Law. Trained and competent technical personnel sufficient for the type of processing performed and in proportion to the volume of work are required.

The Processing Facility Director should indicate personnel responsible for specific activities in the Processing Facility and must confirm that they are approved for the execution of those activities. Their continued competence must be documented. Personnel involved in cell processing must be trained on how to use each piece of equipment properly.

Some Processing Facilities have processing volumes low enough for one staff member to perform the processing; however, there must be a contingency plan if that staff member is unable to perform the necessary duties (e.g., illness, unexpected emergencies). Access to additional qualified individuals to process cellular therapy products and prepare them for administration when backup is needed must be available, although these individuals do not have to be directly employed by the facility. The Processing Facility can use a risk-based approach to determine the number of primary and back-up staff required to adequately cover the scope and volume of work performed.

Evidence:

The adequacy of staffing may be ascertained by reviewing full-time and part-time staffing levels; staff turnover; and frequency and types of errors, accidents, and deviations from SOPs. The inspector must review the plan for staffing in the event of absences. It may also be useful to talk directly with the technical personnel regarding workload requirements and the adequacy of staffing. The inspector should confirm the documentation of continued competency assessment.

Example(s):

Insufficient staffing may be indicated by excessive overtime, rapid turnover of personnel, incomplete record keeping, or an increase in adverse events.

D4: QUALITY MANAGEMENT

STANDARD:

D4.1 There shall be a QM Program that incorporates key performance data.

D4.1.1 The Processing Facility Director shall have authority over and responsibility for ensuring that the QM Program is effectively established and maintained.

Explanation:

The QM Program includes quality assurance, control assessment, and improvement activities. The strategy (QM Plan) and associated policies and SOPs drive the operation of the QM Program. The Processing Facility must define what key performance data it will analyze. Minimally, this should include data necessary to complete the QM activities required by these Standards.

Evidence:

Records to demonstrate an active QM Program with oversight of the Processing Facility should be available to the inspector.

Example(s):

The Processing Facility may choose to participate in an existing QM Program in its affiliated hospital, participate in the Clinical Program's QM Program, use portions of those QM Programs in its own program, or have a stand-alone QM Program.

STANDARD:

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

Explanation:

The QM Plan is the written document that outlines how the QM Program is implemented.

The QM Plan must detail all key elements that affect the quality of cellular therapy products. The specific controlled documents for each of these elements do not have to be fully described in the QM Plan, but they must be referenced within the plan and linked to the appropriate document(s) where the details are described.

The QM Plan does not necessarily need to be stand-alone, serving only the Processing Facility. If a QM Plan is shared, it must include all elements required by the Standards and clarify the nature and extent of participation by other areas or institutions.

Evidence:

The written QM Plan for the Processing Facility will be provided to the inspector prior to the on-site inspection. If policies and SOPs are referenced in the QM Plan, they may be requested in advance to enable the inspector to review the details of the QM Program. The inspector is expected to evaluate implementation of the QM Plan at the facility and assess the understanding of QM by the staff. When the QM Plan is broad (e.g., a shared plan covering an entire cellular therapy department), all aspects of processing of cellular therapy products need to be addressed.

STANDARD:

D4.2.1 The Processing Facility Director shall be responsible for the QM Plan as it pertains to the Processing Facility.

Explanation:

The Processing Facility Director is in charge of the elements of the QM Plan that are directly related to the facility. A designee must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. Delegation to a qualified designee must be documented, either in the QM Plan or in controlled documents related to it.

Evidence:

QM Plan review and approval should provide evidence of the Processing Facility Director's involvement.

Example(s):

A designee can be a member of another department, such as an institutional Quality Assessment and Improvement or Compliance Department, who devotes some time to the QM activities of the Processing Facility, or they could be a member of the processing facility's team. The same person may be responsible for QM of all components of the cellular therapy program or each individual area (clinical, collection, processing) and may have a distinct individual responsibility for QM, as long as there is a mechanism for sharing information to all participating entities.

STANDARD:

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

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

Explanation:

The organizational chart must include titles of key positions and the reporting structure of the Processing Facility and the QM Program. In addition, these charts must illustrate relationships to Clinical, Collection, and Processing Facilities that meet these Standards. Lines of responsibility and communications must be clearly defined in a way that is understood by all involved.

If a Processing Facility services to or from an outside entity, the organizational chart must include the contracted service(s) and summarize the reporting structure in the QM Plan.

Evidence:

The organizational chart for the Processing Facility will be provided to the inspector prior to the on-site inspection. The inspector will verify that the organization and daily function are as described in the chart and QM Plan (e.g., meetings, participants, schedule, reporting, documentation).

Example(s):

Organizational charts for matrix programs, where an individual may report to different people for different duties (i.e., to the Processing Facility Supervisor for technical duties and to the Quality Manager for quality duties), should reflect the sphere of influence of individuals rather than just the lines of legal authority.

STANDARD:

D4.4 The QM 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:

Explanation:

The QM Plan, as approved by the Processing Facility Director, identifies the key personnel for whom documentation of training, competency, and continuing education is expected. This must include all individuals responsible for critical elements of the Processing Facility. Documentation of training for each individual must include all procedural skills routinely practiced. These requirements are detailed in [D3](#). These requirements apply to all personnel in these positions, including those not directly employed by the Processing Facility but who perform processing services.

Evidence:

The inspector should review training records to verify compliance with these Standards. Organization-specific issues and safety training are generally covered by orientation programs and continuing education programs, but inclusion of this content should be confirmed by the inspector. The inspector should review policies or SOPs describing the elements of staff training and continued competency.

The inspector should review the records of one or more personnel to confirm that all of the required elements have been documented.

Example(s):

Although only one job description is needed for each key position, documentation for each staff member is on an individual basis. For example, a medical technologist position will have one job description for that position, but each individual medical technologist needs their own information on file that includes documentation of qualifications, new employee orientation, training, assessment of continued competency, and continuing education as outlined in Standards [D4.4.2.1–D4.4.2.6](#).

EU regulations contain some specific requirements for personnel training that are not specifically stated in the Standards that include:

- Information sufficient for an understanding of the scientific and technical processes and principles relevant to their designated tasks.
- Information on the organizational framework, quality system, and health and safety rules of the establishment in which they work.
- Information concerning the broader ethical, legal, and regulatory context of their work.

The following resources from the HTA provide further guidance for programs in the UK:

- [Code G: Donation of allogeneic bone marrow and peripheral blood stem cells for transplantation.](#)
- [HTA Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment.](#)

STANDARD:

D4.4.1 A current job description for each position.

D4.4.2 A system to document the following:

D4.4.2.1 Initial qualifications.

Explanation:

Initial qualifications generally include minimal educational requirements, formal training that is either required or preferred, and licensing or certification (e.g., Medical Technologist certification, Bachelor's degree, Master's degree).

STANDARD:

D4.4.2.2 New employee orientation.

Explanation:

New employee orientation refers to training employees on general organizational issues upon hire, such as safety, training, or benefits.

Evidence:

Organizational issues are generally covered by institutional orientation programs, but this should be confirmed by the inspector.

STANDARD:

D4.4.2.3 Initial training, competency, and retraining when appropriate for all procedures performed.

Explanation:

Initial training documentation must include all specific procedures that an individual staff member will perform (as defined in the job description) and should clearly indicate when that staff member has been approved to perform each procedure or function. Initial training should also include:

- Relevant scientific and technical material specific to individual duties.
- Organizational structure, quality systems, and health and safety rules specific to the organization.
- Ethical, legal, and regulatory issues specific to the organization.

Example(s):

Training and its documentation may be accomplished in a variety of formats. Training may be facilitated through formal or informal presentations, self-learning by reading suggested materials on the topic, or reviewing previously presented audio or visual presentations. Documentation may

include attendance rosters, attestation statements of attendance, certificates of attendance, or competency assessments following the training.

STANDARD:

D4.4.2.4 Continued competency for each critical function performed, assessed annually at a minimum.

Explanation:

Competency is the ability to adequately perform a specific procedure or task according to direction. Processing Facilities must have a system for documenting competency and retraining, when appropriate, for each critical function performed by a staff member (see [A4](#) for the definition of "critical").

Evidence:

The inspector should review records of employees' initial and annual competencies. The inspector should review policies or SOPs describing the elements of staff training and continued competency assessment and the records of one or more employees to determine whether all of the required elements are documented.

Example(s):

Competency may be assessed by direct observation, the use of written tests, successful completion of proficiency surveys, review of processing procedure endpoints, or as determined by the Processing Facility Director.

STANDARD:

D4.4.2.5 Annual training in applicable GxP.

Explanation:

GxP is an abbreviation that stands for "good practice" following various quality standards (such as [ISO 9001:2015](#)) and regulations (such as U.S. [21 CFR Part 211](#)). The "x" is variable, with further definition of good practices defined by different countries, fields, and laboratories. The type of work that is being performed will define which GxPs should be followed.

The extent and level of GMPs implemented is dependent on the type of manufacturing that is performed (e.g., manufacturing of minimally manipulated HPC cellular therapy products versus investigational and licensed cellular therapy products). GTPs are rooted in GMPs; in other words, the relevant GMPs are included in GTP regulations.

Training topics will depend on the type of work performed in accordance with Applicable Law. There will be local variations depending on Applicable Law for a particular jurisdiction. Comprehensive

training on every aspect of GxPs each year is not expected; rather, there must be some training based on a GxP topic annually.

Evidence:

Many of the procedures performed by personnel already require training in GxPs to perform the work; therefore, GxP training is not required to be separate. However, documentation must provide evidence that the GxPs were included. For example, training in environmental control could include an overview of GTPs or GMPs, the relevant requirements based on the work to be performed, and the specific tasks performed by personnel.

Example(s):

These Standards require training in GxP as they are required by Applicable Law. Third parties such as commercial manufacturers may have different expectations. This responsibility should be defined in the written agreement with the manufacturers.

Collection and Processing Facilities in the U.S. follow a variety of GxPs:

- Good Tissue Practice (GTP) according to [21 CFR 1271 Subpart D](#).
- Good Manufacturing Practice (GMP or cGMP) as it pertains to the activities performed.
- Good Documentation Practice (GDP) and data integrity practices.

The [Guide to the Quality and Safety of Tissues and Cells for Human Application](#) (5th Edition, 2022), published by the European Directorate for the Quality of Medicines & Health Care provides guidance on Good Practice Guidelines based on current scientific knowledge, expert opinion, and the results of many international projects. The use of this guide is becoming more commonplace throughout Europe, including both EU member states and non-EU states who are members of the council (47 countries with approximately 820 million inhabitants). Many competent authorities use it as part of their inspections. The information provided may be applied to HPC transplantation, IEC therapy, and other novel cellular therapies.

STANDARD:

D4.4.2.6 Continuing education.

Explanation:

Staff should adhere to local and governmental continuing education requirements. Processing staff should be offered the opportunity of appropriate education if there is no national requirement.

Evidence:

The inspector should find evidence of educational opportunities for staff related to their duties, such as quality-related meetings, webinars, or FACT or JACIE training sessions, if applicable.

STANDARD:

D4.5 The QM Plan shall include, or summarize and reference, a comprehensive system for document control.

Explanation:

Document control is the Processing Facility's method of establishing and maintaining critical documents required by the Standards or deemed necessary for the effectiveness of the QM program. The hierarchy and number of documents or extent of documentation is dependent on the processes, size and complexity of the Processing Facility and will differ from one program to another.

Controlled Documents serve multiple purposes for the QM Program and can consist of different document types such as policies, SOPs, worksheets, or forms. Controlled documents provide the structure needed for quality assurance through applicable policies and SOPs. Controlled documents also ensure consistent quality control when using forms, worksheets, audit reports, outcomes analyses, training records, etc. The QM Program must identify which documents are critical and describe how they are controlled.

STANDARD:

D4.5.1 There shall be identification of the types of documents that are considered critical, and these shall comply with the document control system requirements. Controlled documents shall include at a minimum:

D4.5.1.1 Policies, Protocols, Standard Operating Procedures, Manuals, and Guidelines.

D4.5.1.2 Worksheets.

D4.5.1.3 Forms.

D4.5.1.4 Labels.

Explanation:

The QM Program must maintain a controlled document hierarchy which provides identification of the types of documents considered critical. A critical document refers to an internal document that is directly related to and could impact patient care or cellular therapy product safety, purity, potency, identity, or integrity. For example, all manuals, SOPs, forms, worksheets, and labels required by these Standards must be considered to be critical documents within the program and must be controlled. Clinical Programs may call documents by different names (such as patient guidelines instead of protocols) and may identify additional types of documents as critical within the scope of the document control system.

It is up to each program to define which documents are controlled under the QM Program. Documents and manuals that are the property of other institutions (e.g., a commercial CAR-T apheresis manual) should not necessarily be controlled by the program. However, programs must ensure that they are referring to the current version of such documents and manuals.

Evidence:

The inspector should review a listing of which documents fall under the document control system. For example, quality manuals, safety manuals, procedural SOPs, and technical guidance are all controlled documents authored by the program which must be available at the inspection.

Example(s):

Controlled documents include the quality manual, SOPs, forms, practice guides and work sheets.

STANDARD:

D4.5.2 There shall be policies or Standard Operating Procedures for the development, approval, implementation, distribution, review, revision, and archival of all controlled documents.

Evidence:

The inspector should review active controlled documents to ensure they have been written correctly, approved by the appropriate staff before being implemented, and comply with the document control system and the Standards. The inspector will observe how the Processing Facility controls modifications of documents and maintains accurate archival systems.

STANDARD:

D4.5.3 The document control system shall include:

D4.5.3.1 A standardized format for controlled documents.

Explanation:

The Processing Facility should be consistent in the format or design of controlled documents, including a standardized date format. The facility should define acceptable date formats for documents where no specific date format is mandated by the form.

The Processing Facility must have an SOP outlining the method by which the Processing Facility creates, approves, implements, reviews, and revises its SOPs (the "SOP for SOPs"). Documents authored by the Processing Facility should follow the document control system; however, departmental and institutional documents may differ.

Evidence:

The inspector must verify that all elements of a controlled document are present as defined in the document control system and that there is consistency in format from one controlled document to another.

STANDARD:

D4.5.3.2 Assignment of a numeric or alphanumeric identifier, version, and title to each controlled document.

Explanation:

The document control system must include a system for numbering and titling that allows for unambiguous identification of documents. The numbering system must allow for identification of revisions of a document with the same title by creating a new unique identifier (e.g., numerical, alpha numerical). Worksheets and forms must also be controlled documents and contain a title, unique identifier, and version identifier.

Evidence:

The inspector must verify that controlled documents are consistently identified, titled, and versioned as defined in the document control system.

STANDARD:

D4.5.3.3 A system for document approval, including the approval date, signature of approving individual(s), and effective date.

Explanation:

The individual approving documents must have appropriate qualifications and responsibility for the document being approved.

The effective date of a controlled document is the day the new version of a document has been implemented and the previous version has been recalled or archived.

Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate person entered the signature.

Evidence:

The inspector must verify that records indicate consistent approval of controlled documents.

STANDARD:

D4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.

Explanation:

The methods of document distribution and storage should control or prevent unwanted or unauthorized document modification or duplication. The intention of this Standard is to make sure that only the currently approved document is available for use.

Evidence:

The inspector should review the storage and accessibility of currently approved documents and archived documents to verify strict access control.

Example(s):

Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software (to lock specific areas or a specific document to prevent printing) or having copies clearly printed with an expiration date, watermarked as copies, or printed with a clear statement that printed copies may not be the current version, which can only be reviewed by going to source library.

STANDARD:

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

Explanation:

Review does not require an amendment of the version identifiers if the document is still current, but there must be clear evidence that the review has taken place. However, if changes to a controlled document are planned or have occurred since the last review, the document should be changed immediately and should not wait for the two-year review.

Evidence:

The inspector should look for documentation of the biennial review. There shall be documentation of review by an authorized person even in the absence of changes.

Example(s):

When an SOP is reviewed, associated documents (e.g., forms, worksheets) must be reviewed concurrently to ensure alignment.

STANDARD:

D4.5.3.6 A system for document change control that includes a description of the change, version, the signature of approving individual(s), approval date(s), communication or training on the change as applicable, effective date, and archival date.

Explanation:

A change control system must include at least the following elements: change proposal, review of proposed change; analysis of change for compliance with the Standards and Applicable Law, risk and impact assessment on existing process and controlled documents, approval of change and revision of documents; communication or training on the change as applicable, and implementation of the change. Changes in practice should not occur before change in the appropriate controlled document has been made and approved. If immediate implementation of a change is required prior to official document edits, then the Processing Facility should issue a planned deviation documenting this deviation from routine practice. A copy of the new document reflecting the changes could suffice for a description of the change.

The effective date of a controlled document is the day the new version of a document has been implemented and the previous version has been recalled or archived.

A staff member may not perform a new or modified SOP until they have been notified of the change, reviewed the SOP, and, if applicable, completed required training and competency assessment. The amount and format of training and competency assessment may differ based on complexity of the changes. Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate person entered the signature.

Evidence:

The change control process should be reviewed to assess if it is effective to prevent unintended changes to processes or controlled documents.

STANDARD:

D4.5.3.7 A system for archival of controlled documents for a minimum of ten (10) years from archival or according to governmental requirements or institutional policy, whichever is longer. The system shall include the inclusive dates of use and their historical sequence.

Explanation:

Archival of controlled documents is essential to enable facilities to go back to previous versions to confirm historic practices and review operational changes and rationale for the change.

Evidence:

The inspector will examine how the Processing Facility archives controlled documents, whether retrospective review is possible, and whether previous documents can be identified (e.g., unique identifier, version, title).

Example(s):

The archival system must include items such as date removed, version number, reason(s) for archival, and identification of the individual who performed the archive.

STANDARD:

D4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

Explanation:

When controlled documents are updated, there needs to be a secure process in place to ensure that any electronic and hard copies of obsolete or inactive versions are not accessible for use.

Example(s):

There should be a system in place to rescind obsolete or inactive documents to prevent unintended use. For example, on paper copies, a visible watermark could indicate that the document may not be current version and direct staff to the source library for the most current version. If paper copies are distributed, there must be a process to rescind obsolete or inactive controlled documents.

STANDARD:

D4.6 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the establishment and maintenance of written agreements.

Explanation:

The Processing Facility must have policies and SOPs describing the requirement, development, and maintenance of written agreements or contracts with external organizations or individuals (e.g., processing, testing, storage or administration of cellular therapy products, donor or recipient follow-up post-treatment). Agreements are also required when critical services are provided by the Processing Facility to external parties (e.g., distribution of cellular therapy products). This Standard does not apply to entities within the Processing Facility's institution.

When an agreement is required, the parties involved must define responsibilities as to who is required to initiate, maintain, and review the agreement.

The content, terms, and conditions within the agreement must be defined and accepted by all parties prior to signing and execution of the agreement.

Evidence:

Written agreements that match current practices must be available for the inspector to review on-site.

Example(s):

The Processing Facility must have a written agreement with all external facilities that are engaged to store cryopreserved cellular therapy products or with laboratories performing testing of cellular therapy products. Agreements may be in the form of memorandums of understanding, purchasing arrangements, service-level agreements, contracts, and preventive maintenance arrangements.

STANDARD:

D4.6.1 Agreements shall be established with external parties providing critical services that could affect the quality and safety of the cellular therapy product or the health and safety of the donor or recipient.

Explanation:

It is the Processing Facility Director's responsibility to determine which internal or external entities provide critical services that require an agreement.

Documented agreements must clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements must be dated and approved by both parties and legal counsel, if necessary. Agreements must also describe the maintenance or transfer of records and cellular therapy products following termination of the agreement.

Evidence:

Written agreements with external parties must be available for the inspector to review on-site.

Example(s):

External facilities may be defined as those that are a different legal entity or those whose activities are not under the control of the Processing Facility Director.

One form of written agreement that may be acceptable for closely related but separately operated laboratories is a shared SOP that describes the collaborative arrangements.

STANDARD:

D4.6.2 Agreements shall include the responsibility of the external party performing any step in collection, processing, testing, storage, distribution, or administration to maintain required accreditations and to comply with these Standards and Applicable Law.

Explanation:

The Standard requires that agreements include defined responsibilities for critical tasks between the program and the external party.

Example(s):

The Processing Facility is responsible for verifying that an external party has maintained required accreditations. Agreements should include language requiring notification if accreditation is lost.

STANDARD:

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

Explanation:

The Processing Facility is responsible for ensuring that an agreement is in place with all external parties. The agreement can be generated and maintained by the external party; however, the Processing Facility must be able to demonstrate that it exists.

Example(s):

When formulating written agreements either for clinical trials or licensed cellular therapy products, the Processing Facility can add language to require that it be notified of information such as:

- If initial incoming material did not meet the appropriate cell (e.g., MNC) dose. Receiving this information as feedback allows the facility to investigate the collection failure.
- Potential issues that impact scheduling or production.

For agreements that provide critical processing services, language can be added to address communication pathways and notification timeframes. For example, the following are questions related to how relevant information will be communicated if the product does not meet release criteria:

- How is updated donor or product testing information communicated?
- Who is responsible for notifying the clinical site of deficiencies related to the product?
- Is the facility required to provide notification of breaches in aseptic processing?
- What is the timeframe in which post-processing documentation is to be provided (e.g., product deviation, exceptional distribution)?

STANDARD:

D4.6.4 Agreements shall be dated and reviewed on a regular basis, at a minimum every two (2) years.

Explanation:

Written agreements should be reviewed internally at least every two years, similar to SOPs, although greater or lesser time intervals may be appropriate under some conditions. The Processing Facility can define whether a formal review and approval is appropriate to complete with the external organization. The effective dates of an agreement could be specified within the agreement itself. It is helpful to have a list of written agreements to ensure each is reviewed appropriately.

Evidence:

The inspector should be able to view documentation that processing agreements have been reviewed or revised, and, if appropriate, approved every two years. There shall be documentation of review by an authorized person even in the absence of changes.

Processing Facilities should have an awareness of, and a review plan for all written agreements. This includes those that the facility does not control (i.e., does not develop or provide authorized signatures), but which are relevant to the clinical care of the patient or donor or impact the cellular therapy product.

Example(s):

A master list of written agreements and a checklist could assist with appropriate review and ensure that important elements are included and that a designee in the Processing Facility is notified when changes are made.

STANDARD:

D4.7 The QM Plan shall include, or summarize and reference, policies and Standard Operating 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.

Explanation:

Outcome analysis is a process by which the results of a therapeutic procedure are formally assessed. Outcome analysis is focused on patient-related issues. Efficacy assessment focuses on cellular therapy products and determines if the cellular therapy products can be demonstrated to produce a desired or intended result.

Evidence:

The inspector should confirm documentation of all activities, from definition of expected outcome to process improvement, when indicated. There must be evidence of ongoing analysis of data in addition to mere data collection.

The inspector should ask to see the data analysis, formal statistical review and peer reviewed publications, meeting minutes, and Processing Facility review of the data, including the personnel in attendance and where data are presented.

Example(s):

Examples of policies can include those related to adverse events, microbial contamination, and DMSO.

STANDARD:

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

Explanation:

Outcome analysis involves the collection, evaluation, and distribution of patient outcome data. Processing Facilities must request engraftment data for both neutrophils and platelets from the Clinical Program and maintain and analyze critical outcome data to verify that the procedures in use consistently provide a safe and effective product. The Processing Facility should use a standardized definition of engraftment as per CIBMTR/EBMT. For non-myeloablative conditioning, the organization must specify their criteria for assessing patient outcomes, including expected indicator(s) of engraftment.

It is the responsibility of the Processing Facility to assess the impact of cellular therapy processing on outcomes to identify trends. When HPC products are being used for nonhomologous use, other criteria need to be defined and monitored. Cellular therapy product efficacy based on outcome may be more difficult to document for other therapeutic cell products, and that assessment will differ for each product type. If a Processing Facility is manufacturing by contract, the outcome criteria may be less rigorous and may include such items as administration safety. The QM Plan must also address the need for the development of a validated potency assay as regulated products enter the later stages of clinical trials. Generally, the Clinical Program is responsible for defining outcome criteria, although the Processing Facility may contribute to the defined criteria through consultation and implementation of assays. Evaluation of patient outcome is required to confirm that the highest quality product has been manufactured and distributed. Any unexpected outcomes must be investigated, including a risk assessment, and a corrective action or process improvement plan should be implemented. Facility personnel should evaluate all aspects of the processing procedure related to any unexpected outcome, including delayed or failed engraftment.

If a Processing Facility provides cellular therapy products to one or more Clinical Programs, it is the responsibility of the facility to solicit engraftment data from each program. There must be evidence of ongoing analysis of engraftment data in addition to mere collection.

When the Processing Facility is only receiving cellular therapy products manufactured by an external facility and preparing them for administration, the facility must still perform some outcome analysis,

although the outcome criteria may be less rigorous (such as focusing only on safety of the administration rather than potency). In these cases, the facility must still be able to request or have access to other outcome data from the manufacturer when needed to perform investigations of adverse events, reactions, errors, or accidents.

If a poor outcome occurs when the cellular therapy product is received from an external source, it is important for the Processing Facility to be able to share results and to trace back to the product source for information such as sterility testing and cell type.

Example(s):

Chimerism studies may be used to analyze the outcome of DLIs.

STANDARD:

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

Explanation:

Outcome analysis should not only be performed on individual cellular therapy products, but also on Processing Facility data as a whole to identify overall trends. The analysis should include observed ranges of engraftment for the various products and transplant procedures performed by the program. Product characteristics, especially cell dose, should also be considered in such analysis.

The Clinical Program is most qualified to determine what constitutes an acceptable time to engraftment. These data can be used to identify changes that might require further investigation.

STANDARD:

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

Explanation:

The responsibility for the collection and analysis of outcome data is an example of a QM requirement that may or may not be performed entirely within the Processing Facility. It is acceptable to share the same data between clinical, collection, and processing; however, the Processing Facility is responsible for ensuring it has access to clinical outcome data to enable it to adequately assess that its processes do not negatively impact outcome. Chimerism assays can be used as a tool for the assessment of the product quality of allogeneic HPC products administered after non-myeloablative treatment.

Example(s):

Timely engraftment of the HPC product in a recipient following a dose intensive regimen is directly related to the quality of the HPC product. Therefore, the Processing Facility personnel must be aware of the time to neutrophil and platelet engraftment for all recipients for whom they have supplied products. This information can be solicited directly by the facility or presented by another section of the cellular therapy program at a common QM meeting where facility personnel are in attendance.

STANDARD:

D4.8 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for, and a schedule of, audits of the Processing Facility's activities to verify compliance with the QM Program policies and Standard Operating Procedures, these Standards, and Applicable Law.

Explanation:

The purpose of a Processing Facility audit is to gather objective evidence to verify whether processing facility activities comply with applicable standards, guidelines, and SOPs. In addition, a clinical audit may provide information on potential improvements that the process owner may want to consider.

The audit process should occur throughout the year in accordance with the Processing Facility's QM Plan and schedule, with reporting of Processing Facility audit results, corrective action, and follow-up on a regular schedule (at least once a year). There must be regular auditing of critical processing activities; frequency will depend on the importance of these activities, and to some extent on the results. Where there are published studies, these should be used to help assess audit results. Additionally, responsibilities of the audit for external parties who provide critical services must be detailed in a written agreement as described in [D4.6](#).

A schedule of prospective processing audits is expected. Required audits for the Processing Facility are listed in [D4.8.5](#), but there may be other audits required in response to specific occurrences. Review by the Processing Facility Director is to be documented. There should be evidence that audit reports are shared with the processing staff, the Collection Facility Director, and the Clinical Program as appropriate and that any open audits are assessed.

Further information is available in the [FACT Quality Handbook](#) and [The JACIE Guide](#).

Evidence:

The Processing Facility should facilitate the on-site inspection with a concise presentation of recent audits, supported by policies and SOPs, and include documentation of CAPA and follow-up. Examples of how results are trended and presented to relevant directors and staff are also helpful. The inspector should review internal audit results and schedule of planned audits, but it is not the

intent to use a facility's audits to identify deficiencies during an inspection, and the inspector shall maintain the confidentiality of the information.

The inspector should expect to find, at a minimum, a written audit plan, assessment and audit results, actions taken, and follow-up assessments and audits.

Example(s):

Required audits within the Processing Facility are included in [D4.8.5](#) and [D4.8.6](#).

STANDARD:

D4.8.1 Processing Facility audits shall be conducted by an individual with sufficient knowledge in the process and competence in auditing to identify problems but who is not solely responsible for the process being audited.

Explanation:

The individual performing an audit does not need to be external to the Processing Facility, but they should not have performed the actions being audited.

The Processing Facility auditor must be knowledgeable in the process and competent in auditing techniques. Sufficient knowledge must include auditing and the subject matter. The organization must demonstrate how they assess auditor competency.

STANDARD:

D4.8.2 An audit plan for each audit shall include:

D4.8.2.1 Title.

D4.8.2.2 Name of individual(s) to complete the audit.

D4.8.2.3 Audit purpose.

D4.8.2.4 Audit scope.

D4.8.2.5 Documentation of review and approval by the Processing Facility Director and the Quality Manager.

STANDARD:

D4.8.3 An audit report shall include:

D4.8.3.1 Approved audit plan.

D4.8.3.2 Identification of auditor.

D4.8.3.3 Date started and completed.

D4.8.3.4 Records or processes audited.

D4.8.3.5 Summary of results to include findings, assessment of the underlying cause of errors, recommendations, and conclusions.

D4.8.3.6 Plan for follow-up, if appropriate, including a timeline.

D4.8.3.7 Documentation of review and approval by the Processing Facility Director and Quality Manager.

Explanation:

Audit reports are an important tool to provide inspectors evidence of adherence to the Standards and effectiveness of implemented CAPAs; to provide management guidance on future actions and decisions; and to document the evaluation process plans and decisions made in response to issues detected.

An acceptable Processing Facility audit report contains the elements described in Standards [D4.8.2–D4.8.3.7](#), and may also include the following elements:

- Audit type (e.g., Yearly Key Element, 2-Year Key Element, Focused, Follow-up).
- Audit location: Processing Facility.
- Date audit is assigned, including name and title of staff who assigned the audit.
- Title of staff assigned to complete the audit.
- Audit period (date range).
- If errors were found but not included in the final analysis, an explanation must be provided.
- Development of an appropriate CAPA, which should be included in the audit report to demonstrate that an appropriate corrective action plan was implemented.
- Auditor signature and date.
- Documented staff review and date of review.
- Quality meeting results presentation date, if required.

Initially, the audit report is completed by the auditor (e.g., quality coordinator) and reviewed and approved by the appropriate personnel (e.g., Quality Manager and Facility Director). At this stage in the audit process, the report does not contain evaluation of the results (determination of the root cause) or the corrective actions, but it may contain recommendations from the auditors. The approved audit report is distributed to the manager of the audited area. It is the responsibility of the manager of the audited area to evaluate the findings and recommendations to determine the appropriate CAPA, including a timeline, and sign the audit. The audit report is considered complete when the CAPA is complete and re-evaluated after implementation.

STANDARD:

D4.8.4 The results of Processing Facility audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement CAPAs when necessary, and follow up on the effectiveness of these actions in a timely manner.

Evidence:

The Processing Facility audit process and example audits must demonstrate that this is an ongoing process and that the QM records demonstrate CAPAs that are based on audit findings. Additionally, when audit results identify corrective action or process improvement, there should be a date designated as the expected date of completion of the corrective action and a planned time to re-audit the process to verify that the corrective actions were effective.

Example(s):

For example, product recovery may be expected to fall within a certain range based on national or international data. Although the cell recoveries continue to fall within that range, a trend downward to the lower end of the expected range may indicate a need to investigate the cause (e.g., new staff, a new piece of equipment, a reagent unexpectedly received from a different supplier).

STANDARD:

D4.8.5 Processing Facility audits shall be performed annually at a minimum and shall include at least the following:

Explanation:

The Processing Facility must have an audit calendar that shows at least these required audits annually. Other processes should be chosen for audits at the discretion of each individual program or identified by risk assessment. Audits that continuously fail to identify potential problems or opportunities for improvement should be replaced on the schedule by a new audit topic.

STANDARD:

D4.8.5.1 Documentation that each external facility performing critical contracted services has met the requirements of the written agreement.

Explanation:

It is essential that audits include a review of external facilities performing critical contracted services so as to confirm that the requirements of the agreements have been met. Such reviews should be performed on a regular basis and should also be performed after there has been a change in the agreement or in Applicable Law that pertain to the agreement.

Example(s):

Audits of external facilities may be accomplished by reviewing the facilities' internal and external audit reports, performing on-site inspections for compliance, or receiving periodic performance reports from the facility, or the Processing Facility can audit its experience with the contracted facility using data that it defines and collects. There may be other alternatives, but the contracting facility must establish that their contracted services are meeting requirements.

Processing Facilities completing audits of external facilities can include the following:

- Critical supplies inventory control.
- Equipment maintenance.
- Environmental monitoring to include temperature, humidity, facility cleaning, and prevention of contamination and cross-contamination.
- Staff training and competency.

STANDARD:

D4.8.5.2 Management of cellular therapy products with positive microbial culture results.

D4.8.5.3 Environmental monitoring as defined in the facility assessment to include environmental parameters that may affect cellular therapy product viability, integrity, contamination, or cross-contamination during processing, storage, or distribution.

Explanation:

Facility requirements differ based on Applicable Law (e.g., EU, FDA, Therapeutic Goods Administration). The Processing Facility must identify the parameters that should be qualified, controlled, and monitored based on their potential effect on the cellular therapy product (see [D2.4](#)). Environmental considerations include temperature and humidity control, ventilation and air filtration, and sanitation of the room and equipment at appropriate times. There must be ongoing

monitoring of any parameters that have been determined to be critical; these should be defined by an SOP, and compliance should be evident through quality records.

Evidence:

Each facility should assess the risk of environmental conditions on the safety of the cellular therapy product. The assessment should be documented, including those instances where an environmental condition included in the list contained within the Standard has been deemed not applicable to a particular facility. Records of environmental conditions such as temperature and humidity and their review should be available for review by the inspector.

STANDARD:

D4.8.6 Additional audits shall be performed as part of a risk-based approach to the follow-up of occurrences.

Explanation:

This Standard ensures that programs implement a proactive and systematic method to monitor and improve quality and patient safety in response to occurrences. The decision to perform additional audits is guided by an evaluation of the potential severity, frequency, and impact of the occurrence. Additional audits are not routine inspections but are focused and issue-specific evaluations designed to identify root causes and contributing factors, assess whether the existing quality system controls were adequate, evaluate the effectiveness of any CAPAs, and prevent recurrence by addressing systemic issues.

By tailoring audit activities to the level of risk, the Processing Facility can allocate resources effectively, maintain quality assurance, and protect outcomes.

STANDARD:

D4.9 The QM Plan shall include, or summarize and reference, policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency.

D4.10 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results that address at a minimum:

D4.10.1 Notification of the recipient's physician, the Collection Facility, and any other facility in receipt of the cellular therapy product.

D4.10.2 Documentation and product labeling.

STANDARD:

D4.10.3 Product quarantine.

D4.10.4 Criteria for the release of cellular therapy products with positive microbial culture results.

D4.10.5 Identification of individuals authorized to approve release, including at a minimum the Processing Facility Medical Director.

D4.10.6 Documentation and investigation of cause.

D4.10.7 Reporting to regulatory agencies as required by Applicable Law.

Explanation:

The Processing Facility, whether operating independently or as part of an integrated cellular therapy program, must have an approach to the management of cellular therapy products with positive microbial culture results that are identified before or after the products have been administered. Policies and SOPs are required to manage the aspects for which the Processing Facility is responsible. This requirement may be satisfied with a single policy or SOP or there may be separate documents. The Policies and SOPs should cover investigation of the cause of the positive microbial culture, detail what action is to be taken, including reporting to regulatory authorities if applicable, identify who is responsible for taking the action, and state the expected timeframe of the actions. In many cases, the actual responsibilities for these activities may belong to the Collection Facility. For this reason, different approaches to management may be acceptable as long as they are consistently followed and meet regulatory requirements.

The Processing Facility is usually first to be notified of a positive culture result. This notification should in turn initiate investigation of all records related to the processing of the affected product to determine if anything in the processing procedure could have contributed to the positive culture result. Processing Facility personnel are responsible for investigation of the relevant processing events.

The Processing Facility should carefully review the processing records and look for evidence of breach of aseptic technique, determination of whether the donor had evidence of sepsis at the time of collection, investigation of laboratory culture procedures to rule out a false positive result, contamination of the sample in the microbiology laboratory, or other causes that do not indicate compromise of the product.

Policies or SOPs should be in place for the disposition of a cellular therapy product that is found to be positive for microbial contamination prior to administration that includes criteria for when such products may be used, how the recipient is to be notified and provide consent, release criteria, and labeling. Biohazard label and warning statements must be used as required by [D7](#) and Applicable Law.

Policies and SOPs must also be in place for the timely notification of clinical staff of the positive culture result so that appropriate care can be delivered to the donor, and, if the product has already been administered, to the recipient. If the product has been shipped or transported to another Processing Facility, that facility must also be notified. The Clinical Program is typically responsible for recipient notification and consent and must assist with urgent medical need documentation.

Of note, Standard [D8.8](#) requires that the Processing Facility shall monitor all products after processing for microbial contamination. For non-cryopreserved products, the results of such testing will not generally be known prior to administration.

Evidence:

The inspector may ask to see the processing record of a cellular therapy product that was found to have a positive microbial culture and review how the Processing Facility managed the process.

Example(s):

Each area in a cellular therapy program may have responsibilities that do not apply to other areas. In this case, an overarching document for the management of cellular therapy products with positive cultures is recommended.

Examples of evidence of compliance with this requirement may include:

- Policies or SOPs on management of products with positive microbial culture results.
- QM meeting minutes containing a report on products with positive microbial results.
- Non-conformance reports for products with positive microbial results.

Examples of investigation and follow-up into a positive culture result may include:

- Review of processing records for any indication of breach in sterile technique or other adverse event, particularly if extensive processing was required.
- Documentation of proper equipment cleaning, particularly for the biological safety cabinet.
- Review of environmental conditions for sources of possible contamination (BSC sterility testing, particle counts).
- Review of staff competency for possible trends.
- Follow-up and review of findings from the collections area for possible breach in aseptic technique, donor sepsis, or other issues.

Evidence of investigation of cause, outcome analysis, and any preventive or corrective action taken as a result of the investigation should be communicated to all areas of the program (clinical, collection and processing) and be evident in QM meeting minutes.

In the U.S., reporting regulations are detailed in [21 CFR Part 1271](#). A cellular therapy product with a positive microbial result must be reported to FDA only if the product is administered, regardless of whether the result was known prior to or after administration. Marrow-derived products with positive microbial results do not need to be reported. Furthermore, regulations for 351 and 361 products should be followed, and the cellular therapy program should have policies that cover responsibility for reporting. In the EU, all adverse events shall be reported to the relevant Competent Authority.

STANDARD:

D4.11 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for occurrences (errors, accidents, deviations, adverse events, adverse reactions, and complaints). The following activities shall be included at a minimum:

Explanation:

One of a QM Program's goals is to continuously improve processes. Monitoring occurrences and trends facilitates recognition of improvement opportunities and reduces the negative impact of an occurrence on the program. There must be policies, processes, and procedures to detect, evaluate, take action, document, and report a summary of the factual details of the occurrence report in a timely fashion to key individuals, including the Processing Facility Director, Medical Director, Quality Manager, and governmental agencies and other entities, as appropriate. The Processing Facility should define errors, accidents, deviations, adverse events, adverse reactions and complaints in SOPs and describe when, how, by whom, and to whom each is reported. Facilities may use the definitions stated by applicable regulatory agencies; however, the definition must meet the intent of these Standards. See [A4: Definitions](#). Management of each of these types of occurrences is slightly different; however, the same steps (detection, evaluation/investigation, documentation, determination of CAPA, and reporting) apply to all types.

Evidence:

The inspector should expect to find a process for documenting occurrences including detection, investigation, documentation, corrective action, preventive action, and follow-up. This should be reviewed by the Processing Facility Director and Quality Manager. The process shall include, as appropriate, reporting to the Collection Facility, the Clinical Program Director, appropriate governmental agencies, and other third parties involved in the manufacture of the cellular therapy product.

STANDARD:

D4.11.1 Detection.

Explanation:

Detection involves the means by which an occurrence is discovered. For example, occurrences may be discovered by audits, analysis of process improvement data, patient surveys, and complaints.

Immediate action must be taken and documented to mitigate further risk to product quality or patient safety.

STANDARD:

D4.11.2 Investigation.

D4.11.2.1 A thorough and timely investigation shall be conducted by the processing staff in collaboration with the Collection Facility, the Clinical Program, and other entities involved in the manufacture of the cellular therapy product, as appropriate.

D4.11.2.2 Investigations shall identify the root cause and a plan for short- and long-term CAPAs as warranted.

D4.11.2.3 Occurrences shall be tracked and trended.

Explanation:

Cellular therapy products affected by deviation(s) are released by the Processing Facility for use by the Clinical Program only when the benefit outweighs the risk to the patient and no alternative is available; although in some cases, the information is not known until after the administration of the product has occurred. The most common deviations encountered involve products with a positive microbial culture or products from ineligible donors.

It is critical to identify cause(s) of occurrences that pose significant risk or severity and to establish and determine what CAPA will most likely be effective. Often "systems" play a role in causation. Processing Facilities should be encouraged to stratify events according to risk or severity and invest more time and energy into management of the more critical issues. Only an understanding of cause allows creation and implementation of new or revised systems or controlled documents that will correct the issue and may prevent recurrence.

STANDARD:*D4.11.3 Documentation.*

D4.11.3.1 Documentation shall include a description of the occurrence, the date and time of the occurrence, the involved individuals and cellular therapy product(s) including the unique identifier for the product involved, as applicable, when and to whom the occurrence was reported, and the immediate actions taken.

Explanation:

As in the investigation, documentation of the involved individuals in any adverse event or other deviation should not be punitive. This information should be used for investigation and trending purposes to identify potential corrective and preventive measures, such as the need for additional training, and staff resources.

STANDARD:

D4.11.3.2 All investigative reports shall be reviewed in a timely manner by the Processing Facility Director, Medical Director, and Quality Manager.

Explanation:

Timing of investigative reports may vary based upon the nature of the investigation, program or institutional policy, or regulatory requirements. Programs must define the schedule of investigative reports.

STANDARD:

D4.11.3.3 Cumulative files of occurrences shall be maintained and include written investigative reports containing conclusions, root-cause analysis, follow-up, CAPAs, and a link to the records of the involved cellular therapy products, donors, and recipients, if applicable.

Explanation:

Documentation should be done as close as possible to the time of detection and concurrently to ensure all critical information including description, personnel involved, date and time, and actions are captured. Sufficient information, such as unique identifiers, should be provided to link the investigative report to the records of the involved cellular therapy products, donors, and recipients, if applicable.

Complaints of cellular therapy product performance, delivery of service, or transmission of disease must be investigated and resolved. In this context, a complaint should be considered as information that implies the product or service did not meet quality specifications, failed to function as expected, or resulted in an adverse event or reactions for the recipient.

The FDA definition of a complaint is more restrictive and deals primarily with the transmission of a communicable disease, likely due to the cellular therapy product or to a failure to comply with practices that might increase the risk of transmission of a communicable disease. Corrective action or process improvement must be implemented to prevent recurrence as defined by an SOP.

Evidence:

The Processing Facility should be prepared to show examples of the cumulative files of occurrences and how they have been managed according to this process. If any deviations have been reported to a governmental agency or other entity, the report(s) should be available for inspector review.

A tracking and filing system must be evident to show that all occurrences are logged, tracked and maintained to facilitate review and trending. Trending data should be presented at the quality meeting to ensure the effectiveness of the system is meeting requirements.

The inspector should review the complaint file and determine if corrective, preventive, or process improvement actions have been identified, implemented, and are adequate to prevent future occurrences and that regulatory agencies have been notified where that is required.

Example(s):

Communication of occurrences, investigations, and conclusions may occur in many formats, such as reporting during a regularly scheduled QM meeting with inclusion in the meeting minutes. Alternatively, a separate report may be generated, distributed, and signed by the appropriate individuals, including the Processing Facility Director, Processing Facility Medical Director, and potentially the Clinical Program Director. As appropriate, some documentation should be included in specific cellular therapy product records related to specific incidents or reactions.

STANDARD:

D4.11.4 Reporting.

D4.11.4.1 When it is determined that a cellular therapy product has resulted in an adverse event or reaction, the Occurrence Report and results of the investigation shall be reported to the donor's and recipient's physician(s), as applicable, to other facilities participating in the manufacturing of the cellular therapy product, registries, grant agencies, sponsors, IBCs, IRBs, Ethics Committees, accrediting bodies, and governmental agencies as required by Applicable Law.

STANDARD:

D4.11.4.2 Occurrences shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product.

Explanation:

The FDA defines an adverse reaction as an adverse event involving the transmission of a communicable disease, cellular therapy product contamination, or failure of the product's function and integrity if the adverse reaction a) is fatal, b) is life-threatening, c) results in permanent impairment of a body function or permanent damage to body structure, or d) necessitates medical or surgical intervention.

Adverse reactions may also include unexpected reactions to the graft that are designated as possibly, probably, or definitely related. For suspected adverse reactions to administration of cellular therapy products, the results of investigation and any follow-up activities must be documented.

Adverse reactions meeting the FDA definition of products regulated under GTP or GMP (products produced under IND or IDE) must be reported to FDA within their specified guidelines. Reporting to other oversight organizations may also be necessary (e.g., accrediting agencies, registries, grant agencies, IRBs or Ethics Committees).

The EU [Directive 2004/23/EC](#) distinguishes between serious adverse events, which are incidents, errors, etc. that have potential consequences, and serious adverse reactions, which are actual reactions in donor or recipient. Both must be documented and reported.

- "Serious adverse event" is defined as any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells that might lead to the transmission of a communicable disease; to death or life threatening, disabling, or incapacitating conditions for patients; or which might result in or prolong hospitalization or morbidity.
- "Serious adverse reaction" means an unintended response, including a communicable disease in the donor or in the recipient associated with the procurement or application of tissues and cells that is fatal, life threatening, disabling, incapacitating, or which results in or prolongs hospitalization or morbidity.

EU Commission Directives [2006/17/EC](#) and [2006/86/EC](#) include equivalent requirements for non-conforming products.

If an unexpected or serious adverse reaction occurs due to cellular therapy product collection or administration, for which there is a reasonable possibility that the response may have been caused by the product, the report of the adverse reaction and its outcome and investigation should be communicated to all facilities associated with collection, processing, and/or administration of the product. This includes graft failure. Usually, the Clinical Program is responsible for making the initial

report; however, each involved facility must participate in the investigation and evaluation of the potential cause, particularly related to its own SOPs that were involved.

Example(s):

The following are examples of adverse events that may need to be reported based on the requirements of the relevant competent authority:

- Adverse events involving the transmission of communicable disease.
- Product contamination.
- Adverse reactions that are fatal, life threatening, result in permanent impairment of a body function or permanent damage to body structure, or necessitate medical or surgical intervention.

STANDARD:

D4.11.5 Corrective and preventive action.

D4.11.5.1 Appropriate 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.

Explanation:

All events may not require immediate corrective action. Follow-up after implementation of CAPA plans is critical to ensure effectiveness. Lack of effectiveness would indicate the need to continue further investigation of cause or other contributing circumstances and additional actions. Clinical Programs should define in their policies or SOPs when events warrant preventive plans, along with their plan to audit the effectiveness of the changes.

Immediate actions are those actions taken for each non-conformity detected in order to minimize and mitigate the impact of the non-conformity. Preventive actions are actions taken to eliminate the cause(s) of the nonconformity in order to reduce the likelihood of recurrence or occurrence elsewhere.

Investigations and corrective actions should, at a minimum, address:

- Identification of the involved individuals or cellular therapy product affected and a description of its disposition, where relevant.
- The date and time of the event.
- The nature of the problem requiring CAPA.
- To whom the event was reported.
- A description of the immediate corrective action taken.

- The date(s) of implementation of the corrective action.
- Follow-up of the effectiveness of the corrective action, where relevant.

STANDARD:

D4.11.5.2 Follow-up audits of the effectiveness of CAPAs shall be performed in a timeframe as indicated in the investigative report.

Explanation:

Short term corrective (immediate) actions are those actions taken immediately upon discovery of the occurrence or shortly thereafter to contain the problem and prevent it from causing further harm. These actions typically address the symptoms of the problem rather than the root causes. Long term corrective (preventive) actions are taken to address the root causes of the problem and are intended to be a permanent solution to the problem, preventing recurrence.

STANDARD:

D4.12 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for cellular therapy product Chain of Identity and Chain of Custody that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

Explanation:

The Processing Facility must have a policy or SOP for Chain of Identity and Chain of Custody to allow tracking and traceability of each cellular therapy product through all steps from collection to administration or final disposition. Documentation in the medical record should include the proper product name, unique product identifier(s), ISBT 128 DIN and product code, EU SEC or equivalent, content of the cellular therapy product, identification of the donor including medical record numbers, unrelated donor registry identifiers including Global Registration Identifier for Donors (GRID), allogeneic donor eligibility status, and the unique identity of the intended recipient including registry identifiers, where appropriate. There must be a process, including the use of the ISBT 128 barcode or other barcode or unique numbering system, to track and trace specimens removed from a cellular therapy product for testing at an external facility such as an HLA testing facility, transfusion service, or microbiology laboratory. This process must ensure linkage between the results of testing and the original product. There should also be a means, direct or indirect, that will allow outcome information to be related back to any other facilities involved in collection, processing, and distribution of the product. The final disposition of the product must be documented, whether the product was administered, destroyed, released, or used for research, remains in storage, or other disposition. The tracking and tracing system must comply with the Standards and all Applicable Law.

Evidence:

The inspection team will review examples of processing records including worksheets and reports and final cellular therapy product labels to determine if tracing and tracking from donor selection through final product disposition and recipient identification is possible. All critical steps should identify who performed the procedure and when they were completed. The Processing Facility must have a system in place to request information, if not initially provided, to identify manufacturing procedures performed by external facilities (e.g., genetically modified cellular therapy products).

Example(s):

A Processing Facility may assign an ISBT 128 DIN as a unique product identifier upon receipt of a cellular therapy product from an unrelated donor collection facility that does not use ISBT 128 labeling, as long as tracking and tracing from the donor to the recipient is possible (i.e., the unique product number assigned at the collection facility is recorded in the processing record to maintain the linkage).

Full implementation of ISBT 128 labeling ensures tracking and traceability of the cellular therapy product and associated pilot vials and segments in a Processing Facility. However, if a Processing Facility removes specimens from a cellular therapy product and sends these to an external laboratory such as an HLA testing laboratory or a transfusion service for testing, the laboratory information system at the testing laboratory might not be compatible with ISBT 128 barcodes. If the testing laboratory assigns a new laboratory or barcode number to these specimens, there must be a system to link the reports generated following testing to the original cellular therapy product.

STANDARD:

D4.13 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event that Processing Facility operations are interrupted.

Explanation:

Processing Facilities should be prepared for situations that may interrupt typical operations so that such interruptions do not adversely affect cellular therapy products, critical supplies, and processes. While a policy or SOP is required that addresses emergencies and disasters, the facility must also have a plan for the management of interruptions that do not rise to the disaster level. It is difficult to anticipate every possible situation that may occur. Therefore, the Standards do not require the facility to outline actions for specific events; rather, the facility is required to describe actions to take when an interruption presents, including who needs to be contacted, how to prioritize cases, key personnel to be involved in identifying alternative steps to continue functions, and notification of staff.

A contingency plan specific to the Processing Facility would convey evidence that risk has been assessed for program-defined potential events of varying impact, such as a failure of the scheduling system; heating, ventilation, and air conditioning (HVAC) supply interruption; or shortage of a critical

reagent. The plan should reflect differences between specific Processing Facility needs and general institutional needs and complement the institutional plan.

As more and more of the Processing Facility's documents exist on an electronic platform, there is increasing risk of temporary or permanent document loss. The institutional Information Technology Department generally confirms that software in use is validated for its function, and that there is a regular schedule of backups to allow for retrieval of information when necessary. Freestanding facilities, as well as programs utilizing desktop storage, must have a plan to create a similar level of security. In either case, the facility also needs a method to produce current versions of critical documents, such as preprinted orders, consent forms, and SOPs, when the electronic format is not available.

Policies, SOPs and associated worksheets and forms must be available to Processing Facility staff at all times. Arrangements must be made so that these documents are available in the event that the computer system goes down. Staff should have periodic training and review of alternate systems so they will be competent in the use of these systems should the need arise.

The Processing Facility should confirm that any electronic records in use meet other standards for validation and regularly scheduled back up of data. This may be in cooperation with the institutional Information Technology Department if available. This Standard covers the processes in place to continue manufacturing and release of cellular therapy products when the electronic records are unavailable. This should include a mechanism to determine and document critical values for determining cellular therapy product release criteria and appropriate product labeling. These records may be hard copies of reports from the system that are periodically produced to be used as a manual record. There may also be forms to be completed that mimic entry screens.

Evidence:

The inspector should review policies and forms to be used in case the electronic record system is unavailable.

Example(s):

It is recommended that a Processing Facility have a contingency plan in the event that it is unable to provide services as intended (e.g., significant personnel change, natural disaster). The contingency plan may require a written agreement with an external facility (e.g., memorandums of understanding, purchasing arrangements, service level agreements, contracts, preventive maintenance arrangements) used for the storage of cryopreserved cellular therapy products or for laboratories performing testing of cellular therapy products.

Examples of interruptions include malfunctioning electronic records systems, drug shortages, power outages, equipment failures, and supply shortages. A contingency procedure would identify alternative sources of supplies, alternative supplies, or alternative preparative regimens.

STANDARD:

D4.14 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services.

Explanation:

Quality can be maintained only if there is control over critical manufactures (including CAR-T manufactures), vendors, equipment, supplies, reagents, facilities, and services. The QM Plan must include a process to qualify these elements to safeguard their consistent function in validated procedures. This process must include the establishment of minimal standards for the acceptance of critical supplies and reagents and must document that those standards are met before they are made available for use.

Where purchasing is beyond the direct control of the Processing Facility, steps should be taken to verify supplier and vendor qualification have been performed by the parent organization.

Control of the manufacturing process can be attained by establishing minimal acceptance criteria for the reagents, materials, and supplies used in processing and by maintenance and calibration schedules for equipment used to safeguard their proper performance as defined by an SOP.

Evidence:

The inspector should find evidence of qualification of manufacturers, vendors, supplies, equipment, facilities, services, and critical reagents. Qualification procedures should include instructions for requalification and under which circumstances qualification is required. Accredited facilities should participate in external inspections as required by Applicable Law.

Example(s):

It is not the intent of this Standard for the Processing Facility to qualify licensed pharmaceutical products, but rather a risk-based approach should be taken to identify items which require qualification. For example:

- DMSO is a critical reagent because omitting it from the freezing medium will cause loss of cells during freezing and thawing.
- Critical documents include a document that is directly related to and could impact donor welfare, recipient care, or cellular therapy product integrity.
- Updated software versions have the potential to materially affect performance of equipment.

For further definitions and examples of qualification, see the [FACT Quality Handbook](#) and [The JACIE Guide](#).

STANDARD:

D4.14.1 Critical equipment, software, supplies, reagents, and facilities used for cellular therapy product manufacturing procedures shall be qualified.

D4.14.1.1 Qualification shall be required following any significant changes to these items.

Explanation:

Clinical Programs may choose to delegate review of qualification studies to the Processing Facility. Clinical Programs may also utilize the assistance of Processing Facilities or institutional quality departments to assist with this task.

Example(s):

If there is a software change or upgrade, the Processing Facility must assess the need to qualify or requalify the software. Requalification would typically be necessary when the software version changes, but smaller upgrades may also critically affect donor safety or cellular therapy product efficacy.

STANDARD:

D4.14.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

D4.14.3 Qualification plans shall include minimum acceptance criteria for performance.

Explanation:

The Processing Facility must have a system in place that confirms that vendors provide materials in a timely and consistent manner that meets their acceptance criteria. Supplier qualification must also confirm that there is a system in place that is consistent with the Standards, that they can demonstrate process control, and vendors are compliant with Applicable Law. Suppliers of laboratory services, such as the Flow Cytometry Laboratory or the Microbiology Laboratory that provides product testing, must also be qualified.

Critical reagents and supplies that come into contact with donors, recipients, or cellular therapy products shall be sterile and approved for human use (appropriate grade for intended use). Qualification of a readily used reagent in the field (e.g., acid citrate dextrose [ACD], NaCl, Plasma-Lyte) may consist of documented evidence of inspection of the reagent for discoloration or damage, use before the expiration date, and review of Certificates of Analysis prior to use.

Equipment qualification is performed to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. An example might be the qualification of a new controlled rate freezer.

Facility qualification is based on the level of manufacturing in the facility and may range from a risk assessment to a full facility GMP qualification based on SOP and regulatory requirements.

STANDARD:

D4.14.4 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Processing Facility Director.

Explanation:

A plan for qualification must be reviewed and approved prior to performing a qualification.

Qualification of critical items should include:

- Design Qualification (DQ).
- Installation Qualification (IQ).
- Operation Qualification (OQ).
- Performance Qualification (PQ).

The qualification plan should be reviewed after the qualification to determine if all acceptance criteria were met. This process must include the establishment of minimal standards for the acceptance and must document that those criteria are met before use.

Example(s):

There are several ways to qualify a vendor of supplies, reagents, and services. The most effective is to perform an audit of the provider. Other, often more practical methods may include one or more of the following:

- A review of third-party assessments by accrediting organizations such as FACT, JACIE, AABB, CAP or others.
- Remote audits by questionnaire.
- An ongoing dialog of resolution of service complaints or suggested process improvements.
- The sharing of internal audit findings and implemented corrective action plans from the provider back to the facility as evidence that deficiencies have been recognized and corrected.
- A documented review of the supplier's past performance history.

Suppliers with pre-existing service agreements preceding the implementation of this Standard can be qualified as meeting expectations by a retrospective review of the quality of service provided.

Documentation, in the form of a brief written statement, that the service provider has met the Processing Facility's requirements, worked with the facility to identify the cause of service failures,

and taken corrective actions in the past may serve as documentation of service provider qualification.

General medical equipment qualification is performed to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. This qualification may be delegated to other institutional departments.

STANDARD:

D4.15 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

Explanation:

Validation is confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process (or SOP) is validated by establishing objective evidence that the process consistently produces a cellular therapy product meeting predetermined acceptance criteria. Validations can be performed prospectively, concurrently, or retrospectively.

Verification is the confirmation of the accuracy of something or that specified requirements have been fulfilled. Verification differs from validation in that validation determines that the process performs as expected, whereas one verifies that the products of a process meet the required conditions.

Example(s):

For further definitions and examples of validation, see the [FACT Quality Handbook](#) and [The JACIE Guide](#).

STANDARD:

D4.15.1 Critical procedures to be validated shall include processing procedures, cryopreservation procedures, testing, labeling, storage, distribution, and preparation for administration, as applicable.

Explanation:

In the Processing Facility, the following should be validated or verified:

- Processing procedures. All processing procedures must be validated. However, a published procedure adopted from another processing facility (e.g., hetastarch, a sedimentation agent used for RBC reduction) may be verified so long as the conditions under which it is used are like those validated elsewhere.

- The intended use of equipment used for processing, release testing, or transport. The introduction of a piece of equipment such as a controlled rate freezer of the same model as already present in the facility would generally require a verification study, whereas the introduction of a different model or a model from a different manufacturer would require a more extensive validation study.
- The intended use of reagents made on-site and those not approved for clinical use. One would validate that a novel reagent used for RBC removal reduces RBCs to the required degree under all the conditions and for all the products that one would use the reagent for, but would then qualify each new lot of the reagent under more limited testing to safeguard its function.
- Labels and labeling. The validation of the label would demonstrate that the labels in use were checked against an approved template, were approved for use, maintain integrity during use, remain affixed or attached as required, are readable, do not contain any blank data points, and do include all of the required elements as listed on the label table (see [Appendix II](#)). Validation of the labeling process should demonstrate completeness and correctness of each data point, as well as the accuracy of data as shown by traceability and trackability of the product from donor to recipient or final disposition.
- Storage of the cellular therapy products prior to distribution.
- Distribution of the product. This may include products transported or shipped within or between facilities.
- Electronic records system, if applicable.

When possible, reagents that have been approved for clinical use should be used for processing cellular therapy products. When this is not possible, a validation study must be performed using mock products with known values to document that the reagent or supply meets acceptable endpoints and does not cause harm to the product (purity, potency and safety) or the recipient of the product. Examples of acceptable endpoints may include but are not limited to nucleated cell recovery, viability, sterility, and RBC reduction.

Supplies or reagents not approved for human clinical use, or not for their intended use, may be used if:

- The supplies or reagents are specified in a SOP that has received IRB approval at the institution requesting FACT accreditation and/or IND or IDE exemption from the FDA.
- The SOP that includes the specified supplies or reagents has been used in IRB-approved clinical trials and has been established in the medical literature to be acceptable for the purpose specified.
- Appropriately qualified or validated.

Evidence:

The inspector should ask to see the SOPs for conducting validation studies and review a sample of validation studies. The inspector should note that studies are properly designed, objectively collect the required data, that outcome and intended actions are summarized, and that both the finalized plan and report are reviewed and approved by the Processing Facility Director and Quality Manager.

Example(s):

A change of reagents used for processing, such as cryopreservation, would need to be validated to verify cellular therapy product nucleated cell recovery, viability, sterility, and potency are maintained at acceptable limits. The potential for adverse reactions and comparison of times to engraftment should also be examined.

Another example of a change that would need to be validated is a change to a different method of RBC reduction. Documentation of RBC content remaining in the products tested as well as confirmation of acceptable endpoints such as nucleated cell recovery and viability should also be included in evaluation of the new method.

If there is a requirement from a manufacturer outside of what is established in a program's SOP, this can be managed by a separate SOP applicable to manufacturer requirements.

STANDARD:

D4.15.2 Each validation or verification shall include at a minimum:

Explanation:

Validation studies should be performed according to a validation SOP, utilizing a consistent format for approval of the validation plan, conducting of the studies, collection and documentation of results, data analysis, conclusions, and approval of the studies. A validation study performed because of a proposed change in a process or SOP shall include a documented assessment of the risk involved in the change to donor and recipient health and safety and the quality and safety of cellular therapy products.

The design of the validation study should be adequate to determine if the process reproducibly achieves the purpose for which it is intended. The validation plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. Any change in the planned study that occurs during the study requires explanation. There should be an explanation, follow-up, and/or repeat of any test that fails to meet the expected outcome.

Validation should confirm acceptable endpoints can be achieved while maintaining purity, potency and safety of the cellular therapy product. Examples of acceptable endpoints may include nucleated cell recovery, viability, sterility, and RBC reduction.

STANDARD:

D4.15.2.1 An approved plan, including conditions to be assessed.

D4.15.2.2 Acceptance criteria.

Explanation:

Validation of the processing procedure should confirm that acceptable endpoints can be achieved while maintaining the purity, potency, and safety of the cellular therapy product. Examples of acceptable endpoints may include, but are not limited to, nucleated cell recovery, viability, sterility, and Hematocrit of the product (showing sufficient RBC reduction).

STANDARD:

D4.15.2.3 Data collection.

D4.15.2.4 Evaluation of data.

D4.15.2.5 Summary of results.

D4.15.2.6 References, if applicable.

D4.15.2.7 Review and approval of the plan, report, and conclusion by the Quality Manager and the Processing Facility Director.

Explanation:

Review and approval need to be completed by a minimum of two individuals. One must be the Quality Manager, and the second must be the Processing Facility Director. A Quality Manager designee may need to be utilized when the Quality Manager is unavailable (e.g., on vacation, in the process of hiring for that position, on paternal leave). In this situation, the Quality Manager designee must be a qualified member of the QM team to complete the review and approval process.

STANDARD:

D4.15.3 Significant changes to critical procedures shall be validated and verified as appropriate.

Example(s):

Use of a new system for processing would require validation to confirm the system performed as expected with no compromise of the purity, potency, or safety of the collected product.

STANDARD:

D4.16 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for evaluating the risk of changes to critical procedures to assess the effect(s) elsewhere in the operation.

Explanation:

Evaluation of risk is a process to assess and document the risks involved in a change in a practice, process, SOP, or environment that has the potential to affect a critical procedure; direct patient care; and/or the cellular therapy product integrity, sterility, viability, or recovery. Critical procedures requiring risk assessment should be defined by the facility. Examples include processing, distribution, labeling, and storage of cellular therapy products.

Evaluation of risk may be documented in the SOP, in a validation plan or as a separate document. Documentation may include:

- Identification of a risk.
- Context.
- Evaluation.
- Impact.
- Management response.

Evidence:

The inspector should ask to see the SOP for evaluation of risk for changes to a practice, process, SOP, or environment and preferably an example of how it has been applied.

Example(s):

Identification of a risk can be made by providing a description of a potential or known risk. Establishing the context or scope means all the possible risks are identified and the possible ramifications or impact in all areas are analyzed thoroughly. Once the context or scope has been established, the next step is identification and evaluation of potential risks as either source or effect. During source analysis, the source of risks is analyzed, and appropriate mitigation measures are put in place. This risk source could be either internal or external to the system. During problem analysis the effect rather than the cause of the risk is analyzed.

A general description of the issue and identification of the specific risk(s) should be included. After the risk has been identified, it must be assessed on the potential of criticality or on its likelihood of occurrence and potential impact, including quantitative and qualitative evaluation. Risk prioritization is when the 'likelihood of occurrence × impact' is equal to risk.

There are many different approaches to calculating risk, and there are tools that can help assist in defining the probability of the effect occurring, the root cause, effects and magnitude of risk under different scenarios. Examples of tools that a program might use include The Five Whys technique

for root cause analysis, FMEA (Failure Mode and Effects Analysis), an Ishikawa or fishbone diagram, or SWOT (strengths, weakness, opportunity, and threats).

Once the risk assessment is established then a risk management plan can be developed and implemented. It is comprised of the effective controls for mitigation of risk. Risk Management includes justification and rationale for accepting the risk and how to manage the impact, if applicable. This can often be established in a simple one-page document for change with low impact and risk. An example might be a change in a reagent or supply of acceptable grade.

Below is an example of a risk assessment matrix that combines the concept of likelihood and severity.

		Probability (Likelihood of occurrence)			
		Occasional (Possible to occur in time, if not corrected)	Likely (Will probably occur in most circumstances)	Frequent (Expected to occur in most circumstances)	
Risk Matrix	Severity of Incidence	Minor (low risk to the product or patient)	Low (1)	Low (1)	Medium (2)
		Moderate (Probable risk to product or patient)	Medium (2)	Medium (2)	High (3)
		Major (High risk to product or patient)	High (3)	High (3)	High (3)

STANDARD:

D4.17 The QM Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining and reviewing feedback and taking action when appropriate.

D4.17.1 Feedback shall be obtained from associated Clinical Programs and Collection Facilities.

Explanation:

The QM Plan must describe how the Processing Facility obtains feedback from the Collection Facility and Clinical Program. Feedback received by the Clinical Program or Collection Facility from donors, recipients, and legally authorized representatives can be reviewed.

Evidence:

Evidence to show compliance may be:

- Minutes of QM meetings where issues are discussed.
- Mutual resolutions of non-compliances.
- Records of compliments and complaints.
- A survey of resolution of complaints.

STANDARD:

D4.18 The Processing Facility Director shall review the quality management activities with representatives in key positions in all elements of the cellular therapy program at a minimum quarterly.

D4.18.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

D4.18.2 Performance data and review findings shall be reported to key positions and staff.

Explanation:

QM activities, including the results of audits, shall be reported quarterly at a minimum to review the performance of the QM Program and its objectives. This is to determine whether the elements in the QM Plan are relevant and effective, and necessary actions are taken in a timely manner.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported with each audit while others may be retrospectively analyzed and reported at defined intervals. The data should be analyzed, assessed, and trended over time to identify improvement opportunities on a regular basis, such as at each QM meeting. Strategies for improvement should be identified and implemented. The results of these implemented strategies should be measured and the improvement strategies either continued or new alternatives developed, depending on the results.

Minimally, quarterly meetings are required. The minutes and attendance list of regularly scheduled QM meetings are effective ways to document QM activities and communication of quality assessments to key individuals within participating facilities in the cellular therapy program. Having multidisciplinary meetings that involve several academic disciplines or key personnel is an acceptable approach to develop recommendations for performance improvement.

Evidence:

The inspector should ask to see evidence that, at a minimum, a summary of key performance data and review findings have been reported to staff (although all findings can be shared) within all participating entities in the cellular therapy program. The inspector should ask to see the minutes of the QM meetings, which should document who was in attendance and what topics were covered. At a renewal inspection, it is particularly important to ask for QM meeting minutes that represent the time since the previous accreditation in order to determine that the QM Program is and has been ongoing. Minutes should summarize activities such as training performed, documents reviewed, audits performed, SOPs introduced or revised, and outcome parameters reviewed.

STANDARD:

D4.18.3 The Processing Facility Director shall not have oversight of their own work if this person also performs other tasks in the Processing Facility.

Explanation:

Any person responsible for overseeing QM activities should not be directly responsible for review of work solely performed by that person. It is important that the final review be unbiased and that there has been sufficient time away from the work for the review to be objective. Alternatively, in small facilities where there may be only one person responsible for most of the processing activity, the Processing Facility Director, Processing Facility Medical Director, or a person from the Clinical Program or Collection Facility may be designated to review these activities. It may be acceptable, however, for an individual to review their own work at a time and place removed from the actual performance of the work.

Evidence:

The inspector should assess if the person documented as performing the task is also the person reviewing or approving the work. For example, the Processing Facility Director should not be the sole approver on a planned deviation for the director's work product.

STANDARD:

D4.19 The Processing Facility Director shall review the effectiveness of the QM Program annually.

D4.19.1 The annual report and documentation of the review findings shall be made available to key personnel, the Clinical Program Director, the Collection Facility Director, and staff of the program.

Explanation:

The ultimate responsibility for performance and monitoring of the QM Program, including internal or contracted components, belongs to the Processing Facility Director. If the Processing Facility is part of an integrated cellular therapy program, a single annual report is sufficient.

The overall effectiveness of the QM Program must be reviewed and reported to staff on an annual basis. The annual report will provide a year-long view of the overall function of the QM Program, its effect on and interactions with the Clinical Program and Collection Facility, and provide clues on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated.

The annual report should also contain trending information related to key indicators that are monitored, patient outcomes, patient satisfaction, adverse events, and other important elements utilizing data from prior years and goals for the coming year.

Example(s):

Processing Facility Directors may wish to report on the performance of the QM Program more frequently than once a year. If so, the report should utilize some data from the previous 12 months to provide a longitudinal perspective of how the QM Plan is functioning over time. Examples of sections to include in the report on the performance of the QM Program are:

- Overall programmatic indicators (e.g., accreditation achieved, new faculty, moves, data updates).
- Quality measures:
 - Product outcomes (e.g., cell counts, viabilities, recovery data, sterility, absence of microbial contamination).
 - Facility and environmental monitoring data.
 - Other events such as complaints or deviations.
 - Audits.
 - Validations.
 - Risk assessments.
- Service-level agreements.
- Process improvements.
- Goals for the coming year.

D5: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

D5.1 The Processing Facility shall establish and maintain policies or Standard Operating 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:

Explanation:

Each Processing Facility must have written policies or SOPs that comprehensively address all aspects of the facility. The policies and SOPs required in D5 are operational in nature, whereas those required in [D4](#) pertain to the QM Program. A policy describes a course of action or mission statement in general terms. An SOP gives specific step-by-step instructions on how to perform a particular task. The policies and SOPs must be detailed, unambiguous, and adequately define all operational aspects of the Processing Facility. The Standards allow the facility to create its document hierarchy based on its own internal requirements and policies. The facility is not required to have both a policy and SOP for each item, nor is a dedicated policy or SOP required for each item on the list as long as each item is addressed somewhere within the appropriate document. The items listed

in D5.1 include the minimum requirements; a facility may exceed these requirements but not omit any of them.

The Processing Facility can utilize institutional policies and SOP but retain the responsibility for verifying that those policies and SOPs meet the requirement of the Standards. In those circumstances where program or institution standards vary from these minimal requirements, the program will be held to the higher standards. Policies and SOPs must comply with the document control requirements listed in [D4](#). Review and approval of all policies and SOPs shall be performed at the time of document creation, at each revision, and every two years thereafter.

Evidence:

The inspector will be provided a list of SOPs with the pre-inspection material. This list must include all policies and SOPs required by the Standards under which the Processing Facility operates. The list should be examined by the inspector for evidence of SOPs addressing each item before arriving at the inspection site. Prior confirmation that a specific SOP has been generated will reserve limited on-site inspection time for evidence of implementation of written SOPs and other activities that can only be verified in person at the inspection site.

When multiple topics are covered by a single SOP, it will aid the inspection process if the Processing Facility prepares a crosswalk between the list of required SOPs in Standard D5.1 and the facility's SOPs.

If a Processing Facility is operated out of a larger organization or institution (e.g., transfusion services) and shares certain SOPs or policies with the other service or the organization, then an index of the shared policies and SOPs should also be submitted.

Example(s):

Policies and SOPs can be generated within the Processing Facility or in collaboration with other institutional infrastructures. The facility may have a policy in place for patient confidentiality. The policy would provide a general overview of institutional SOPs and guidelines in place for the entire institution for patient confidentiality.

Some Processing Facilities may handle cells as starting material or as final cellular therapy products for third party manufacturers. These manufacturers may require processes different than what is outlined in the facility's SOPs for its usual activities. When this occurs, the facility may handle different manufacturer requirements via the planned deviation process (acceptable for infrequent situations), additions within existing SOPs, or separate SOPs for those processes. The Processing Facility is responsible for verifying that the different process achieves the intended results.

Both FACT and JACIE have published Quality Handbooks (the [FACT Quality Handbook](#) and [The JACIE Guide](#)) to provide additional explanation of quality principles. These handbooks can be used as additional resources to develop policies and SOPs in compliance with the Standards.

STANDARD:

D5.1.1 Donor and recipient confidentiality.

Explanation:

Confidentiality is a critical aspect of care management, and it is applicable in every case. How programs manage confidentiality will look different based on the type of program (e.g., autologous, related allogeneic, unrelated allogeneic).

Example(s):

Donor and recipient confidentiality includes confidentiality of records.

STANDARD:

D5.1.2 Cellular therapy product receipt.

D5.1.3 Processing and process control.

D5.1.3.1 Appropriate processing procedures for specific products, including cryopreservation and thawing.

D5.1.4 Processing of ABO-incompatible cellular therapy products, including a description of the indication for and processing methods to be used for RBC and plasma reduction.

Explanation:

Major ABO incompatibility (donor's RBCs have antigens missing on the recipient's cell surface, towards which the recipient has circulating isohemagglutinins) requires most frequently an intervention in case of bone marrow grafts, as immediate or delayed hemolysis, delayed erythropoiesis and pure red cell aplasia may occur. Graft management in pediatric patients is even more challenging, as described in [*ABO incompatible graft management in pediatric transplantation*](#) (Balduzzi, Böning, Jarish, et al. *Bone Marrow Transplant*. 2021;56(1):84-90).

Example(s):

ABO incompatibility in relation to volume is a specific specialized topic that requires dedicated training and competency assessment, as cellular therapy product issues are different among apheresis, marrow collection, cord blood collection, and others.

Similarly, cord blood preparation for administration requires clinicians have dedicated training and competency in providing proper orders for washing, diluting, or reducing RBCs from the cellular therapy product.

STANDARD:

- D5.1.5 Prevention of mix-ups and cross-contamination.*
- D5.1.6 Labeling, including associated forms and samples.*
- D5.1.7 Cellular therapy product expiration dates.*
- D5.1.8 Cellular therapy product storage, including alternative storage.*
- D5.1.9 Release and exceptional release.*

Explanation:

Release is defined as the removal of a cellular therapy product from in-process status when it meets specified criteria. Processing Facilities must have release criteria for when a cellular therapy product can be distributed to the Clinical Program or outside facility. Release criteria are not only applicable to directly releasing a cellular therapy product for administration, but also to releasing a cellular therapy product to another facility (e.g., to another Processing Facility for processing and storage, third-party manufacture).

Each cellular therapy product must be verified to have met release criteria before being released. SOPs must outline how this verification takes place and who approves the release. There may be times when a product does not meet release criteria. An SOP must define the process for exceptional release, outlining the steps to take for documentation and approval.

Evidence:

The inspector will review the SOP(s) describing the release criteria and the process for release of cellular therapy products that meet those criteria. The inspector will also verify existence of an SOP for exceptional release, including documentation and approval.

Example(s):

In addition to release to a Clinical Program, cellular therapy products may be released from the Processing Facility directly to outside manufacturers or unrelated donor registries.

Examples of release criteria include, but are not limited to:

- Correct labeling, including storage temperature and expiration date.
- Sealed secondary container.
- Completed allogeneic donor eligibility documentation.

STANDARD:

- D5.1.10 Packaging, transportation and shipping, including methods and conditions within the Processing Facility and to and from external facilities.*

Explanation:

Processing facilities must have an SOP for both transportation and shipping, even if the Processing Facility does not currently perform one of those distribution methods. A need may arise for transportation or shipping on an ad hoc basis.

STANDARD:

- D5.1.11 Cellular therapy product recall, including a description of responsibilities and actions to be taken, and notification of appropriate regulatory agencies.*
- D5.1.12 Cellular therapy product disposal.*
- D5.1.13 Critical equipment, reagent, and supply management, including recalls and corrective actions in the event of failure.*
- D5.1.14 Equipment operation, maintenance, and monitoring, including corrective actions in the event of malfunction or failure.*
- D5.1.15 Cleaning and sanitation procedures, including identification of the individuals responsible for the activities.*
- D5.1.16 Environmental control, including a description of the environmental monitoring plan.*

Explanation:

The Processing Facility must have policies and SOPs defining how environmental concerns will be managed including factors which directly affect the cellular therapy product, equipment, or personnel performance.

STANDARD:

- D5.1.17 Handling and disposal of medical and biohazard waste.*
- D5.1.18 Processing Facilities utilizing genetically modified cellular therapy products shall incorporate or reference institutional or regulatory requirements relating to biosafety practices, including handling and disposal.*

STANDARD:

D5.1.19 Cellular therapy emergency and disaster plan, including the Processing Facility response.

Explanation:

SOPs addressing safety, infection control, biohazard disposal, radiation safety, and planned emergency response to disasters may be standardized throughout the institution. However, in cases such as an institutional disaster plan, such plans usually outline general actions to be taken. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for review and approval. The Processing Facility's disaster plan must include actions to be taken in case of a disaster (such as how to locate and use emergency power) and include specifics such as how to proceed if a cellular therapy product is undergoing cryopreservation at the moment of the disaster or what to do if products need to be moved.

Example(s):

Examples of disasters include fires, hurricanes, floods, earthquakes, nuclear accidents, and pandemic disasters. Infectious threats include failure of isolation facilities; outbreak of aspergillosis, respiratory syncytial virus (RSV), or (para) influenza; or pandemics, leading to an emergency closure or modifications to practices of the Processing Facility. The Processing Facility shall maintain a detailed list of all controlled documents, including title and identifier.

In cases where institutional policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the facility, the facility must develop its own policies and SOPs. The article [*Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program*](#) (Wingard, Leahigh, Confer, et al. *Biol Blood Marrow Transplant*. 2006;12(11):1229-38) provides a framework for disaster plans that can be customized for individual facilities.

Additionally, the FDA offers information on its webpage [*Impact of Severe Weather Conditions on Biological Products*](#) (2018).

STANDARD:

D5.1.20 Chain of Identity.

D5.1.21 Chain of Custody.

Explanation:

Chain of Custody and Chain of Identity policies and procedures in this document pertain to the cellular therapy product. The Processing Facility must have a policy or SOP for the linkage to allow tracking and traceability of each product through all steps from collection to administration or final disposition. Documentation in the medical record should include the proper product name, unique product identifier(s), ISBT 128 DIN and product code, EU SEC or equivalent. There must be a process, including the use of the ISBT 128 barcode or other barcode or unique numbering system, to track

and trace specimens removed from a cellular therapy product for testing at an external facility such as an HLA testing facility, transfusion service, or microbiology laboratory. This process must ensure a linkage between the results of testing and the original product. There should also be a means, direct or indirect, that will allow outcome information to be related back to any other facilities involved in the collection, processing, and distribution of the product. The final disposition of the product must be documented, and whether the product was administered, destroyed, released, or used for research, remains in storage, or other disposition. The tracking and tracing system must comply with the Standards and Applicable Law.

While linkage must be maintained, the identity should not be readily apparent in the later stages of processing and storage. With the requirement to maintain long-term linkage with the donor, there is information collected and stored that could allow tracing of the donor by an interested third party. The Processing Facility must demonstrate processes in its record system that prevent the unnecessary display of such demographic information.

STANDARD:

D5.2 The Processing Facility shall maintain a detailed list of all controlled documents, including title and identifier.

Explanation:

Controlled documents must be maintained in an organized fashion so that all current documents can be found. Many Collection Facilities have adopted an electronic method of compiling their policies and SOPs, which is acceptable. Hard copy, bound manuals also meet the intent of the Standard. There must be a list of all SOPs to serve as a master index or table of contents from which personnel can determine which SOPs exist.

Evidence:

The detailed list should be organized in such a manner that the inspector can ascertain that the controlled documents are comprehensive and define all aspects of the Processing Facility.

Example(s):

A Processing Facility may choose to have one detailed list of controlled documents or divide controlled documents into several manuals or electronic folders by subject. For example, a technical procedure manual in conjunction with quality, policy, and database manuals may serve to better organize information if the facility chooses this format.

STANDARD:

D5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual Standard Operating Procedure shall include:

Explanation:

Policies and SOPs must be detailed, unambiguous, and adequately define all operational aspects of the Processing Facility. Policies in general should identify an intended goal and include the elements required to meet that goal. However, policies may need one or more associated SOPs to actually describe the actions that are taken. The minimal elements must be included in all SOPs; if one of the items is not applicable, this should be indicated with N/A.

Evidence:

Compliance with most of the Standards in this section can be determined before the on-site inspection by review of the document control system and submitted SOPs contained within the pre-inspection material. However, additional SOPs should be reviewed during the inspection for compliance.

Example(s):

In some Processing Facilities, the actual "SOP" may be limited to minimal work instructions, and required elements such as a reference list may be found only in higher level documents. Such variability is acceptable if all elements are documented and readily available to staff. [*The Art of Writing and Implementing Standard Operating Procedures \(SOPs\) for Laboratories in Low-Resource Settings: Review of Guidelines and Best Practices*](#) describes suggested practices for writing SOPs (Barbé, Verdonck, Mukendi, et al. *PLoS Negl Trop Dis.* 2016;10(11):e0005053). Adherence to a uniform format is required to maintain documents.

STANDARD:

D5.3.1 A clearly written description of the objectives.

D5.3.2 A description of equipment, reagents, and supplies used.

D5.3.3 Acceptable endpoints and the range of expected results.

Example(s):

The Processing Facility should establish a range of acceptable results, when appropriate, for each procedure. Examples include nucleated cell recovery, absolute CD34 cell counts, viability, hematocrit, sterility, DMSO concentration, and plasma volume. The range for a given parameter can be determined within the facility by retrospective analysis of its own data. Determination of a mean $\pm$ standard deviations from such an analysis may be used to define an acceptable range. Alternatively, if local data is insufficient or unavailable, reference ranges may be established from available literature.

STANDARD:

- D5.3.4 A stepwise description of the procedure.*
- D5.3.5 Reference to other policies or Standard Operating Procedures required to perform the procedure.*
- D5.3.6 A reference section listing appropriate and current literature.*
- D5.3.7 Documented approval of each Standard Operating Procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation and every two (2) years thereafter.*
- D5.3.8 Documented approval of each procedural modification by the Processing Facility Director or Medical Director, as appropriate, prior to implementation.*

Explanation:

The Standards require documented review of each SOP by the Processing Facility Director or by the Processing Facility Medical Director every two years. Policies or SOPs that affect the clinical use of cellular therapy products, such as those for reporting adverse reactions to product administration or SOPs for reporting results of microbial testing, should be approved and reviewed by the Processing Facility Medical Director. It is important that the documentation of review every two years clearly indicates the version of each policy or SOP that was reviewed.

Example(s):

A review signature on the document itself or on a listing of the reviewed documents by name that includes the unique identifier and version is acceptable proof of document review. A validated electronic review system is also acceptable. A single page in the manual with a signature and a date is not sufficient since SOPs may be revised throughout the year. Approving several SOPs at once with a single signature and date is not sufficient, as it does not demonstrate that individual SOPs were actually reviewed and approved.

STANDARD:

- D5.3.9 Reference to a current version of orders, worksheets, reports, labels, and forms.*

Explanation:

Current versions of worksheets, reports, labels, and forms, where applicable, must be present and may be identified in or attached to each SOP. The purpose of this Standard is to confirm that these documents are easily accessible to a reader of the SOP and that it is clear what documents may be required for the performance of that SOP. Review of SOPs should include review of the applicable worksheets, forms, and attachments.

Example(s):

It may be prudent to attach one or more completed forms to illustrate possible real-life scenarios. Reference to additional policies and SOPs necessary to perform a procedure is required as is a listing of worksheets, forms, and/or other necessary documentation. For electronic systems, the use of links is acceptable.

STANDARD:

D5.4 Controlled documents relevant to processes performed shall be readily available to the facility staff.

Explanation:

The written copy or electronic version (with provisions to an appropriate backup copy, such as a hard copy or access to a backup electronic version on a downtime computer as necessary) of the Processing Facility's policies and SOPs relevant to the work schedule and duties must be immediately available to all relevant employees in their working environment. Similar to the ability to divide related SOPs into different SOP manuals, facilities may choose to only have necessary SOPs to perform specified processes at a workstation. However, all SOPs that an employee must comply with must be readily available to them for reference when needed.

If an electronic manual is used, there must be a mechanism to obtain access to the SOPs at all times, even if the network is not available. Policies, SOPs, and associated worksheets, reports, and forms must be available to each staff member at all times. The current version of electronic documents should be accessible with proper access codes.

Evidence:

The written copy or electronic version of the SOPs should be readily identifiable and available to the inspector. The inspector should expect to see the appropriate SOPs or electronic access to SOPs in all performance areas of the Processing Facility. The inspector should look for evidence that procedures are performed as written in the SOPs, and that appropriate backups are easily accessible in the event electronic access is down or unavailable.

STANDARD:

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

Explanation:

Before a staff member is allowed to perform new and revised procedures, they must have reviewed or received the applicable training. The level of training is dependent on the impact of the revision to the policy or SOP. Processing Facilities must document an individual's review or training before that person uses the revised policy or SOP.

Example(s):

Sometimes a revision to a policy or SOP is minor, such as an update to a referenced regulation or grammatical corrections. In these cases, full training may not be necessary, and review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

It is recommended that every policy and SOP and associated revisions have a specific signoff sheet to document that each staff member required to review the policy or procedural revision has done so prior to performing the task(s) described. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each procedure and to any major revision also facilitate documentation of appropriate training of staff.

STANDARD:

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

Evidence:

The inspector should observe on-site that procedures are performed according to the written SOPs.

STANDARD:

D5.7 Planned deviations shall be pre-approved by the Processing Facility Director or Medical Director and reviewed by the Quality Manager.

Explanation:

Planned deviations should be approved by the Processing Facility Director or Medical Director at a minimum. Retrospective review by the Quality Manager must be performed in compliance with processes designed for deviations. Processes set up for review of planned deviations are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately.

Example(s):

Planned deviations may be necessary in the following scenarios:

- Expired reagents.
- Alternative reagents.
- Release of product with pending sterility results.
- Release of expired product.

D6: EQUIPMENT, SUPPLIES, AND REAGENTS

STANDARD:

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

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

Explanation:

The amount of relevant equipment in the Processing Facility should be appropriate for the type of processing performed, proportionate to the volume of work done, and should be conveniently located. It is not acceptable to share equipment with other laboratories under conditions in which the sterility, integrity, or viability of the cellular therapy product may be compromised.

For critical pieces of equipment (e.g., biological safety cabinets, centrifuges), there should be backup equipment immediately available, or a well described backup plan should exist in the case of primary equipment failure. This plan should identify alternative equipment that can be used and should describe how that equipment is qualified for use to confirm it meets the requirements of the procedure.

Evidence:

The inspector will evaluate whether there is adequate equipment available in the Processing Facility, if the equipment is being used appropriately, and if there is a backup plan in the event of equipment failure.

The inspector should review documentation that adequate materials are present, and have been present, for the level of activity conducted by the Processing Facility. A well-stocked supply cabinet or supply area would indicate adequate materials are in inventory. The center should have an inventory list that defines critical supplies and their quantity based on the scope and the activity of the center. A policy or SOP outlining material management, including how availability and adequacy are ensured, must be verified.

Example(s):

Examples of inadequate equipment include:

- Sharing a biological safety cabinet for the purpose of cell processing with any other laboratory whose activities might pose a risk of microbial contamination; for example, samples used by a microbiology department and research staff.
- Having limited or remote access to a cell counter, leading to processing delays.

- Using a refrigerator or freezer for reagents that is also used for food or beverages.
- Performing different procedures on multiple cellular therapy products in the same biological safety cabinet simultaneously.

Frequent “emergency” orders might suggest that an inadequate supply of material is being kept in inventory.

Just-in-time is a materials management system of centralized inventory control where necessary materials, supplies, and reagents are delivered at the time of need. Documentation of “just-in-time” policies and SOPs for management of materials needed for cellular therapy product processing is acceptable so long as this practice can be confirmed by the inspector as having the desired result.

STANDARD:

D6.3 There shall be a process for inventory control that encompasses equipment, containers for transport and shipping, supplies, reagents, and labels.

Example(s):

Examples of containers for transport and shipping include cryopreserved vials, bags, syringes, and cartridges. Secondary containers can include cartons, metal cassettes, or thermal insulated cases with the appropriate refrigerants such as dry ice or liquid nitrogen. Each container must be appropriate for the product’s intended use.

STANDARD:

D6.3.1 There shall be a system to uniquely identify, track, and trace 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.

Explanation:

Cellular therapy product quality, as measured by adequate viability, integrity, lack of microbial contamination, or lack of cross-contamination, may be affected by the equipment used for processing. Therefore, equipment used in processing must be identified and tracked. For this purpose, there must be a system by which the critical equipment can be uniquely identified.

Critical materials must be defined by the Processing Facility and tracked under its materials management system. Processing records for each cellular therapy product must include the identity of all critical supplies and reagents used in the procedure. This is generally tracked by including a listing of the name of the item, manufacturer, lot number, and expiration date (where available) of the material in the processing record. The materials management system must also allow tracing of all products manufactured using a given lot of reagent or supply. There are a variety of ways this can be accomplished, so long as the information can be easily obtained.

It is also important that the system in use allows for the identification of all cellular therapy products that are processed using a given piece of critical equipment. An identifier must be assigned to critical equipment even if there is only one in the Processing Facility.

Evidence:

The inspector should request documentation that demonstrates that critical equipment is numbered in a consistent fashion, that the use of the equipment is tracked by some mechanism (usually date and time of use) as appropriate, and that the equipment can be traced back to each cellular therapy product that was processed using the equipment.

Example(s):

This can be achieved by using a pre-existing serial number but may be better achieved by assigning a unique identifier that is visible on the piece of equipment. A more casual designation, such as "Brand X centrifuge," may be less desirable since over the course of time more than one centrifuge might fit that description. A reagent or consumables log in the processing record could be used.

For situations in which there is a product recall of a lot of human serum albumin (HSA) found to be contaminated with a virus, it is important to be able to easily identify all products processed using that lot of HSA to be able to determine if they are acceptable for use.

The inventory control system may be manual or electronic. Ordering and stocking procedures to limit the number of different lots of reagents and supplies in the Processing Facility at a given time may be part of an inventory control program.

STANDARD:

D6.3.2 Each supply and reagent used to manufacture cellular therapy products shall be visually examined for damage or evidence of contamination.

D6.3.2.1 Supplies and reagents shall be quarantined prior to use until verified to have met acceptance criteria.

D6.3.3 Records of receipt shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.

D6.3.4 Materials shall be stored under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix-up or unintended use.

Explanation:

Supplies and reagents used for processing must be stored according to the manufacturer's recommendation and in a manner that preserves their function and sterility. For items requiring

storage at defined specifications such as temperature and humidity, the conditions of the storage area must be monitored and documented.

Locally sourced reagents used in cellular therapy product processing requiring GMPs must also be GMP grade or have a COA or Drug Master File. If not GMP grade, they must be part of an IND and be qualified for use.

Evidence:

The inspector should observe storage areas and confirm that supplies, reagents, and containers used for shipping and transport are stored under the conditions specified by the manufacturer. The inspector should confirm that the storage area is clean and sanitary and that suitability for use of supplies and reagents is not compromised during storage.

When refrigerators and freezers are used to store cellular therapy products, supplies, or reagents, the inspector should look for evidence that each is appropriately labeled and adequately separated so as not to cause confusion or compromise the integrity or sterility of the contents.

Example(s):

This can be accomplished by storing cellular therapy products on a designated shelf that is appropriately labeled for that purpose, utilizing designated labeled compartments, or by other procedures. It is recommended that outdated supplies and reagents and those not intended for clinical use be stored in a separate unit from those designated for patient care if possible. When this is not possible, outdated or research materials must be clearly distinguished from clinical materials and appropriately labeled.

STANDARD:

D6.3.5 Supplies and reagents coming into contact with cellular therapy products during processing, storage, or distribution shall be qualified, sterile, and meet predetermined specifications for the intended use.

Explanation:

Supplies and reagents that come into contact with cellular therapy products must be free of microbial contamination. Clinical or pharmaceutical grade products should be used. If such products are not available, an equivalent substitute shall be identified for the specified purpose and undergo functional qualification to show that it demonstrates consistent performance and is acceptable for human use (see [D4.14](#) and its guidance).

Evidence:

The inspector should request COAs or manufacturer documentation that the supply or reagent meets pre-determined specifications. SOPs or policies should be available that define supply and reagent specifications and qualification.

Example(s):

Examples include a COA or the manufacturer's certification of sterility.

STANDARD:

D6.3.5.1 Reagents shall undergo initial qualification and meet predetermined specifications for the intended use.

D6.3.5.2 Reagents shall undergo risk assessment as part of their initial qualification to ensure product integrity and safety.

Explanation:

All reagents should undergo initial qualification and risk assessment to ensure the reagents are acceptable for cellular therapy product integrity and safety. For reagents specifically designated as pharmaceutical or clinical grade, review of package inserts, labeling, and COA may be sufficient. However, when no acceptable clinical or pharmaceutical grade reagents are available, reagents should undergo initial functional qualification and lot-to-lot verification.

Evidence to support reagent qualification may include:

- Use under IND, IDE, or other exceptions approved by the appropriate regulatory agency.
- Data supporting that no acceptable, equivalent reagent of the appropriate grade is available.
- Literature supporting use of the reagent for the specified purpose.

Any significant change to a reagent (e.g., different reagent, different manufacturer) requires additional qualification and risk assessment to demonstrate that there are no adverse effects to processes.

In situations when obtaining donor cellular material solely for the purpose of functional verification is not feasible, the first run performed with a new lot (under a planned deviation) may serve as the validation or verification run for the new reagent.

Reagents that are not approved for clinical use may be used if an equivalent reagent of appropriate grade is not available, if the use has been authorized by the national authorities.

Example(s):

Qualification of a reagent used in processing (e.g., washing, freezing, other cellular therapy product manipulation) can often be achieved by review of the COA. This document should list contents and concentration of the reagent and state if the reagent is sterile and safe for human use.

Examples of statements that are used on COAs of reagents considered to be of the appropriate grade include:

- "A Sterile and Endotoxin Free (According to Ph.Eur. [European Pharmacopoeia]/USP [United States Pharmacopeia]) Non pyrogenic cryopreservative solution."
- "Complies with USP" or "Complies with Ph.Eur."
- "This batch complies with the specifications of the USP and Ph.Eur."
- "Grade: USP" or "Grade: Ph.Eur."
- "Cryoprotectant for the cryopreservation of human cells and tissues for transplantation."

For products undergoing more than minimal manipulation, a relevant example would be the use of human AB serum or Fetal Bovine Serum as a supplement used in the manufacturing process. According to federal regulations, this reagent should be checked prior to its first use to ensure that it was properly tested and donors appropriately screened for adventitious agents, does not contain xenogeneic components, and has undergone testing for sterility and endotoxin. The reagent would then be tested for functionality by testing it against a representative standard or testing it in the manufacturing process itself. Typically, samples from a minimum of three lots are tested for functionality, and the most functional reagent lot is then purchased in bulk.

STANDARD:

D6.3.5.3 Reagents shall undergo lot-to-lot verification to ensure that the new lot meets specifications.

D6.3.6 Non-disposable supplies or instruments shall be cleaned and sterilized using a procedure verified to remove infectious agents and other contaminants.

Explanation:

For some specialized processing procedures, equipment or instruments that come into contact with the cellular therapy product may require cleaning and sterilization between uses. When this is the case, the Processing Facility must verify that the cleaning and sterilization methods used remove infectious agents.

Evidence:

The inspector should review the records of this verification process.

Example(s):

Surgical equipment for tissue manipulation, such as scissors, forceps, and scalpel handles, are examples of non-disposable supplies or instruments that may be included in processing procedures.

STANDARD:

D6.3.7 Supplies and reagents shall be used in a manner consistent with manufacturer instructions.

Explanation:

It is recognized that reagents typically utilized in processing may be used for indications that are not specifically indicated on the manufacturer's instructions. In these cases, "consistent with manufacturer's instructions" would include considerations such as sterility and final mode of administration and could be compliant with this requirement.

Evidence:

The inspector should request and review product package inserts and supply and reagent information that describes the supply or reagent and its intended use.

Example(s):

Package inserts from supplies and reagents such as antibodies, serum components, or packaging supplies would meet this requirement.

STANDARD:

D6.3.8 There shall be a process to prevent the use of expired reagents and supplies.

Explanation:

There should be a mechanism to monitor the flow of supplies and reagents within the Processing Facility to prevent the use of outdated supplies and reagents. This system should also be able to identify the location of a given lot of a supply or reagent in the event that there is a manufacturing recall.

Evidence:

The inspector should evaluate the inventory control system to determine if it is adequate to prevent the use of outdated or damaged supplies and reagents.

Example(s):

A first expired, first out system is one that is most commonly encountered. This mechanism can be tracked on paper or via a computer program.

STANDARD:

D6.3.9 Equipment, supplies, and reagents for processing shall conform to Applicable Law.

Evidence:

Where applicable, the inspector should review documentation of relevant regulation for CE/UL (Underwriters Laboratories) marking.

Example(s):

European Directive [2006/17/EC](#) Annex IV 1.3.10 specifies that where possible, equipment that is compliant with the CE Marking Directive must be used for cellular therapy product processing. CE marking is a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation implementing certain directives. Staff using such equipment must have appropriate training.

In the U.S., Nationally Recognized Testing Laboratories (NRTLs) are testing facilities recognized by OSHA and are primarily private-sector organizations that provide product safety testing and certification services to manufacturers. UL, a recognized Nationally Recognized Testing Laboratory, is one such independent, not-for-profit product safety testing and certification organization that issues UL marks and certifications. An example of appropriate equipment marking is UL testing certification for a water bath/circulator.

Nationally Recognized Testing Laboratories cooperate with code authorities (e.g., building, electrical, fire, plumbing) to safeguard that the equipment installations they authorize will be safe for community use. For example, the UL Mark indicates compliance with the applicable safety requirements in effect in North America and is evidence of UL certification, which is accepted by model North American installation codes such as the National Electrical Code (NEC) and the Canadian Electrical Code.

In contrast, the CE Marking is not a safety certification mark, is generally based on self-declaration rather than third-party certification (e.g., Nationally Recognized Testing Laboratories) and does not demonstrate compliance to North American safety standards or installation codes. A product that bears a CE Marking may also bear a certification mark such as a UL Listing Mark. However, the CE Marking and the UL Mark are not associated. For more information, visit <https://www.osha.gov/nationally-recognized-testing-laboratory-program>.

STANDARD:

D6.4 There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration.

D6.4.1 Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner. Equipment shall be located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules, as described in Standard Operating Procedures, and in accordance with the manufacturer's recommendations.

D6.4.1.1 The equipment shall be inspected for cleanliness and verified to be in compliance with the maintenance schedule prior to use.

Explanation:

There must be a schedule for equipment cleaning and maintenance. Schedules may vary based on frequency of use, performance stability, or recommendations from the manufacturer. Equipment used for processing or cellular therapy product testing must be located to allow access for maintenance and calibration. Preventive maintenance shall meet manufacturer recommendations. It is also important to maintain a schedule of equipment cleaning, sanitation, and disinfection that is described by an SOP.

The Processing Facility must perform a risk assessment (at a minimum to include the manufacturer's recommendations) of its equipment to determine how often the maintenance schedule must be reviewed and how compliance will be documented.

Evidence:

The inspector should verify that equipment is evaluated for cleanliness and that maintenance records have been reviewed for compliance prior to use. The inspector should confirm by visual inspection that equipment can be easily accessed for cleaning, disinfection, and maintenance.

Example(s):

The Processing Facility should define in its policies and SOPs the maintenance schedule for each piece of equipment used. A risk-based approach can be used when determining which items need to be inspected prior to each use or after a defined number of consecutive uses (e.g., after every ten uses). Manufacturers' recommendations should always be followed at a minimum. It is recommended that recent records of regularly scheduled maintenance, cleaning and calibration be readily available for each piece of equipment.

STANDARD:

D6.4.2 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.

Explanation:

Equipment SOPs must also describe how the equipment is operated or refer to relevant operations manuals that are available within the Processing Facility. Maintenance and calibration are required to detect malfunctions and defects and to safeguard that the critical parameters are maintained within acceptable limits at all times. There must be a schedule for equipment maintenance and quality control. Calibration and maintenance may be contracted with another entity, such as a biomedical department or manufacturer. The Processing Facility is responsible for maintaining a record that calibration and maintenance were performed appropriately.

Logs should be available near the equipment, or tags or stickers should be visible on the equipment, indicating that calibration parameters have been met, the date preventive maintenance and calibration were performed, and when such testing is next due. Where applicable, calibration procedures should include limits for accuracy and precision.

Evidence:

On-site, the inspector should see a sampling of calibration records and confirm that traceable standards have been used. The inspector should look for SOP(s) describing the corrective action to be taken when precision and accuracy limits are not met and written instructions to be followed if the equipment fails. Records to document these activities, including investigation of potential adverse events caused by cellular therapy products, should be available to the inspector.

Example(s):

Schedules may vary among Processing Facilities, based on frequency of use, performance stability, or recommendations from the manufacturer. It is recommended that recent records of regularly scheduled maintenance and quality control be readily available for each piece of equipment.

STANDARD:

D6.4.2.1 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.

Explanation:

Equipment identified by the Processing Facility to have a critical measuring function, such as thermometers, timers, and scales, must be calibrated against a traceable standard. A traceable standard is one that can be directly linked to a provider that has documented the accuracy of the measuring device.

Example(s):

Examples of traceable standards include National Institute of Standards and Technology (NIST) for the U.S., CE label or DIN Norm (*Deutsches Institut für Normung* or German Institute for Standardization) for the EU, reference thermometers, stop watches, and tachometers. Other vendors may provide similar products, but they must have a direct link to records indicating accuracy to a known standard. An alternative to using the actual traceable standard is to calibrate a similar device against the traceable standard and use the newly qualified device for routine measurements. If a traceable standard cannot be obtained, then the Processing Facility must document how they determined the measurement reading to be accurate.

STANDARD:

D6.4.2.2 Calibration shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.4.2.3 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.

Explanation:

When equipment is found to be out of calibration or specification, the validity of previous measurements and decisions based on those measurements should be reviewed. There should be documentation that the cellular therapy products manufactured during this period of uncertainty have been evaluated and determined to conform to specification, or that corrective action has been documented. This should include an investigation of potential adverse events related to manufactured products using the equipment tracking system. Note that if critical equipment used in processing is located outside of the Processing Facility, such as sterilization equipment, it is the facility's responsibility to confirm that equipment is properly maintained and calibrated.

Evidence:

The inspector should review maintenance records to determine what actions were taken for equipment that failed a calibration or specification test.

Example(s):

A centrifuge used for washing cells after culture was found to have 25% less centrifugal force than the settings indicated at the most recent calibration. The processing records of cellular therapy products produced using that instrument since the last calibration should be reviewed to determine if there was cell loss outside of expected ranges or any other effect of the inadequate washing. If there are concerns, the clinical outcome of patients receiving the affected products should be analyzed and the patients' physician(s) notified.

STANDARD:

D6.5 Lot numbers, expiration dates, manufacturers of critical reagents and supplies, and key equipment used in each procedure shall be documented.

Explanation:

There must also be a complete record of lot numbers and expiration dates for reagents and disposables used for the procedure. Likewise, the identity of the key equipment used during processing must also be documented. It is critical to be able to link reagents, supplies, and equipment to the processing of each cellular therapy product in the case of an adverse event or recall of reagents, supplies, or equipment. Implementation of a carefully planned inventory control system helps to facilitate documentation of lot numbers; prevention of the use of outdated or quarantined supplies; and linkage of products processed to reagents, supplies, and equipment in a timely manner.

Evidence:

Processing chart records are required to contain a listing of the required reagent and supply lots and the equipment used. Those records should be available for inspector review.

D7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

STANDARD:

D7.1 ISBT 128 AND EUROCODE CODING AND LABELING

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

Explanation:

ISBT 128 is the international information standard for transfusion and transplantation. Initially, ISBT 128 was developed for blood and blood component transfusion but has now been extended to include cellular therapy products and tissues. [ICCBBA](#) is the not-for-profit organization that is responsible for the development and maintenance of the ISBT 128 standard. ICCBBA maintains the databases for facility identification and product coding, assigns new product codes, and provides technical support.

Several volunteer technical advisory groups support and inform ICCBBA. The Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) comprises representatives from major cellular therapy professional organizations. Its purpose is to advise ICCBBA of the needs of cellular therapy organizations for coding and labeling.

The two main pieces of the standard terminology used to unambiguously describe a cellular therapy product are class and attributes. Classes are broad descriptions of products (such as HPC, Apheresis) and attributes are additional characteristics that uniquely define the product. A group of attributes, called Core Conditions, are required; these conditions include anticoagulant or additive, nominal collection volume, and storage temperature. There are also other characteristics called groups and variables that can be used to provide more information about the product. The intent is to capture relevant characteristics about the product from the donor and collection through the final processing. It is not intended that products would be relabeled at the bedside, so attributes such as “thawed” would only be applied if that process occurred in the laboratory.

Cellular therapy products must be labeled using the ISBT 128 standard terminology. The labels must contain both machine-readable electronically stored information (e.g., bar codes) and eye-readable text. The text may be in the native language of the country in which the product is collected. The machine-readable technology must be universally understood such that international transport and exchange will be facilitated.

The standard terminology is structured in a manner that allows revisions, additions, and deletions as necessary on a continuous basis. In this edition of Standards, under “Definitions” then “Products,” the common major classes of cellular therapy products have been defined as was current at the time of publication. Attributes were not included because of their sheer number and complexity. As the responsible body for the development and maintenance of the databases for product coding, ICCBBA is the appropriate authority for maintaining publications on current terminology. To prevent use of obsolete terminology, the Collection Facility is instructed to refer to Chapter Three, Cellular Therapy, of the [*ISBT 128 Standard Terminology for Medical Products of Human Origin*](#) for current terms and definitions related to cellular therapy. The website also includes resources and tools for identifying and assigning standardized codes for cellular therapy products or requesting a code for a new unique product. Additional information and assistance can be obtained by contacting ICCBBA directly.

To utilize ISBT 128 and obtain a unique facility identification code that becomes part of each product’s unique alphanumeric identifier, facilities must register with ICCBBA. Facilities in or affiliated with hospitals may find that their blood bank has already registered and a unique facility code already exists. Stand-alone facilities can register individually.

Eurocode-IBLS provides an international non-profit standard for labeling blood products and tissues to enhance security in blood transfusion and tissue transplantation.

The main benefits of Eurocode-IBLS are:

- One bag - one number (unique product bag number worldwide).
- Unique coding of product properties.
- Country codes following [*ISO 3166*](#).
- Center codes according to national agreements.

- Matching enhanced space-saving barcode systems.
- Charge-free access to all information via Internet.

Eurocode-IBLS assigns, publishes and maintains the databases for Eurocode facility identification (Center Codes) and product coding.

Centers using Eurocode require a Eurocode membership. All resources, such as Eurocode's technical specification, guidelines, and the databases including all product and center codes, can be accessed on <https://www.eurocode.org/>.

Eurocode product codes characterize each product by the product group it belongs to, supplemented by a set of properties laid out in up to 18 predefined categories, such as anticoagulant used, storage temperature, donor/recipient relationship, and intended use. These property categories are called "qualifiers."

Both ISBT 128 and Eurocode product codes are compliant with the EU SEC.

Evidence:

Inspectors will inspect Processing Facilities according to the current ISBT 128 or Eurocode terminology and definitions, as applicable.

Example(s):

The appropriate product name for HPCs collected by apheresis is HPC, Apheresis. The acronym HPC(A) would be an acceptable abbreviation in documents and on partial labels. However, the U.S. FDA does not allow abbreviations on final product labels for licensed products.

STANDARD:

D7.1.2 Coding and labeling technologies shall be implemented using ISBT 128 or Eurocode.

Explanation:

The use of ISBT 128 or Eurocode for all cellular therapy products provides a uniform coding and labeling system worldwide that is supported by FACT, JACIE and numerous other cellular therapy organizations. Such standardization is beneficial for, and thus required for, autologous as well as allogeneic products. The most recent version of the [ISBT 128 Standard Terminology](#) is published on the [ICCBBA website](#), as well as resources to help centers implement ISBT 128. The [Eurocode website](#) features guidelines, product codes, and other resources.

Implementation of ISBT 128 or Eurocode is required for FACT accreditation, although as stated above, FACT does recognize that not all cellular therapy products previously collected will use this coding system.

STANDARD:

D7.1.3 Cellular therapy collections for further manufacturing should be labeled with the standardized ISBT 128/manufacturer label specified in [ICCBBA ST-018](#).

Explanation:

Using the standardized ISBT 128/manufacturer label specified in [ICCBBA ST-018](#) for cellular therapy products intended for further manufacturing is crucial for standardization and traceability, regulatory compliance, and minimized risk of errors. Further manufacturing refers to the processing, modification, or expansion of collected cellular products to create a final therapeutic product. Unlike cellular therapy products intended for direct infusion into a patient, those designated for further manufacturing serve as raw material for advanced therapies.

Example(s):

An example of a product collected for further manufacturing is an MNC product collected for the manufacturing of CAR T cells.

STANDARD:

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.

Explanation:

Labels must be pre-printed or printed on demand. Labeling operations must be described in an SOP. The use of labels and the method of labeling must be part of a processing SOP or described in a separate labeling SOP. The SOP(s) describing the process for pre-ordering labels should include each of the following:

- Ordering: initial orders and reorders.
- Receipt, quarantine, and reconciliation.
- Verification of accuracy.
- Proper storage.
- Version control.
- Inventory control.
- Destruction of obsolete or unusable labels.

Evidence:

Example labels will be available prior to the inspection visit, and label content (discussed below) will have been pre-reviewed by the FACT/JACIE office or by the respective inspectors. On-site, the inspector should verify that the labels submitted are in fact the labels in use at the Processing Facility and are being used appropriately. The inspector should focus more time on other aspects of the labeling process, specifically assessment of its adequacy to confirm proper identification of cellular therapy products and product samples.

Example(s):

Labeling processes should be reviewed during inspection (e.g., mock labeling, cellular therapy product chart) to determine if labels submitted are the same labels in use as per the SOP and how verification of label accuracy is documented.

STANDARD:

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

Explanation:

Labels must be stored in a designated area where access is limited to authorized personnel. Stocks of unused pre-printed labels and tags, such as biohazard labels and supplemental labels, must be stored separately to prevent errors. Labels should be organized physically or electronically so staff can readily identify the labels and be able to distinguish labels of different cellular therapy products from one another. It is not acceptable to have different labels stored together with no separation. The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors.

Evidence:

The inspector should observe that there is an organized storage area for the labels and that they are arranged in a manner to prevent mislabeling.

Example(s):

Printed labels can be in containers to provide separation of each label type. Electronic labels can be in separate file folders for each label type.

STANDARD:

D7.2.1.2 Obsolete labels shall be restricted from use.

Evidence:

The inspector should verify that the destruction process is documented and that there are no obsolete labels in the processing or storage area.

STANDARD:

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

Explanation:

New labels must be placed in a quarantine area upon receipt. The new labels must be reviewed for:

- Manufacturing or printing defects.
- Form or version number, if applicable.
- Legible and correct eye-readable information.
- Correct bar-code scanning.
- Identity to source (original) label that has been approved for use by the Processing Facility Director.
- Verify that specifications of the new lot match what has been validated.

The process and outcome must be documented prior to release of the labels from the quarantine area. It is recommended that the inspection of labels at receipt or after printing be performed by one person and independently verified by a second person. If bar code scanning technology is used, verification of appropriate scanning of the label should be included in this comparison before release. This Standard applies to pre-printed labels produced by the Processing Facility as well as those produced by a commercial manufacturer.

Evidence:

The process should be reviewed by the inspector to confirm that the intended labels are being generated.

Example(s):

A log or form(s) are often used to document receipt, quarantine, inspection against a master label book of pre-printed labels or label templates, evidence of accurate bar code scanning, and release for use or rejection pending disposal. Documentation should identify staff and dates when activities are performed.

STANDARD:

D7.2.3 A system of label reconciliation shall be used to ensure the final disposition of all labels allocated to a specific product is documented.

Explanation:

Label reconciliation applies to both pre-printed and on-demand labels.

The final fate of all pre-printed labels must be documented to ensure that a label allocated to a particular donor cannot be associated with the product, concurrent plasma, or related samples of another donor. The purpose of reconciliation is to ensure that all labels have been accounted for and no mix-up occurred. A system for label reconciliation that documents the number and type of labels received by the Collection Facility, the number of labels used, and the number of labels passed to another unit or destroyed shall be used.

Evidence:

The inspector shall review the relevant SOPs that detail the label reconciliation process in use and shall review examples of documentation of labels received, used, and passed to another unit or destroyed that relate to processing. The method of destruction of unused labels should be verified.

Example(s):

A form detailing the number of labels received, used, and passed to another unit or destroyed may be captured on processing worksheets, on another form associated with processing, or on a separate label reconciliation form. Unused labels may be affixed to the label reconciliation form or relevant processing-related form, crossed through and annotated to explicitly state that they are no longer in use.

STANDARD:

D7.2.4 Label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Processing Facility Director.

Explanation:

The system used to generate labels must be validated to confirm that each label type is in compliance with the template approved by the Processing Facility Director.

The validation plan will be dependent on the complexity of the labeling system but generally includes details about:

- Installation qualification (IQ), which tests and verifies that the hardware, software, and interfaces are installed properly and that the computer systems are maintained and backed up appropriately, including the user access and security requirements.
- Operational qualification (OQ), which tests operating parameters of the system at the limits, including process variables and repeated test cases to show system reliability under different conditions of use (typically the worst-case scenarios).
- Performance qualification (PQ), which includes test cases to demonstrate the system works as intended for use.

The SOP should include each of the following:

- Layout of the labels.
- Transfer of information to the label.
- Verification of accuracy.
- Proper storage.
- Version control.
- Destruction of obsolete or unusable labels.

When Processing Facilities print labels on demand, the manner in which the database is being generated needs to be validated. For automatic labeling systems using computer-assisted label verification of parts of the label, electronic verification must be part of the label system validation.

Evidence:

The validation of labels and the complete process should be reviewed by the inspector to confirm that the intended labels are generated. The validation of automatic label generation, including test cases and associated documentation and software-defined tables, should be reviewed by the inspector and provide evidence of the mechanisms used by the software to control and verify label content, including the use of bar-coded information. Validation of software-controlled labeling systems used to create or modify labels should be documented in a validation plan at the site. Testing by the supplier or vendor is not adequate.

STANDARD:

D7.2.5 A system for label version control shall be employed.

Explanation:

The document control system used for these various elements and what constitutes a label version must be defined by the Processing Facility. Any change in the label or label element that would change the interpretation of the label would constitute a version change. The version number may or may not appear on the label, as defined by the labeling process at each facility. Only the current version of each label should be available for use in the processing area. SOPs shall be in place to define system upgrade frequency (e.g., version upgrades to electronic systems). SOPs shall define when revisions shall be performed and what process of validation is to be used.

Evidence:

The label version control should be reviewed by the inspector to confirm that the intended labels are generated. The way archived labels are stored must be inspected. For label changes, there should be a process for controlled versioning and implementation of changes in systems, including archived label examples or templates and reconciliation of available and inventoried labels, as applicable to the labeling systems in use. SOPs should address the timeframe for retention consistent with Applicable Law.

Example(s):

A checklist where changes to a label's content are described is an example of how to document labeling changes. This could also include documentation of label content accuracy and destruction of obsolete labels. A master list of labels in use with version numbers helps with document control.

STANDARD:

D7.2.5.1 Representative obsolete labels with inclusive dates of use shall be archived for a minimum of ten (10) years after the last cellular therapy product was distributed or as defined by Applicable Law, whichever is longer.

Explanation:

Obsolete or unusable label stock should be defaced immediately to prevent their accidental use and then destroyed. However, as a controlled document, representative obsolete labels (or label templates) and their inclusive dates of service must be archived minimally for ten years after the last cellular therapy product was distributed, or as defined by Applicable Law, whichever is longer.

Evidence:

The inspector should review documentation of obsolete labels that have been destroyed. There should be no obsolete version of labels available to staff, and labels in use must be the same as the approved labels. The inspector should verify that the destruction process is documented and that there are no obsolete labels in the processing or storage area.

The inspector should review examples of archived obsolete labels and inclusive dates of service within the document control system.

STANDARD:

D7.2.6 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

D7.2.6.1 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process or two (2) qualified staff members.

Explanation:

No fewer than two people must confirm that manually entered information on the label is accurate. One person may verify information if a validated process, such as computer checks or barcoding, is used. New labels are usually generated only when the cellular therapy product is being processed. However, if relabeling needs to be conducted, for example, when confidentiality needs to be preserved in the case of a matched unrelated donor transplant, the SOP must include details on how to prevent errors. When transferring a cellular therapy product, labeling of new containers or samples shall meet the labeling requirements of the Standards, including documentation of verification of correct labeling information, whether by manual or automated methods.

Whether the Processing Facility verifies information by one qualified staff member using a computer-based system or by two qualified staff members, there must be documentation that the verification has been completed. In addition to confirming correct content, the label verification should include confirmation that:

- The label is correctly affixed to the product.
- The correct label is positioned appropriately.
- The label is identical to the one specified in the SOP.
- Handwritten information is written with indelible ink.
- All information is legible and accurate.
- The unique identifier is firmly affixed to the product bag and identical to the identifier on facility associated forms.
- The label is not damaged or defaced.

Evidence:

The inspector should confirm that the Processing Facility has documentation that the process was complete and verify that records of manual additions to cellular therapy product labels include the identity of the staff making the label modification and the staff verifying the information and date. For systems using computer-assisted label verification (such as bar-code scanning), SOPs and records should show how the automatic verification works. If relabeling is performed, the relabeling SOP must be adequately described.

STANDARD:

D7.2.6.2 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.

Explanation:

This Standard requires Processing Facilities to have a careful process for electronically transmitting information (e.g., a bar code) and to double-check the information rather than becoming solely dependent on the technology to work correctly.

STANDARD:

D7.2.6.3 Cellular therapy products that are subsequently repackaged into new containers shall be labeled with new labels before they are detached from the original container.

Explanation:

Labels for re-packaged cellular therapy products must conform to the proper label content as described in [Appendices II](#) and [III](#) as applicable. The criteria for repackaging of products and tracking mechanism shall be included in SOPs.

Evidence:

If a cellular therapy product is repackaged, the Processing Facility needs to be prepared to demonstrate that there are mechanisms in place (either on the label itself or via accompanying paperwork) to trace the product from its origin to the final disposition.

STANDARD:

D7.2.7 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.

Explanation:

The cellular therapy product container should not be covered such that the contents cannot be viewed. Inspection of the content is essential in determining abnormal color of plasma that could be due to hemolysis, bacterial contamination that could affect the safety of the product, and clots that could reduce the efficacy of the product.

Evidence:

The inspector should examine labeled cellular therapy products on-site to verify that labels are firmly attached or affixed and that sufficient area of the product remains uncovered to allow examination of contents.

STANDARD:

D7.2.8 Labeling elements required by Applicable Law shall be present.

Explanation:

Label elements that are required by Applicable Law must be clearly visible. The Processing Facility should review FDA, EU, Health Canada, or other applicable governmental requirements for labeling and format labels accordingly.

STANDARD:

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

Explanation:

All data fields on labels must be complete. If information is not required, the data field should be marked "not applicable" or "none."

Evidence:

The inspector should examine labeled cellular therapy products on-site to verify the presence of appropriate information on the labels.

Example(s):

In some cases, a base label is used, with stickers applied containing specific elements based on the cellular therapy product type or the modification that was performed. Also, many facilities apply biohazard labels and warning statements, if applicable, using tie tags.

STANDARD:

D7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

Explanation:

Often the only hand-written data is on the final processed product. Staff can complete representative labels using a variety of pens and then wipe the labels using agents that may be applied to the labels in the Processing Facilities (such as alcohol wipes or sprays) to determine the smear resistance of each pen's ink. The Processing Facility can then determine the type of pen to be used, and a formal validation of the indelibility of the preferred pen's ink can be carried out. Indelible ink must be used to record any information entered manually on the label. To support label integrity, computer-assisted labeling should include a check to confirm label stock is appropriately aligned in the printer and ink is smear-proof. Labels must have been validated to ensure they remain legible under the conditions in which they are used. This is of particular importance for labels used on cryopreserved products and after thawing of the product in a water bath.

Evidence:

Documentation of evidence that the inks and labels were demonstrated to be resistant to water, alcohol wipes, or sprays should be available to the inspector. The inspector should verify that all labels are completed clearly and legibly.

STANDARD:

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.

Explanation:

Adhesives that are applied directly to the cellular therapy product bag have the potential to leach through the plastic into the product itself. Processing Facilities must use materials that meet criteria, if any, established by applicable regulatory authorities.

Example(s):

Processing Facilities in the U.S. should contact the FDA regarding any labels affixed directly to the cellular therapy product bag to determine what data are needed to demonstrate that the labels meet FDA requirements. For further information, see the FDA guidance document [Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels](#) (2024).

STANDARD:

D7.2.12 The label shall be validated as reliable for storage under the conditions in use.

Explanation:

Adhesive labels affixed either directly to a cellular therapy product bag or to the base label of a product bag must remain affixed to the product bag (or base label) for as long as the product remains in the bag. The product's exposure to alcohol wipes or sprays or periods of cold storage, whether while still in the control of the Collection Facility or once in the Processing Facility's control, must be considered. For example, the Processing Facility may transfer the product into a storage bag after applying alcohol wipe or spray to the bag's surface, or the product may remain in the collection bag (with its label[s] affixed) through cold storage, thawing, and infusion. It is critical that the label(s) affixed to the product bag remain affixed throughout the bag's use so that product tracking and tracing are not compromised.

Evidence:

Documentation of evidence that the label(s) applied to the cellular therapy product bag remained affixed to the bag under all relevant storage conditions should be available to the inspector.

Example(s):

A validation of the adhesiveness of the labels applied to the cellular therapy product bag in the Processing Facility under all relevant product bag storage conditions.

STANDARD:**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 donor samples shall be labeled with the same identifier.

D7.3.1.2 If a single cellular therapy product is stored in more than one (1) container, there shall be a system to identify each container.

Explanation:

When a single cellular therapy product is stored in more than one container, there shall be a unique product identifier that confirms the original product and part of the sub-product, such as 1/3H000000 or 2/3H000000.

STANDARD:

D7.3.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.

Explanation:

The cellular therapy product identifier must be unique for each donation event so that all parts of the donation and samples collected are labeled with the same product identifier. Unique is defined as not being used for any other purpose. Thus, it is not acceptable to use only patient information (such as medical record number or social security number) or only the donor information (e.g., name, medical record number, registry identifier) to identify the product. Generally, a unique identifier also implies that there is reasonable confidence that it will not be used for another purpose. Products collected from a single donor at different times must be distinguished from each other by different unique product identifiers.

The essential point is that each cellular therapy product can be unambiguously traced from donor to recipient, and through all transport steps, processing and labeling steps, and storage locations. The label must clearly indicate the identity of the facility that assigned the product identifier, with the exception of cellular therapy products shipped by registries, where the source facility must remain confidential. In such cases the records that accompany the product must allow tracing to the Collection Facility.

Each Processing Facility must have an SOP indicating how a unique identifier is assigned and tracked to all parts of the donation and samples obtained at the time of donation and include acceptable

modifications that can be made to the cellular therapy product label or identifier. When a product from a single donor is divided into multiple containers, each container must be uniquely labeled; however, that identifier must trace back to the original donation. In some cases, products collected on different days may be pooled for further processing. Note that only products from a single donor may be pooled unless specifically allowed for a given protocol by the appropriate regulatory authority. The pooled product must also be uniquely identified, and that identifier must trace back to include all donations involved.

Product and donor samples collected at the time of cellular therapy product collection should be labeled so as to prevent misidentification. At a minimum, this must include the donor's name (except for the case of unrelated donors), product unique identifier, and date of sample collection.

One of the major purposes of ISBT 128 is to serve as an internationally harmonized product identification system. Implementation of ISBT 128 cellular therapy product labeling will eliminate the need for creation of a subsequent unique identifier when the product is distributed. The ISBT 128 identifier should be the main identifier for required tracking and tracing, and Processing Facilities are encouraged to retain the original identifier upon receipt of the product rather than assigning a new unique identifier.

Evidence:

The inspector must review the SOP for labeling the cellular therapy product with the unique identifier and how the identifier is assigned. There should be evidence that the product identifier is not duplicated, such as the use of a product identifier log. The inspector should perform a review to determine that the product identifier can be traced to the records used from collection to distribution of the product. The SOP for processing shall be sufficiently detailed to permit the inspector to match the processing records to a uniquely identified final collected product and to the donor and recipient.

Example(s):

The donor or recipient registry number (e.g., the WMDA Global Registration Identifier for Donors [GRID]) can be used by the local site as the sole or additional identifier if it is combined with other information that makes it unique, such as the collection date, so long as each cellular therapy product can be uniquely identified.

Identification of cellular therapy products with multiple containers may occur by modifying the unique identifier on each container with a suffix (either letter or number) or by modifying the cellular therapy product label on each bag (such as Bag 1 of 2, division codes added to the product code). If products are being pooled, the pool identifier must allow tracing to the original products. A pool identifier could be new (the pooled CPL11001 and CPL11002 could be CPL11003 so long as the new identifier is traceable to the original identifiers through the laboratory record) or could be a combination of the original identifiers (for the example above, CPL11001+CPL11002).

EU [Directive 2006/86/EC](#) requires that the expiration date shall be part of the product information for all tissues and cells, and there shall be an indication of the status of the product (in quarantine or ready for use). The unique identifier must be retained for 30 years per EU requirements.

Exceptions for assigning a new ISBT 128 identifier to cellular therapy products already given a unique identifier may include older cellular therapy products (products labeled prior to ISBT 128 implementation) and, potentially, products received from non-FACT or JACIE accredited sources.

STANDARD:

D7.3.1.4 Supplementary identifiers shall not obscure the original identifier.

Explanation:

The Processing Facility may assign additional identifier(s) to a cellular therapy product; however, it is recommended that no more than two sets of identifiers from separate facilities should be affixed to a product container, and the original identifier may not be obscured. New labels are not to be placed over an old label. If a unique identifier is replaced with a new one, records must link the current unique identifier to the original.

STANDARD:

D7.3.1.5 The facility associated with each identifier shall be named in the documents to accompany the cellular therapy product.

D7.3.1.6 If the original donation identifier is replaced, documentation shall link the new identifier to the original.

Evidence:

If supplementary identifiers are used, the inspector should check that the identifier is affixed to the cellular therapy products, verify the entire original identifier is visible and legible, and confirm that the facility responsible for each identifier is part of the label or extended label. The Processing Facility must be able to provide evidence that if original identifiers are removed from the product, or if the product is repackaged, the supplemental identifier is traceable to the original identifier. Typically, this process is described in a policy or SOP. Tracing a unit through the labeling process is an effective method to verify these Standards are met.

Example(s):

Labeling records (forms and logs or computerized records) can be used to demonstrate that the original unique identifier can be linked to the new identifier so that the Processing Facility and staff responsible for assigning a new identifier are documented and the records support traceability.

A cellular therapy product initially labeled in compliance with ISBT 128 should not be relabeled. An exception to this would be a product that bears the identifier assigned by the distributing facility (e.g., cord blood collected by a hospital and distributed to the Processing Facility).

STANDARD:

D7.3.2 An ISBT 128 Chain of Identity Identifier should be assigned before or at the time of collection to each collection intended for further manufacturing.

D7.3.2.1 If more than one (1) donation is needed to deliver a given therapy, the Chain of Identity Identifier shall link all donations.

Explanation:

The purpose of the ISBT 128 Chain of Identity Identifier is to link all collections that may go into a final product. This Standard applies to cellular therapy products collected for further manufacturing.

The Processing Facility should have a process to verify that the Chain of Identity Identifier has been applied when a product is received or, if not, to apply a Chain of Identity Identifier. The cellular therapy product identifier must be unique. Unique is defined as not being used for any other purpose. Thus, it is not acceptable to use only patient information (such as medical record number or social security number) or only the donor information (name, medical record number, or registry identifier) to identify the product. Products collected from a single donor at different times must be distinguished from each other by different unique product identifiers.

The essential point is that each cellular therapy product can be unambiguously traced from donor to recipient and through all transport steps, processing steps, and storage locations. The label must clearly indicate the identity of the facility that assigned the product identifier with the exception of products shipped by registries, where the source facility must remain confidential. In such cases, the records that accompany the product must allow tracing to the donor.

Third-party manufacturing organizations may not want patient-identifiable data visible on the product label or accompanying information and may have specific requirements in relation to information that is visible on the product label and/or accompanying documentation at the point of product distribution from the Collection Facility into their control. At a minimum, a unique identifier must remain on the product bag and accompanying documentation on distribution from the facility into the responsibility of the third-party organization. This will ensure that the unique identifier can be associated with the product during its passage through the third-party organization and must accompany the final product when it is distributed from the third-party organization for clinical use. For autologous products, this will allow confirmation that the product assigned to the patient originated from that patient, and, for allogeneic products, this will allow vein-to-vein tracking and traceability.

There must be an SOP that indicates how a unique identifier is assigned and tracked and that includes acceptable modifications that can be made to the cellular therapy product label or identifier. When a product from a single donor is divided into multiple containers, each container must be uniquely labeled. If products are being pooled, the pool number must allow tracing to the original products. Note that only products from a single donor may be pooled unless specifically allowed for a given protocol by the appropriate regulatory authority.

"Additional information regarding the Chain of Identity Identifier can be found on the ICCBBA website ([ST-018](#)) and in the FACT "[ISBT 128 Hybrid \(Split\) Label Webinar](#)."

Evidence:

The inspector must review the SOP for labeling the cellular therapy product with the unique identifier and how the identifier is assigned. There should be evidence that the product identifier is not duplicated, and this could be demonstrated with a product identifier log. The inspector should perform a review to determine that the product identifier can be traced to the records used from collection to distribution of the product. The SOP for processing shall be sufficiently detailed to permit the inspector to match the processing records to a uniquely identified final product and to the donor and place of final distribution.

Example(s):

The donor or recipient registry number can be used by the local site as the sole or additional identifier if it is combined with other information that makes it unique, such as the collection date, so that each cellular therapy product can be uniquely identified.

STANDARD:

D7.4 LABEL CONTENT

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

Explanation:

Requirements for labeling cellular therapy products are detailed in ISBT 128 and can be found at [ST-004 ISBT 128 Standard Labeling of Cellular Therapy Products](#).

STANDARD:

D7.4.2 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.

Explanation:

It is important for the staff of the Processing Facility to verify the accuracy of the donor and patient information and to confirm that the labels are verified for completeness and legibility before removing them from the processing area.

The label verification should include:

- Label is correctly affixed to the component (e.g., tie tag).
- The correct label is positioned appropriately.
- The label is identical to the one specified in the SOP.
- Hand-written information is written with blue or black indelible ink.
- All information is legible and accurate.
- The unique identifier is firmly affixed to the product bag and identical on associated forms and accompanying records and documents.
- The label is not damaged or defaced.

In addition, there should be a documented verification of patient and donor identity prior to issue.

Evidence:

The inspector should verify that labeling during processing, at the completion of processing, and at distribution contains all the information listed in [Appendix II](#) and contains appropriate biohazard and warning statements as specified in "Table 2. Biohazard and Warning Labels..." of the [Circular of Information for the Use of Cellular Therapy Products](#).

Example(s):

Although it is not specified by the Standards, it may be useful to include information on the cell types present in the cellular therapy product. For MNC products in particular, the cell content may be critical to the efficacy or safety of the product and should be confirmed with the physician order prior to administration. Alternatively, this information may be in the accompanying records and should be verified by the processing and administration staff at the time the product is distributed for administration.

Cellular therapy products from unrelated donors shall contain the ISBT 128 DIN supplied by the registry with or without the identification of the Collection Facility, according to local laws or regulations.

STANDARD:

D7.4.3 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](#).

D7.4.4 At distribution for administration the final cellular therapy product label shall include at a minimum two (2) identifiers which link the product to the intended recipient to maintain the Chain of Identity.

Explanation:

The required label content as specified in [Appendix II](#) represents minimum requirements and must be present as indicated at the various stages of cellular therapy product collection, processing, and distribution. For minimum required elements such as the use of anticoagulants and additives, establishment of an expiry date, and recommended storage temperature ranges, the Processing Facility must describe and validate their process.

Labeling must be consistent with Applicable Law. Local interpretations may differ. The identity and address of the Collection Facility or registry as well as identity and address of the Processing Facility, as applicable, must be part of labeling at issue. The identity of an unrelated donor is not included in labeling due to confidentiality. This may be extended to the Collection Site per some interpretations of local laws and regulations.

Evidence:

Examples of all labels in use by the applicant organization will be provided to the inspector prior to the on-site inspection. For organizations performing both allogeneic and autologous transplants, examples of labels will include collection, processing, transport, and distribution labels for both types of transplants. In addition, labels illustrating each cellular therapy product source handled by the organization should be included. Partial labels, if used, should be included. Cryopreservation labels, tie tags, instructions to the infusionist, biohazard, and warning labels should also be included. If any expected label is not provided to the inspector prior to the inspection, the inspector should request it from the applicant through the FACT or JACIE office, as applicable.

Inspectors should examine labels to confirm that confidential donor information is not included in the label per Applicable Law and that appropriate identities and addresses of the Collection Site or registry and processing lab are part of the extended label, as applicable to the setting, and that the information provided allows for adequate traceability to the donor of the product.

Example(s):

Labels should be reviewed for autologous, related, and unrelated allogeneic products, as applicable to the site, to verify the requirements of these Standards are met.

Per EU Commission [Directive 2006/86/EC](#), the identity of the tissue establishment is part of the label at issue. In the U.S., the identity of the establishment responsible for determining the cellular therapy product meets release criteria and is available for distribution must be part of the label. This information may appear as part of the affixed, attached or extended labeling as part of the accompanying documentation per Applicable Law.

STANDARD:

D7.4.5 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.

Explanation:

A biohazard label must be attached or affixed to any cellular therapy product from a donor who has tested positive for a relevant communicable disease (as listed in [B6](#) and its subStandards except CMV) or when donor screening indicates a risk factor for a relevant communicable disease or disease agents. "Table 2. Biohazard and Warning Labels..." of the inter-organizational *Circular of Information for the Use of Cellular Therapy Products* outlines when biohazard labels must be used. Biohazard labels must not be applied indiscriminately, as they are meant to denote a greater hazard than that posed by any biological product. Biohazard labels can only be applied to products not required to be labeled biohazard when specific circumstances for their use are defined by Processing Facility or Clinical Program policy. Using biohazard labels on all products without documented rationale is considered a deficiency.

Warning labels are required to be affixed or attached to the cellular therapy product when product testing or screening is positive for infectious disease risk or is incomplete (see [Appendix II](#)). Note that residence in a country on the U.S. Department of Agriculture list as at risk for bovine spongiform encephalopathy (BSE) is considered to constitute a risk identified by donor screening. Thus, allogeneic cellular therapy products require a biohazard label and the statement "Warning: Advise recipient of communicable disease risks."

If any of the required allogeneic donor eligibility requirements are not completed, the statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" must be attached to and/or accompany the product. For example, this would apply in the following situations:

- A product not tested at all for relevant communicable disease agents and diseases.
- A product tested for only a subset of relevant communicable disease agents and diseases.
- A product screened and tested for all relevant communicable disease agents and diseases but using diagnostic tests rather than donor screening tests.
- A product screened and tested for all relevant communicable disease agents and diseases but not within the required time period (e.g., within 30 days for HPC, within 7 days for MNC products) or still pending at the time of labeling.

- A product screened and tested for all relevant communicable disease agents and diseases using approved donor screening testing, but for which no official donor eligibility determination was made.

Products for which donor testing is positive must also include the statement “Warning: Reactive test results for (name of disease agent or disease)” with the name of the disease agent or disease specified.

Communicable disease testing is not required for autologous donors in relation to cellular therapy product collection unless required by Applicable Law, nor is there a requirement for donor eligibility determination. Programs may, however, decide to carry out communicable disease testing and eligibility determination in autologous donors to help standardize processes, reduce the risk of error, and facilitate non-segregated autologous and allogeneic product storage. Relevant policies and procedures will reflect this decision and the relevant Standards within [B6.4](#) will apply. Organizations that do not perform autologous donor testing must carefully establish processes that maintain compliance with FDA regulations for labeling.

Autologous cellular therapy products must be labeled with “FOR AUTOLOGOUS USE ONLY.” If an autologous donor is missing any of the testing and screening required for an allogeneic donor, the cellular therapy product label must contain the statement “NOT EVALUATED FOR INFECTIOUS SUBSTANCES.” In addition, if the autologous donor undergoes at least some of the testing or screening prior to collection and is found to be positive or at risk for a relevant communicable disease, the product label must also bear a biohazard label and the statement “WARNING: Reactive test results for (name of disease agent or disease).” Since autologous recipients are not at risk of contracting a communicable disease from themselves (i.e., they already have the disease), the statement “Warning: Advise recipient of communicable disease risks” is not required on autologous product labels even if donor testing results are positive, although a biohazard label is required.

The immediate packaging of an investigational cellular therapy product regulated under section 351 of the PHS Act in the U.S. must be labeled with the statement “Caution: New drug limited by federal law for investigational use.” Currently HPC, Apheresis products and some HPC, Cord Blood collected from unrelated donors for NMDP are regulated under an IND held by NMDP and thus have labeling with this statement.

Evidence:

The inspector should confirm that biohazard labels and warning statements are utilized as described in Table 2 of the [Circular of Information for the Use of Cellular Therapy Products](#). Autologous cellular therapy product labels should be examined to confirm that the statement “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” is used when any of the testing and screening required for an allogeneic donor is missing.

STANDARD:

D7.4.6 A cellular therapy product collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documentation table in [Appendix IV](#) at the time it leaves the control of the Processing Facility.

Explanation:

See [Appendix IV](#) for explanations, evidence, and examples for cellular therapy products collected in or designated to the U.S.

STANDARD:

D7.4.7 Any container bearing a partial label at the time of distribution shall be accompanied by the information required by the Cellular Therapy Product Labeling table in [Appendix 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.

Explanation:

If the Processing Facility utilizes a partial label at the time of distribution to a Clinical Program or other entity, the inspector must confirm that the SOP describes the use of the partial label, provides an example of the partial label, and includes the mechanism for providing the additional information that is not included on the partial label.

Accompanying paperwork should be packaged in a secondary bag with non-frozen cellular therapy products for shipment or transport to the external facility or infusion site. The paperwork may be placed in the canister of a frozen product. When shipping or transporting multiple product bags from different donors using partial labels, it is not acceptable to include all the additional information on a single inventory sheet, but rather each product and paperwork from each donor should be segregated in a way to prevent mix-up.

Evidence:

Inspectors should verify partial labels at the time of distribution meet requirements as defined in these Standards and the Processing Facility's SOPs.

STANDARD:

D7.4.8 For allogeneic cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after distribution of the cellular therapy product and that the physician using the product was informed of the results of that determination.

Explanation:

The Processing Facility must inform the physician of the results of any testing or screening that was completed after the cellular therapy product was distributed. The provision of this information must be documented in the processing records. If any result is positive, it is the responsibility of the physician to notify the recipient and to document the patient notification in the clinical record.

Evidence:

SOPs and processes should define release criteria for incompletely tested products, including staff involved, notification of the recipient's physician, labeling, and donor eligibility completion. Inspectors should review the forms, logs or other documentation to confirm the eligibility was completed and the appropriate physician was notified. The inspector should be able to determine what was complete and incomplete at the time of release of the product and when and how the physician was notified of the pending results and information, as well as documentation that the physician acknowledged receipt of the information. Forms, logs or other documented records should clearly identify the staff involved in the notification process and timeframes involved.

STANDARD:

D7.4.9 Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "For Nonclinical Use Only."

Explanation:

According to the ICCBBA, if the cellular therapy product is not intended for administration, the upper right quadrant should reflect this. Instead of a standard ABO/Rh code, the code "Mr" (for research use only) should be selected. The words "For Nonclinical Use Only" (in the local language) should appear.

STANDARD:

D7.4.10 Cellular therapy products from third-party manufacturers shall be labeled with product labels that conform to FACT-JACIE requirements and Applicable Law.

Explanation:

Compliance with the ISBT 128 Standard for product labeling is important for donor and recipient safety, traceability, and regulatory adherence. Standardized labeling under ISBT 128 enables global interoperability, enhances Chain of Identity and Chain of Custody tracking, and ensures

compatibility with electronic medical records and inventory systems. When a label is received from a third-party manufacturer that is not compliant with the ISBT 128 Standard, the facility must label the product with labels that conform to FACT-JACIE requirements and Applicable Law. The Processing Facility can use a partial label per the FACT-JACIE Standards as an additional label.

The Processing Facility can utilize a proactive approach to this issue by leveraging quality agreement negotiations with manufacturers. By incorporating ISBT 128 compliance requirements into contractual agreements, the Processing Facility can:

- Define clear expectations regarding product labeling and data standardization.
- Require manufacturers to adopt ISBT 128 for all distributed products, ensuring alignment with industry best practices.
- Implement compliance audits as part of vendor management to monitor adherence.
- Encourage regulatory alignment by demonstrating how ISBT 128 compliance supports accreditation standards (e.g., FACT, FDA).

Encouraging universal adoption of ISBT 128 ultimately benefits the broader cellular therapy community by fostering consistency and reducing risks associated with labeling discrepancies.

Example(s):

The facility can use a partial label per the FACT-JACIE Standards as an additional label to the manufacturer label.

D8: PROCESS CONTROLS

STANDARD:

D8.1 There shall be a process for controlling and monitoring the manufacturing of cellular therapy products so that products meet predetermined release specifications.

Explanation:

The establishment of process control is a primary objective of the Processing Facility QM Program. Since cellular therapy products are biological, there is inherent variation among cellular therapy products that cannot easily be controlled. The consistent use of validated processing procedures and the use of testing to monitor processing can greatly reduce variability and result in high quality products. SOPs are required that describe each processing procedure and its associated process control (see [D5.1](#)).

Example(s):

Processing records, batch records, and lot preparation sheets are all examples of documentation that, when used effectively, can assist with the controlling, monitoring, and documentation of cellular processing.

STANDARD:

D8.1.1 The Processing Facility Director shall define tests and procedures for measuring and assaying cellular therapy products to ensure 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.

Explanation:

The Processing Facility Director is responsible for defining release criteria for cellular therapy products distributed by the facility and for identifying the tests to be performed and the testing intervals during processing. This information must be clearly outlined in an SOP. All test results that are available at release must be present in the processing record.

Evidence:

The inspector should review processing records to determine if all required testing was performed within the required timeframe and if the results are recorded. Documentation that the cellular therapy product met release criteria prior to distribution must be present. For products that did not meet release criteria, the required documentation for exceptional release should be present.

Example(s):

For cellular therapy products that are CD34-enriched for the purpose of removing mature T cells, testing of the final product should include Total Nucleated Cell count (TNC) (required for all processing that affects TNC), sterility testing (required for all products at administration), viability, CD34 cell content, and CD3 cell content. Other testing may be performed at the discretion of the Processing Facility Director.

For HPC, Apheresis products undergoing processing for plasma removal, so long as the Processing Facility can document that the plasma removal step does not significantly affect TNC, CD34 cell content, or viability, those tests would not need to be repeated after the plasma removal. However, those tests should have been performed prior to the plasma removal step.

STANDARD:

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.

Evidence:

To determine that test samples can be appropriately linked to the donor or recipient, the inspector should observe how sample tubes are labeled and distributed for testing and how results are posted.

Example(s):

Test sample labels should include the cellular therapy product unique identifier and the sample source (and, if appropriate, the stage of processing). EU regulations also require that there be a record of the location at which a specimen was taken.

STANDARD:

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.

Explanation:

There should be a mechanism that identifies the individual procuring the sample and the date and time it was obtained.

STANDARD:

D8.1.2.2 Samples obtained for testing shall be representative of the cellular therapy product to be evaluated.

Explanation:

It is critical that the sample obtained for testing represents the cellular therapy product to be tested. Most often this requires that a product be well-mixed prior to sampling and the sample to be taken at the appropriate step in processing.

Example(s):

The supernatant may be considered representative of the cellular therapy product depending on when it is used and for what tests. For example, the supernatant of a cord blood unit at the time of the last wash for administration could be used for sterility testing. Supernatant from processing steps further upstream before cryopreservation would not be considered representative of the product because contamination could occur during or after storage. Supernatant would not be considered representative of the product for purposes of TNC or CD34 analysis; samples for these tests must come from the product itself.

STANDARD:

D8.1.3 There shall be established, appropriate, and validated assays and testing procedures for the evaluation of cellular therapy products, including as applicable:

D8.1.3.1 ABO group and Rh typing.

D8.1.3.2 Microbial testing after processing.

D8.1.3.3 Cell count including total nucleated cells and viability.

D8.1.3.4 CD34 numeration and viability assays.

D8.1.3.5 Assay of target cell population for products that have been enriched, expanded, or depleted.

Explanation:

Test methods that are used for these assays are not specified by the Standards. Rather, it is up to the Processing Facility to determine what assays are appropriate and to confirm that they have been validated for the cellular therapy products that are being tested. Testing must be performed using appropriate equipment, reagents, and controls. Validation procedures should be determined by the program and described in the facility's SOPs. Equipment control requirements may differ based on government regulations (e.g., U.S. regulations require daily controls, European requirements specify "regular" controls). In the event an assay is unavailable, defined release criteria such as those specified in an IND or ATMP must be utilized.

Evidence:

The inspector must utilize their judgment and knowledge of the field to assess if the appropriate assays are in use. For all procedures and assays utilized by the Processing Facility, including those considered uncommon for the facility, the inspector should verify that SOPs are in place; there is a record of method validation; reagent and instrumentation controls are used; and there is evidence that the technologists performing the procedure have been trained, participate in proficiency surveys, and are evaluated for ongoing competency for these procedures. The inspector should pay particular attention to procedures and assays that may be newly implemented, including flow cytometry, endotoxin and mycoplasma testing, cell selection, and cell purging. Methods for microbial testing, in particular, should have been validated for the range of cellular therapy products being tested.

The inspector may recommend periodic documentation of continued reproducibility. However, if a procedure requires more than minimal manipulation and additional cell counts are not performed, the inspector should ask to see evidence of reproducible recovery of cells in the form of a validation study. If such a study has not been performed, the inspector may determine that additional cell counting and viability assessment must be performed during and/or post-processing.

The inspector should ask to see evidence of reproducible recovery of CD34 cells as part of any validation study of processing procedures involving HPC products.

STANDARD:

D8.1.4 The following assays and testing procedures for the evaluation of cellular therapy products shall be performed:

D8.1.4.1 For all cellular therapy products, a total nucleated cell count and viability measurement shall be performed.

D8.1.4.2 For HPC products intended for restoration of hematopoiesis, an assay measuring viable CD34 shall be performed.

Explanation:

A number of published studies have shown a correlation between CD34 cell content and the kinetics of platelet and granulocyte engraftment below a threshold number of CD34 cells. Review of the CD34 cell content at the end of processing shown to affect CD34 cell content in conjunction with outcome analysis at time to engraftment should be used, especially for recipients whose engraftment appears to be delayed.

Post-thaw assessment of cellular therapy products that are directly thawed and administered is not typically performed and cannot be easily done, especially if products are thawed outside of the Processing Facility. For products that are manipulated in the laboratory, such as those undergoing a Dextran/Albumin wash, a TNC and viability assessment should be done. Repeat CD34 cell assessment of thawed cells is technically more difficult but should be performed in the context of procedure validation. Based on those results, the facility may not need to do this assay for every thawed product. In the case of cord blood units where CD34 test results may not be available, CD34 testing should be performed. Determination of post thaw viability and establishment of stability program for cryopreserved HPC product is discussed in [Cryopreserved hematopoietic stem/progenitor cells stability program-development, current status and recommendations: A brief report from the AABB-ISCT joint working group cellular therapy product stability project team](#) (Reich-Slotky, Vasovic, Land, et al. *Transfusion*. 2022;62(3):651-662).

STANDARD:

D8.1.4.3 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.

Explanation:

Target relevant cells include those that affect the effectiveness and safety of cellular therapy products. This includes cells that perform the actual function intended by the product and cells that may cause side effects.

Example(s):

When processing procedure validation demonstrates a loss of CD34 cells and/or a loss in total nucleated cells (e.g., after density gradient separation for MNC preparation), testing for the affected cell type(s) must be performed at the end of processing and prior to administration or cryopreservation.

STANDARD:

D8.1.5 For tests required by these Standards performed within the Processing Facility:

Explanation:

Requirements of the Processing Facility providing these testing services must be in accordance with the requirements for the same testing performed by a certified or accredited clinical laboratory. That is, while the facility does not have to be formally certified or accredited, there must be a process in place to safeguard that the results are accurate. Minimally, the reagents used for testing should be confirmed to give the expected results using previously assayed control materials where those are available or compared to the previously used reagent lots. Instruments and test methods should include day of use positive controls, and appropriate controls for instrumentation function must be performed. Acceptable control materials may not be available for manual procedures commonly performed in Processing Facilities, such as manual cell counts of Trypan Blue viability assessments. In such cases, processing personnel are required to participate in proficiency testing programs (when available) for the procedures and tests that they perform. While separate accreditation for the tests performed by the facility may be available, it is not required by the Standards. However, performance of such testing should be consistent with the standards of other such accrediting bodies.

STANDARD:

- D8.1.5.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.*
- D8.1.5.2 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.*

Example(s):

Reference material for reagent and day of testing controls can be purchased as fixed cells for flow cytometry controls for lymphocyte subsets and detection of CD34 cells and for hematology analyzers. Processing Facilities should confirm that the control cells purchased are appropriate for the instrument in use. Fixed cells used as flow cytometry controls may also be used to confirm the activity of the 7-Aminoactinomycin D (7-AAD) viability assay since the majority of fixed cells will stain positive. The expected range of positive cells can be established for the control cell type used.

It is acceptable to use the COA, datasheets, and visual inspection of the reagent as verification.

STANDARD:

- D8.1.5.3 Where available, controls shall be used each day of testing and shown to give results within the defined range established for that material.*
- D8.1.5.4 Function checks shall be performed for testing instruments prior to testing donor, recipient, or cellular therapy product samples.*
- D8.1.5.5 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 and outcomes reviewed with the staff.*

Example(s):

Examples of testing with available proficiency testing programs include automated cell counting, colony assays, and flow cytometry. Several organizations (e.g., CAP, Stem Cell Technologies, Centers for Disease Control and Prevention, National Institute for Allergies and Infectious Disease, United Kingdom National External Quality Assessment Schemes) provide a variety of proficiency tests applicable to the activities of a Processing Facility. Alternatively, the facility may establish its own proficiency testing program, particularly for site-specific activities not routinely performed by other laboratories and for which no external proficiency test is available. For tests such as manual cell counts, the manual method can be compared with results obtained from a validated hematology analyzer. Likewise, Trypan Blue viability may be compared to flow cytometry-based assays such as 7-Aminoactinomycin D (7-AAD) using the same samples. TNC for products whose function is dependent on cell dose is sometimes an appropriate surrogate for viability measurement.

STANDARD:

D8.1.6 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.

Explanation:

Some of the specified testing may be performed by an external laboratory. Testing not performed by the Processing Facility must be performed by an appropriately certified laboratory. Such laboratories must have valid and current licenses and accreditation and are expected to meet minimally the same requirements specified for testing performed within the facility.

Evidence:

Documentation that external laboratories performing required testing are appropriately certified or accredited must be reviewed by the inspector. Although the actual certifications are not required to be on-site at the Processing Facility, they should be readily available for review.

STANDARD:

D8.1.7 Infectious disease testing required by these Standards shall be performed using screening tests licensed, approved, or cleared by the governmental authority for cellular therapy product donors.

Explanation:

Communicable disease testing is specifically required by GTP regulations to be performed using testing kits approved and authorized for donor screening in a laboratory that is accredited or licensed according to Applicable Law. Since communicable disease testing is usually facilitated by the Clinical Program or by the Collection Facility and is performed prior to collection, the Processing Facility must have a system in place whereby a summary of these results is available to the facility. Standard [B6.4.18](#) applies.

Evidence:

The inspector should be able to verify compliance with this requirement by reviewing a copy of communicable disease testing results with explanation of results and acceptable values. The tests used should be on the list of approved tests by the regulatory authority. The Processing Facility should also provide documentation that the laboratory providing the results is accredited or licensed as required.

Example(s):

An example of evidence that can be provided to the inspector may be communicable disease test reports from a licensed blood center testing facility.

In the U.S., testing is specifically required to be performed using test kits approved by the FDA for donor screening in a CLIA-accredited or FDA-registered laboratory.

STANDARD:

D8.1.8 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.

Explanation:

The release of a cellular therapy product that does not meet allogeneic donor eligibility requirements, or for which allogeneic donor eligibility determination is not yet complete, requires medical justification and a risk assessment. The recipient's physician provides clinical justification confirming the immediate need for the cellular therapy products and, if applicable, the potential consequences of delays. The Processing Facility Medical Director evaluates whether the product meets quality and safety standards despite the fact that the product does not meet allogeneic donor eligibility requirements/donor eligibility determination is not yet complete. Both perspectives help evaluate whether medical justification and the risks are clearly assessed, documented, and communicated.

STANDARD:

D8.1.9 Notification of the recipient's physician of nonconforming cellular therapy products and approval for their release shall be documented.

Explanation:

Cellular therapy products that do not meet established release criteria are not used in a patient without full awareness and explicit approval from the treating physician. It is a fundamental requirement to safeguard patient safety, uphold clinical transparency, and maintain regulatory compliance. These deviations may pose clinical risks or alter the expected efficacy of the product. When a nonconformance is identified, the standard requires prompt notification of the recipient's physician. This enables the physician to assess the clinical implications of the deviation, consider alternative treatment options, and make an informed risk-benefit decision regarding the use of the product. Physician notification must include a detailed description of the nature of the nonconformance, potential risks, and available supporting data.

Use of a nonconforming product may be clinically justifiable in urgent or life-threatening scenarios. However, documented approval from the recipient's physician is mandatory before the product can be released for infusion.

STANDARD:

D8.2 There shall be a written request from the recipient's physician specifying the cellular therapy product type, recipient and donor identifiers, the type of processing that is to be performed, and the anticipated date of processing before a cellular therapy product is processed, shipped, or otherwise prepared for administration.

Explanation:

Before processing begins, a physician's order must be received by the Processing Facility and must specify how and when the cellular therapy product should be processed as well as the identifiers of the donor and recipient. For example, if a product is to be split in order to infuse an initial cell dose and reserve the remaining cells for a subsequent administration (DLI or tandem transplant), this must be clearly indicated on the medical order. For standard processing procedures, precise parameters do not have to be indicated on the medical order as long as the SOP is sufficiently specific to indicate the appropriate endpoints and expected ranges.

Stored cellular therapy products from more than one donor collected for a given recipient may be present in the Processing Facility. In such cases it is important that the physician order clearly specifies the identifier of the donor to be used.

Evidence:

The inspector should review the physician order form in use and verify that it contains the required elements.

Example(s):

Examples of processing to be performed may include the extent of plasma or RBC reduction, purity of selected or purged cell products, cryopreservation volume, and number of bags frozen.

STANDARD:

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.

Explanation:

Before the Processing Facility can distribute allogeneic cellular therapy products for administration, regulations require that allogeneic donor eligibility be confirmed. This determination is performed by the Clinical Program or Collection Facility, not the Processing Facility.

In order to distribute the cellular therapy product after processing, donor eligibility information must be obtained from the facility making that determination. For allogeneic donors not meeting eligibility requirements, the reason must be provided and, for such donors, release cannot proceed without documentation that the criteria for urgent medical need have been met and the physician overseeing the recipient has approved use.

In some cases, a cellular therapy product may be needed before donor eligibility determination is completed. In those situations, the physician must be notified that testing and screening has not been completed. See [Appendix IV](#) for the detailed requirements.

Evidence:

The inspector should request and review donor eligibility paperwork and urgent medical need documentation when required.

Example(s):

For example, allogeneic donor eligibility documentation with approval signatures can be used as documentation of compliance with this requirement.

STANDARD:

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.

Explanation:

The Processing Facility Director should determine what and how processing methods will be validated. Validation may be retrospective, concurrent, or prospective. Validation should include retrospective or ongoing evaluation of processing results, data analysis, establishment of expected ranges and means or medians, and periodic documentation that the procedure is yielding results within the expected range.

Any new procedures introduced into the Processing Facility should undergo prospective validation when possible. Prospective validation of a processing procedure may be accomplished by performing a mock procedure using a surrogate cellular therapy product. Surrogate products may include those collected for research with IRB approval, those previously collected and stored for a recipient who has no further need for that product, or blood products collected from donors for therapeutic purposes that are otherwise discarded. When no surrogate products are available for a full-scale procedure, validation using a small portion of a product and a scaled-down procedure may be adequate.

Ultimately, validation of the quality of the cellular therapy product is determined by timely engraftment of the transplanted cells and the clinical outcome of the recipient. However, there should be in vitro studies demonstrating that the desired endpoint of the processing procedure was achieved.

In some cases, the Processing Facility may implement a processing procedure or process that has been validated by an external facility or has been published. In such cases it may not be necessary to undergo a full validation study; rather the facility may need only to verify that the procedure or process results in comparable cellular therapy products when performed locally. It remains important that a formal process be followed and that acceptance criteria that can be shown to be objectively met are established.

Evidence:

The inspector must review one or more validation or verification studies to confirm they are being performed as required by the Standards. The inspector should specifically review that all testing procedures are defined by SOPs.

Example(s):

For standard procedures that were adopted and implemented prior to establishment of the Standards and have remained unchanged, retrospective or concurrent validation is acceptable. Examples may include controlled rate freezing, cryopreservation using DMSO, automated cell washing, and buffy coat preparation and RBC reduction protocols.

STANDARD:

- 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 RBC-reduced prior to cryopreservation shall be washed prior to administration.*
- D8.4.4 Cord blood units that have been RBC-reduced prior to cryopreservation should be diluted or washed prior to administration.*

Explanation:

Processing of cord blood units (i.e., when to dilute or wash) may be dependent on many variables (e.g., ABO mismatches, RBC contamination content, pediatric risk factors).

The main goal of diluting and washing cord blood units is to remove RBC stroma which may result in toxicity at the time of administration. Diluting and washing a thawed cord blood unit also limits exposure of thawed cells and recipients to high concentrations of DMSO. The choice between dilution and washing takes into account the volume of the cryopreserved cord blood units, the number of cord blood units to be readministered, and the maximum tolerable volume of fluid to

be readministered to the recipient. See Akel S, Regan D, Wall D, Petz L, McCullough J. [Current thawing and infusion practice of cryopreserved cord blood: the impact on graft quality, recipient safety, and transplantation outcomes](#). *Transfusion*. 2014;54(11):2997-3009.

STANDARD:

D8.4.5 Preparation for administration of cellular therapy products manufactured by third parties shall follow the instructions provided by the manufacturer.

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

D8.4.5.2 If relabeling of prepared third-party products is required, the label shall follow Applicable Law.

Explanation:

Cellular therapy products manufactured by third parties are increasingly used in FACT or JACIE accredited programs (e.g., HPC, cord blood, CAR T cells). These may be licensed or investigational products. The products must be prepared for administration following the requirements of the manufacturer. Given the investigational nature of some products, there may be specific or unique requirements that should be considered. The Processing Facility should review requirements prior to receipt of the product and determine what SOPs, processes, and training needs to be established.

Labeling and accompanying documentation of prepared products must follow the manufacturer's requirements. Many third-party products will not follow FACT-JACIE Standards and may not comply with ISBT 128 label requirements. The facility preparing the product should not modify manufacturer requirements without permission. If the manufacturer does not provide instructions, labeling should follow established Processing Facility practice. The elements listed in [Appendix II](#) for "Label at distribution for administration" may serve as a guide, but all elements may not be feasible. Some normally expected label elements (e.g., ISBT 128 product codes, label format) may not be feasible since the facility preparing the product is not the product manufacturer.

It is understood that there may be situations in which a Clinical Program requests the Processing Facility to store, thaw, or wash cellular therapy products with which the facility has little or no experience. In these cases, the facility's ability to perform validation studies is limited. The facility must communicate with the third-party manufacturer or registry regarding the manufacturer's instructions for preparation for administration to determine if the facility has the appropriate personnel competencies, equipment, storage space, supplies, and reagents.

Even if inexperienced with a certain type of cellular therapy product, it is still the responsibility of both the Clinical Program and the Processing Facility to verify that the facility's staff, supplies, reagents, and processes are adequate to ensure patient and product safety. In these cases, Clinical

Programs should facilitate requests for practice units for the facility to verify the preparation procedure prior to performing the procedure on products intended for administration to a recipient.

Since different facilities may have varying procedures for their cellular therapy products, it is important to document when the use of products manufactured using different procedures are administered and to document the processes that were used to prepare and administer such products.

For products with erythrocyte content (e.g., HPC, cord blood), the Processing Facility should consider consulting the Clinical Program, Processing Facility Medical Director, or the manufacturer regarding possible handling requirements.

Evidence:

Inspectors may verify compliance with this standard by reviewing processes and SOP for cellular therapy product preparation for administration, occurrence management, validation or verification studies including documentation of practice runs, and product records.

Example(s):

FDA regulations require that manufacturers of cellular therapy products validate preparation for administration or thaw procedures and provide instructions to the Clinical Program administering the product. Transplant programs that receive cryopreserved cord blood units for transplantation are not manufacturers. Their Processing Facilities' processes (e.g., thaw, dilute, wash) are considered "preparation for administration" of the product. It is recommended that the cord blood bank's instructions be followed. Facilities wishing to perform their own validated method should consult the Clinical Program and manufacturer.

Investigational CAR-T or other cell therapy products may require preparation for administration in the Processing Facility. These operations can result in a final product container that requires labeling. The label should follow manufacture requirements even if not consistent with FACT-JACIE Standards, including compliance with ISBT 128. If no instructions are provided, the Processing Facility should follow established labelling practice with the understanding that full ISBT 128 compliance may not be possible for some label elements (e.g., proper product name, product code).

STANDARD:

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

Explanation:

The Processing Facility Director is responsible for defining tests and procedures for measuring and assaying cellular therapy products to verify product quality and that they meet release criteria. It is further specified that tests should be identified that are critical to this objective and that those tests are defined by SOPs.

Evidence:

The inspector should request and review SOP(s) for cellular therapy products that clearly define the expected endpoints of processing. Critical control points for the assays or tests performed should be indicated in the SOP.

Example(s):

For example, if endotoxin is used as a release criterion, the processing SOP should indicate what the expected results are. In addition, if there are critical steps (control points), such as sample preparation that would affect the final result, these control points should be clearly indicated.

STANDARD:

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

D8.7 Methods for processing shall employ aseptic technique, and cellular therapy products shall be processed in a manner that minimizes the risk of cross-contamination.

D8.7.1 Where processing of tissues and cells involves exposure to the environment, processing shall take place in an environment with specified air quality and cleanliness.

D8.7.2 The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.

Explanation:

The simultaneous presence of cellular therapy products from more than one donor in a Processing Facility is a frequent occurrence. SOPs must be in place to prevent the possibility of mix-ups or cross-contamination of products in such circumstances. SOPs should define safeguards to be employed, such as forbidding products from more than one donor to be in the biological safety cabinet at any one time and should describe the cleaning and disinfection practices to be used for sequential processing using the same equipment.

Whenever possible, closed systems should be used for all processing steps. This is important not only to reduce the likelihood of microbial contamination during processing, but also to prevent cross-contamination with other infectious agents or even with cells from other cellular therapy products. GTP regulations specifically forbid the pooling of products from more than one donor during processing so as to reduce the risk of communicable disease transmission. In double cord blood transplantation, it is acceptable to sequentially thaw and infuse products from different donors, but it is not acceptable to pool the products into a single container for administration.

For some cellular therapy products processed under approval by regulatory agencies as specified in INDs, IDEs, or equivalent approval pathways, pooled cells may be part of the manufacturing

process. However, this step would have been reviewed by the applicable regulatory agency or competent authority and would thus be allowed under the FACT-JACIE Standards.

Evidence:

The inspector should observe the Processing Facility in operation and should ask personnel what processes are in place when multiple cellular therapy products are received into the facility on the same day. The inspector should determine (from direct observation or by reviewing SOPs) that aseptic technique is utilized during processing.

Example(s):

Other methods to prevent mix-ups may include identification of reagents as dedicated to a single processing procedure and a separation of records and labels to confirm that there is no mix-up of information.

STANDARD:

D8.8 The Processing Facility shall monitor and document microbial contamination of cellular therapy products after processing as specified in Standard Operating Procedures.

D8.8.1 The results of microbial cultures shall be reviewed by the Processing Facility Director in a timely manner.

D8.8.2 The recipient's physician shall be notified of any positive microbial cultures in a timely manner.

Explanation:

Any portion of a processing protocol performed outside of a closed system should be closely monitored for microbial contamination. Use of a biological safety cabinet may be indicated. Biological safety cabinets should be routinely monitored for airflow and regularly maintained to safeguard the proper functioning of filters.

It is a requirement that microbial testing be performed post-processing at a minimum. Additional training in aseptic techniques and modification of cleaning protocols may be appropriate. Gram stains of cellular therapy products may be performed as a rapid release test but are not sensitive indicators of contamination and should not be the only form of contamination testing performed. Depending upon the culture methods used, it may be one to two weeks before final culture reports are available for Processing Facility Director review. Once a microbial culture shows growth, the product is to be considered to have positive microbial cultures even if subsequent tests show no growth. It is also inappropriate to wait for a second culture before notifying the physician.

It is the responsibility of the Processing Facility to confirm that the recipient's physician is notified of positive culture results in a timely manner. The timeframe for notification of positive microbial cultures should be defined in an SOP. There should be documentation that the most recent

microbial reports available have been reviewed by the Processing Facility Director prior to the release of cellular therapy products that have been cryopreserved. Cryopreserved products may be administered at the physician's discretion prior to the final culture reports or even in the presence of microbial contamination provided there is documented approval for release as part of the product record. This documented approval includes approval by the Processing Facility Medical Director and the physician. Policies and SOPs for the management of products with positive microbial culture results are required in [D4](#). Contaminants should be identified to the level required to allow for antibiotic coverage appropriate to the organism(s) at the time of or following administration of a known contaminated product.

When there is a positive result, the Processing Facility Director must review the report, and the Clinical Program must be notified as quickly as possible if the cellular therapy product has already been administered to the recipient. The Processing Facility must participate in the investigation with the clinical and collection representatives to determine if contamination occurred during collection or processing, or if the donor was septic at the time of collection.

Evidence:

The inspector should ask if any processing procedures are performed outside of a closed system and review the records for those procedures. The inspector should review the microbiology report results to assess for microbial growth and determine the frequency of positive results.

In the event of frequent contamination, the inspector may recommend that microbial testing be performed at the initiation of processing and at intervals during processing to determine the point at which contamination occurs (e.g., when the facility received the product, while the product was in the microbiology lab, during processing).

STANDARD:

D8.9 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 can be accurately traced.

D8.9.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.

D8.9.2 Records shall include the test results and, where appropriate, the interpretation.

Example(s):

The Processing Facility may develop a processing record that will allow documentation of detailed processing steps in real time and identification of staff performing the procedure. Labeling and release of cellular therapy products may be included in such a processing record. Use of electronic records should have the concurrent documentation elements. In the U.S., concurrent record keeping is required in [21 CFR 1271.270\(a\)](#).

STANDARD:

D8.10 The Processing Facility Director shall review the processing record for each cellular therapy product prior to release or distribution.

Explanation:

The processing records must be reviewed in a timely fashion to detect errors that may affect patient outcome. The intent of timely review of processing records is to ensure that isolated or systematic errors are detected as rapidly as possible. Certain records should be reviewed immediately in cases where an error would potentially cause a serious adverse event. Examples include:

- Calculation of cell doses.
- Labeling procedures.
- Planned deviations from SOPs.
- Determination of reagent concentrations.

Review of processing records may occur on several levels. Critical calculations should be checked by a second person whenever possible.

Other records may be reviewed within a reasonable time after processing. Examples include:

- Sterility testing results.
- Flow cytometry results.
- Chart review.
- Analysis of freeze curves.
- Reagent and supply lot number recording.

All reviews and any follow-up actions must be documented. The entire processing record and recipient file should be reviewed as soon as possible after all results have been obtained.

The Processing Facility Director is responsible for determining when processing records and recipient files should be reviewed and by whom. Individuals assigned the responsibility for processing record review should not review their own work. There must be documentation that the patient's physician is notified when clinically relevant endpoints are not met. Such deviations must include remedial actions when appropriate, which also must be documented in the processing record.

Resolution of processing errors or situations when cellular therapy products failed to meet specifications should include, at minimum, a summary of the investigation that was conducted (may be in the form of an adverse event report), corrective action, examination of relevant outcome data (e.g., engraftment, GVHD, infection), and notification of appropriate individuals.

STANDARD:

D8.11 There shall be documented notification to the recipient's physician and the Processing Facility Medical Director of clinically relevant processing endpoints not met and remedial actions taken.

Evidence:

The inspector should ask to see written procedures that describe the review process and indicate by whom and when the review takes place. Recipient files should be examined to verify that these procedures are in effect as described in the SOP. The Processing Facility should be prepared to provide examples of processing errors or cellular therapy products that failed to meet specifications so the inspector can determine how the situation was resolved.

Example(s):

The inspector should ask to see an event information report (or equivalent document) that describes the problem, indicates who was involved, when and how the event occurred, an investigation of the event, and any CAPAs taken to prevent a future occurrence (including follow-up activities).

STANDARD:

D8.12 Processing using more than minimal manipulation shall only be performed in accordance with institutional policies and Applicable Law and with the written informed consent of the donor, if applicable, and the recipient of the cellular therapy product.

D8.12.1 Documentation of approvals by the IRB, Ethics Committee, or equivalent, and the IBC or equivalent shall be maintained.

D8.12.2 The Processing Facility shall adhere to Good Manufacturing Practice (GMP) appropriate for the degree of cellular therapy product manipulation.

Explanation:

Due to the investigational nature of more than minimal manipulation, recipients and donors must sign consent forms for any graft manipulation beyond minimal as defined by the Standards and Applicable Law. Assurance of recipient safety and the ability to conduct responsible research are equally important goals central to the missions of FACT and JACIE.

For cellular therapy products in the U.S., manufacturers of HCT/Ps regulated as medical devices must comply with the Quality System regulations ([21 CFR Part 820](#)) and applicable CGTP requirements. The FDA guidance for industry document [Current Good Tissue Practice \(CGTP\) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products \(HCT/Ps\)](#), section III. E. (2011) provides a list of CGTPs that are applicable to HCT/Ps regulated as devices, drugs, and/or biological products.

Evidence:

If procedures are performed in the Processing Facility other than minimal manipulation, the inspector should inquire if IRB and the appropriate IND or IDE approval have been obtained.

Example(s):

Many centers require that all processing procedures be performed with informed consent, while in others certain processing procedures have become standard of care. In these cases, the protocol per se is not IRB reviewed, but the recipient should still consent to the procedure. In most institutions, consent forms are not part of the processing record; instead, consent forms are part of the recipient or donor chart records. In such cases, the Processing Facility Director must know that consents have been signed, and this should be verified by the inspector.

STANDARD:

D8.13 For allogeneic cellular therapy products containing RBCs at the time of administration:

D8.13.1 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.

D8.13.2 Results for an RBC antibody screen on the recipient shall be available.

Explanation:

ABO group and Rh typing are performed on blood and/or cellular therapy products from allogeneic donors and recipients to avoid the unintentional use of ABO-mismatched products containing RBCs or anti-RBC antibodies that might result in an adverse reaction during or after product administration. This testing is required to provide an easily and inexpensively obtained measure of patient safety from gross hemolytic reactions and/or late hemolytic reactions that might result from engraftment of B-lymphocytes producing anti-AB or anti-Rh antibodies, and it is not intended in any way to be a poor secondary patient or donor identifier. While the Processing Facility will generally not be responsible for collecting these samples or conducting the testing on them, there should be documentation present to demonstrate that the facility has confirmed these results prior to product release.

The Standards require testing on two independently collected samples. The timing of the collection of these samples is not specified; however, the entire process of collecting the two samples must be distinct from one another (i.e., different needle sticks and different phlebotomists if staff allows). It is not acceptable to collect the two samples at the same time. The results of both tests should be available to clinical, collection, and processing. The cellular therapy program determines who collects the samples and who performs the testing. Note that these are minimum requirements, and the cellular therapy program may elect to perform more testing, more frequent testing, or testing on the first day of collection as it determines to be appropriate.

The Standards do not dictate how ABO- and Rh-mismatched cellular therapy products should be processed. However, the Processing Facility must have a policy regarding management of products that are ABO- and/or Rh-mismatched between the donor and recipient (see [D5.1](#)). The policy should indicate when and if compatibility testing is to be performed, how many mismatched RBCs (or volume of RBCs) are acceptable for administration, and what, if anything, should be done in the case of ABO-mismatched plasma. The policy should also include instructions for recipients or donors with positive antibody screens (other than ABO antibodies). Processing protocols must clearly state how to achieve the stated guidelines for ABO- and Rh-mismatched products. There must be protocols indicating what the facility's responsibilities are and what should be done with the product in the case of an administration reaction that is suspected to be the result of RBC antibodies.

In the event that the Processing Facility routinely performs compatibility testing on all donors and recipients, regardless of the ABO type, consideration should be given to the consequences of labeling a product for administration as ABO-mismatched. Under these circumstances, there should be an SOP at the Clinical Program which explains and justifies the use of ABO-mismatched cellular therapy products and distinguishes these products from standard blood products. Likewise, if RBC compatibility testing is performed on some but not all donors and recipients, there must be an SOP available to the clinical staff that explains the circumstances under which RBC compatibility testing is and is not performed. If RBC compatibility testing is not performed and the label includes a place for these results, the label should be marked with "N/A" or other appropriate response.

Evidence:

The inspector will look for records of ABO and Rh typing results and antibody screening in the processing chart records.

Example(s):

Allogeneic donors may be tested at the time they are initially evaluated for donor suitability and eligibility, and a second test may be performed at the time of cellular therapy product collection. Alternatively, both tests may be performed prior to collection.

STANDARD:

D8.14 There shall be a Standard Operating Procedure to confirm the identity of cord blood units if verification typing cannot be performed on attached segments.

Explanation:

The WMDA has reported an incident in which the incorrect cord blood unit was distributed and administered to a recipient, thus illustrating the importance of verifying the receipt of the correct unit. HPC, Cord Blood products are manufactured with a limited number of attached segments (one to three) when cryopreserved. Verification HLA typing is typically performed when a cord blood unit is under consideration for a recipient. Most Clinical Programs obtain verification typing on several units before they select the optimal unit for their patient. Thus, a given unit may be typed but not

selected for administration by the initial Clinical Program requesting the first verification typing. Due to the limited number of segments attached to a given unit, verification HLA typing may not be repeatable by subsequent Clinical Programs. A unit that has been previously typed for verification may be selected by a subsequent Clinical Program without repeating this test, as long as the verification typing results match the original typing on the unit and are provided to the subsequent Clinical Program.

Example(s):

If no integrally attached segments or samples are available for verification typing, Clinical Programs may wish to verify typing by a more limited panel of HLA tests or with the use of other genetic markers, such as STRs.

STANDARD:

D8.15 One (1) or more samples representing the cryopreserved cellular therapy product shall be stored under conditions that achieve a valid representation of the clinical product and in accordance with Standard Operating Procedures.

Explanation:

This Standard requires that one or more samples of individual cryopreserved cellular therapy products be available not only until administration of cellular product but after final disposition in case further testing of the product is required. Samples from products that have been cryopreserved must be stored under conditions that allow the sample to represent the product. Such samples should be stored at the same temperature range as the product.

The method by which cellular therapy product samples are cryopreserved is determined by the Processing Facility Director. It should be acknowledged that methods for cryopreservation of a small aliquot versus the product may not be considered to produce identical results, regardless of whether they are frozen at the same time in the same controlled-rate freezer or separately using different procedures. However, the availability of a sample of the product to be administered has potential value for quality control or investigative purposes. Privacy regulations may prohibit the use of stored aliquots for research unless IRB approval is obtained.

The Processing Facility Director should verify that the appropriate consent and/or IRB approval is in place before stored aliquots are used for research projects. Routine tests performed on aliquots for quality control purposes should be determined by the director. For HPC products, this testing often includes the assessment of viability and cell recovery, colony-forming unit (CFU) content, and CD34 content. Whatever testing is performed must be specified in the processing SOP, and those tests must be validated and controlled.

For some cryopreserved cellular therapy products, storage of additional samples is not possible due to low volume or low cellular content of the final product. In such situations, a cell-free sample that represents the final steps of the processing shall be stored so repeat evaluation of microbial

contamination, if needed, can be performed. For example, the negative fraction from cell-enrichment processing may substitute for the supernatant from the final product wash in preparation for freezing. The most appropriate step during processing to collect such a sample shall be determined by the Processing Facility Director.

The cellular therapy product sample(s) that are not used for testing must be stored according to institutional SOPs.

Evidence:

The inspector should request an inventory log for samples of cryopreserved cellular therapy products that are, or have been, stored.

Example(s):

It is preferred but not required that samples from cryopreserved cellular therapy products be stored in the same freezer as the product so as to represent not only the product freezing conditions but also the storage conditions.

For investigational products or products with specific regulatory requirements, the regulations for storing those products should be followed. For products without specific regulatory requirements, it is recommended that a retention sample be maintained at a minimum for a duration of time necessary to monitor clinical outcomes. While there may be scientific value in maintaining product samples longer, it is appreciated that cryopreservation storage space may be at a premium. The inspector should review the Processing Facility's policies and SOPs for storage of archive samples.

D9: CELLULAR THERAPY PRODUCT STORAGE

STANDARD:

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

Explanation:

During hours when Processing Facility staff are unavailable, other areas of the organization may receive a product. The Processing Facility must have policies or SOPs and agreements in place to manage the safety of the product.

STANDARD:**D9.2 STORAGE DURATION**

D9.2.1 Conditions and duration of storage of all cellular therapy products from their collection to final disposition shall be defined and validated.

D9.2.1.1 Validated procedures shall include non-cryopreserved, cryopreserved, and thawed products.

Explanation:

Validations for condition and duration of storage apply to all products that meet these criteria.

STANDARD:

D9.2.2 Processing Facilities processing, storing, or releasing cellular therapy products for administration or further manufacturing shall assign an expiration date and time for non-cryopreserved products and for products thawed after cryopreservation.

Explanation:

The expiration date of a commercial cellular therapy product is the responsibility of the manufacturer and will be included on the product label. If situations arise in which product administration is needed after the expiration date, such as a change in a patient's clinical status, the Clinical Program must follow its exceptional release process.

STANDARD:

D9.2.3 There shall be a written stability program that annually evaluates the viability and potency of cryopreserved cellular therapy products.

D9.2.3.1 Samples should include those representative of all processing methods and those representative of maximum storage duration.

Explanation:

The maximum duration of storage of cellular therapy products that maintains potency is unknown and may be affected by various factors in the collection, processing, cryopreservation, and storage conditions. The purpose of a stability program is to assess cellular therapy products over time in storage for potency and viability.

Cellular therapy product stability and establishment of product expiration depend on processing and storage methods. The validation of new products, or the validation of changes in processing or cryopreservation, require that the stability testing program be established and maintained. Cellular therapy product stability for non-cryopreserved products must be validated.

There must be a stability program in place that evaluates cellular therapy products each year with predefined criteria but is not prescriptive in terms of the number of products, which products are tested in a given year, or other details. Retrospective studies are acceptable. For HPC products, potency is generally measured by CD34 recovery and total viability. For cellular therapy products in early phase trials, the stability program should be in place but may not have mature data available. The stability program for all cellular therapy products should assess characteristics that affect the safety and efficacy of the product, including sterility during processing and storage, container and label integrity, and other characteristics as defined by the Processing Facility.

It is recommended that processing and cryopreservation methods and storage conditions be assessed annually by testing a minimum of three cellular therapy products in storage to ensure potency is maintained. Cellular therapy products stored for various periods may be assessed; however, the oldest products in storage for each processing method must be included in the assessment.

The assessment of cellular therapy products in the stability program must include pre-determined acceptance criteria for potency and viability. The stability program should also define actions to take if any products fail to meet specifications, including at a minimum, assessment of additional products.

Evidence:

The inspector should review exceptional distribution practices when cellular therapy products are released after their established expiration date.

The validation process of new cellular therapy products from a third-party manufacturer should be the responsibility of the third-party manufacturer.

Example(s):

Stability testing can be performed using cellular therapy products stored for more than a year that are scheduled to be discarded or could be performed with samples from products that were frozen and stored under the same conditions as the actual product. Testing of products intended to restore hematopoiesis can include TNC viable cell recovery post-thaw as a useful alert that there might be problems with the freeze run. An assessment of the recovery of viable CD34 cells or recovery of other cell populations where applicable, such as viable T lymphocytes recovery for cells to be used for donor lymphocyte administration, should be included. Determination of post-thaw viability and establishment of stability program for cryopreserved HPC product is discussed in the article [Cryopreserved hematopoietic stem/progenitor cells stability program-development, current status and recommendations: A brief report from the AABB-ISCT joint working group cellular therapy product stability project team](#) (Reich-Slotky, Vasovic, Land, et al. *Transfusion*. 2022;62(3):651-662). Processing Facilities are encouraged to adopt single platform technology to determine flow cytometry-based cell viability and diagnostic kits that include a viability marker.

The inspector should review written agreements with third party manufacturers of cellular therapy products (e.g., genetically modified cellular therapy products) for acceptable endpoint parameters established by the stability program of the third-party manufacturer.

STANDARD:

D9.3 STORAGE TEMPERATURE

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

D9.3.2 Non-cryopreserved cellular therapy products shall be maintained within a specific temperature range to maintain viability and function.

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.

Explanation:

The Processing Facility must establish a process to ensure that cellular therapy products are stored in a manner that maintains their integrity and potency and that assures that products are not released prematurely before all release criteria have been met. Standard [D2](#) requires that defined areas for storage be established and that these areas be controlled to prevent the possibility of mix-ups, contamination, or cross-contamination. This process is further defined as to require control of the storage duration and the appropriate storage temperature.

The Processing Facility should define what constitutes storage. Storage often occurs prior to processing, either within the Processing Facility or at the Collection Facility, as well as after processing is complete. Storage temperature and duration shall be defined by the storing facility and shall include conditions for non-cryopreserved, cryopreserved, and thawed cellular therapy products. Products that have been processed and are awaiting the results of release testing (e.g., CD34 cell assessment by flow cytometry, the completion of allogeneic donor eligibility determination) may be held in quarantine at one temperature (i.e., up to four hours at room temperature) but stored for longer periods at another temperature (i.e., 1–8°C). Temperature ranges and duration must be determined for each type of product and should be based on the medical literature or on the facility's own experimental data. For liquid products, including thawed products, temperature ranges, storage duration, and product expiration date and time must be established to safeguard adequate viability and to decrease the risk of contamination. Processing procedures should specify the temperatures at which products are handled and processed prior to storage. Likewise, transport and shipping temperature both from the Collection Facility to the Processing Facility, and at distribution from the Processing Facility, must be defined.

The medical literature reports a variety of cryoprotectant agents used to store HPC products, as well as temperatures ranging from -80°C to liquid phase nitrogen (-196°C). The chosen storage

temperature must be adequate for the preservation of the desired cell type, as documented either in the medical literature or the Processing Facility's own experience. When possible, storage of cryopreserved cellular therapy products at temperatures $\leq -150^{\circ}\text{C}$ is advisable. Methods to reduce the risk of contamination or cross-contamination must be included. No upper limit of storage time for products stored at temperatures equivalent to the vapor (-120°C to -155°C) or liquid phase (-196°C) of liquid nitrogen has been reported, provided the product has been maintained at that temperature throughout the storage period. The effects on storage time of temperature fluctuations above -120°C are largely unknown; however, failure to maintain the product in a frozen state can result in a loss of viability within minutes to hours. The viability of products in any low-temperature storage device that has not maintained the proper temperature is potentially compromised. The validation of cryopreservation procedures must include evidence that the prescribed storage temperature range adequately preserves the products being stored. Expiration date and time do not have to be attached or affixed to the label for cryopreserved products if storage conditions are shown to be adequate based on the medical literature or are justified by validation studies, where applicable. Expiration dates for cryopreserved products can be in the accompanying documentation for product release.

Storage temperatures for cellular therapy products from third-party manufacturers must be defined by the third-party manufacturer.

In the case of autologous or related donations, donors, recipients, and associated clinical programs should be informed of the conditions of storage and storage duration, preferably before product collection.

Evidence:

Storage criteria must be defined by Processing Facility SOPs or policies. The inspector should review the facility's established storage criteria for all relevant cellular therapy products and any related contracts or consents. A written plan for determining the stability of cryopreserved products and the acceptable endpoint parameters must be present.

Example(s):

In the EU, the expiration date must be part of the cellular therapy product information for all tissues and cells. For licensed products, such as cord blood in the U.S., the Processing Facility should maintain the products at the temperature recommended by the organization that provided it. Applicable Law may specify what testing and frequency of testing to establish cryopreserved product stability is required.

STANDARD:

- 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.*

Explanation:

The Processing Facility (or Clinical Program on its behalf) must communicate with the distributing external facility regarding the details of the cellular therapy product being sent, such as the size and type of container, how many containers, and appropriate storage conditions.

Example(s):

Cord blood units are one example of a cellular therapy product for which special arrangements may need to be made at the Processing Facility. These products are often in canisters that may be too small for the racks typically used for other types of products, and special arrangements should be made in advance.

STANDARD:

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 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 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 Law.*

Explanation:

Evidence has been published demonstrating the possibility of cross-contamination of cellular therapy products stored in the liquid phase of liquid nitrogen with infectious virus (Tedder,

Zuckerman, Goldstone, et al. [Hepatitis B transmission from contaminated cryopreservation tank](#). *Lancet*. 1995;346(8968):137-140).

Infections occurring in recipients following the administration of cryopreserved cellular therapy products shall be reported to the Processing Facility so that the facility can undertake an investigation of possible cross-contamination when unusual patterns are seen and report to the proper authority as required by Applicable Law.

Quarantine is defined in [A4](#) as the identification of 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. It also refers to segregated storage of products known to contain infectious disease agents to reduce the likelihood of cross-contamination.

Quarantine of cellular therapy products that have not undergone complete allogeneic donor eligibility determination, are from known ineligible donors, or have not yet completed other required release testing (e.g., sterility cultures) is required. Quarantine does not require physical segregation of such products, but it does require a mechanism to minimize the potential for cross-contamination of communicable disease agents and to prevent product distribution when release is not approved.

Appropriate labeling should be used to distinguish cellular therapy products that are in quarantine, such as the use of quarantine tie tags that clearly state that the product may not be released without physician notification and approval.

Evidence:

The inspector should review the Processing Facility's program to reduce the likelihood of cross-contamination of containers in liquid phase storage. The inspector should review the systems that are in place to distinguish quarantined cellular therapy products and to prevent their inappropriate release.

Example(s):

A quarantine program may include one or more of the following practices:

- Protective outer coverings over the primary freezing bag.
- Use of vapor-phase storage.
- Use of mechanical freezer storage.
- Use of a validated electronic release system that prevents inappropriate release of cellular therapy products.

These procedures are recommended at this time, but until scientific studies validating the effectiveness of one or more of these approaches are available, no standard method can be specified.

Quarantine may be accomplished physically by storing quarantined cellular therapy products on a separate shelf or in a separate rack or compartment of the storage unit. The methods suggested above are effective in minimizing the potential of cross-contamination of products that are stored in frozen form. Non-cryopreserved products may more appropriately be stored in a separate area in the Processing Facility while release testing is being performed. If an electronic system is used for product release, an audit trail that indicates who was responsible for the release must exist.

STANDARD:

D9.5 STORAGE MONITORING

D9.5.1 Storage devices in which 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.

Explanation:

It is required that the storage temperature be monitored on a continuous basis and that temperatures be recorded at least every four hours for vapor phase storage. Temperature records of stored cellular therapy products, including alarm conditions, must be reviewed prior to product distribution. Failure of the device to maintain the target temperature represents a deviation that must be documented and that includes the appropriate investigation and follow-up actions required to determine the integrity and potency of the product. The Processing Facility should establish critical values that, if exceeded, require documentation in the processing and storage records for those products in the storage freezer that did not maintain target temperature. In the case of suspected out of specification temperature swing or thawing of cryopreserved products, the recipient's primary transplant physician must be notified. The primary transplant physician or Medical Director, in collaboration with the Processing Facility Director, makes a decision regarding continued storage of the product. As specified elsewhere in the Standards, the facility must have written SOPs specifying actions to be taken in the case of cryopreservation failure.

STANDARD:

D9.5.2 There shall be a mechanism to confirm that levels of liquid nitrogen in liquid nitrogen freezers are consistently maintained to ensure that cellular therapy products remain within the specified temperature range.

Explanation:

For cellular therapy products stored in liquid nitrogen, temperature monitoring does not have to be continuous or even every four hours, but at intervals determined by the Processing Facility

Director to be sufficient to safeguard that levels of liquid do not fall below set limits between measurements. The objective is to confirm that products are continuously maintained at the target storage temperature. Validation studies may be especially important to ensure that the level limits that trigger alarms are acceptable to allow sufficient time to rescue products before they reach temperatures that might compromise their viability and functionality.

STANDARD:

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.

Explanation:

The failure of mechanical or liquid nitrogen freezers can result in the loss of potentially irreplaceable cellular therapy products stored for future use. It is essential that precautions be taken to prevent loss of any stored products. Alarm systems and mechanical freezers must be supplied with backup power systems (battery- or generator-based) to confirm they are continuously active. See [D2.11](#) Standards for safety information regarding alarms where liquid nitrogen is in use.

Evidence:

The inspector should review records of storage device alarm checks of function and triggering at the appropriate limits (e.g., temperature, liquid level).

STANDARD:

D9.6.3 Alarm systems shall be checked for function according to the manufacturer's recommendation or annually at a minimum.

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 Storage devices of appropriate temperature shall be available for cellular therapy product storage if the primary storage device fails.

Explanation:

Backup storage devices (either internal or external) capable of maintaining cellular therapy products with an acceptable storage temperature range must be identified in advance in the event of interruption ([D4](#)) or mechanical failure of the storage device (e.g., rupture of liquid nitrogen storage tank) or the event of a disaster ([D5.1](#)). Instructions describing the actions to take must be in the form of an SOP (see [D5.1](#)). Records of temperatures during storage must be available, with notations made for action taken when temperatures fall outside of the designated range.

Example(s):

Failure of a primary storage device or a disaster may result in activating preplanned use of a backup device available either in the same or a different facility. The plan should factor in prioritization based on recipient status (e.g., imminent transplant).

If multiple groups of people are using the same room, the devices regulated by these Standards must be located in a secure area and be accessible only to authorized personnel.

STANDARD:

D9.7 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.

Evidence:

The inspector should review the action plan in case of failure, including the mechanism for notifying responsible Processing Facility personnel. The inspector should also verify that instructions to be followed in the event of a storage device failure are posted in the immediate area of the storage device. The inspector should review these instructions. Audible and visible alarms in the vicinity of the applicable facilities can be supplemented by other effective notification systems (e.g., phone call, text message).

Example(s):

Instructions may include information on “who to contact” and are particularly applicable in Processing Facilities that do not provide 24-hour service but have arranged with their institutions’ facilities and engineering departments, security, or other service departments to be the on-site responder to a freezer alarm. Instructions may also include “what to do” and may consist of a troubleshooting flowchart located at the freezer device for quick reference and immediate response by the technical staff.

STANDARD:

D9.7.1 Instructions shall include a procedure for notifying processing personnel.

STANDARD:

- D9.8 Storage devices shall be located in a secure area and accessible only to personnel authorized by the Processing Facility Director.*
- D9.9 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:*
- D9.9.1 Cellular therapy product unique identifier.*
 - D9.9.2 Recipient name or unique identifier.*
 - D9.9.3 Storage device identifier.*
 - D9.9.4 Location within the storage device.*

Explanation:

There must be a mechanism by which cellular therapy products and sample vials from the products can be located in storage devices and a system to track remaining units. This is to prevent retrieval of the wrong product and minimize exposure of products to temperatures outside acceptable limits during the storage or the retrieval process. Audits must be performed periodically to confirm proper function.

The system shall include the elements described in this Standard. These elements should allow tracing back to additional cellular therapy product information, such as the recipient's name or unique identifier (if known), the date of collection or processing, the date of issue, and the disposition.

Evidence:

The inspector should ask for a demonstration of the system, including verification that the cellular therapy product can be located in the storage container. The inspector should also review the processes in place to make changes in inventory entries when products are added or removed to ensure the integrity of the system is maintained.

Example(s):

The inventory control system may be in the form of an electronic database or may consist of logbooks or other manual systems.

D10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

STANDARD:

D10.1 Standard Operating 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.

Explanation:

The Processing Facility must assess risks of distribution to cellular therapy product integrity and recipient status (i.e., imminent transplant). This process must include container validation and courier qualifications.

The Processing Facility shall have written policies and SOPs for the distribution of cellular therapy products to and from the facility. Such SOPs include transport or shipping from internal sites, such as from the Collection Facility to the Processing Facility, at release to internal Clinical Program sites, or to external facilities. These SOPs must include maintenance of optimal temperature during distribution. The product container and tubing must be securely sealed and packaged to protect it from potential harm during transit and to prevent exposure of individuals involved in its transport or shipping to potentially infectious agents.

Human tissue, regardless of infectious disease testing, must be considered potentially infectious. For non-cryopreserved products, absorbent material in the transport container is no longer required by the Standards but is a recommended practice in the event of breakage.

Evidence:

The inspector must determine if the transport and shipping SOPs in use within the Processing Facility are adequate for the conditions. The inspector should review receipt records of both non-cryopreserved and cryopreserved cellular therapy products shipped and received by the facility for adherence to the Standards. Inspectors should verify that there is a process and that container validation is adequate to maintain product security and integrity during expected transit time and ambient temperature conditions.

STANDARD:

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

Explanation:

For non-cryopreserved cellular therapy products, a thermally insulated container should be used with appropriate temperature stabilizing material such as cold packs, temperature stabilizing packs, or phase-change materials specific to the validated container system(s) in use, which are necessary

to maintain the required temperature. Containers utilizing thermal insulation chamber panels made of a hard plastic and that contain phase-change material in liquid form may be considered the equivalent of thermal insulation because the product is protected from frozen material by the outer hard plastic. These types of containers require process validation. The secondary container must prevent leakage.

STANDARD:

D10.3 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

D10.4 Cellular therapy products transported internally shall be packaged in a closed and rigid outer container.

Explanation:

Internal transport includes the transport within an institution that does not involve crossing public roads. The distance and characteristics of the transport may vary from program to program.

For non-cryopreserved cellular therapy products, a closed outer container must be used and must be made of materials and insulation that will withstand leakage of contents.

The closed and rigid outer container must withstand transport. A tray is not a valid container. Wrapping the secondary bag with a cloth, with the primary container inside, is also not a valid means of transporting cells.

For cryopreserved products, a dry shipper is frequently used even in short internal transport. Dry ice or other methods might be considered depending on the characteristics of the internal transport.

STANDARD:

D10.4.1 The outer container for internal transport shall be labeled as defined in [Appendix III B](#).

Explanation:

During the risk assessment the facility must determine if there is a need for additional information to be added to the label.

STANDARD:

D10.5 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.

Explanation:

For transported or shipped cellular therapy products, an appropriate shipping container should be utilized whether product distribution is internal or external. The shipping container must be validated for its intended purpose for all types of products transported (e.g., fresh unfrozen products, cryopreserved), and the temperature at receipt of the product should be documented. For cryopreserved products, the container should maintain the temperature at least 48 hours beyond the expected time of arrival at the receiving facility and be “charged” for use following the manufacturer’s instructions.

STANDARD:

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.

Explanation:

Containers for distribution of cryopreserved and non-cryopreserved cellular therapy products that leave the Processing Facility must be made of durable material and insulation that will withstand leakage of contents, shocks, pressure changes, and temperature extremes. Transport containers containing cellular therapy products should not be exposed for prolonged periods to extreme heat or cold. Since cryopreserved product primary containers are susceptible to breakage, they must be packaged so as to minimize movement during transit. At a minimum, the acceptability of all products must be verified at receipt. Documentation of this inspection and container temperature at receipt is required for the processing records of the receiving facility for all products.

STANDARD:

D10.5.2.1 The temperature of the shipping container shall be continuously monitored during shipment of cellular therapy products.

Explanation:

When cryopreserved cellular therapy products are shipped to another facility and are not in the control of the Processing Facility or receiving facility personnel, the temperature during shipment must be continuously monitored, and that record must be maintained by the distributing facility. For cryopreserved products that are transported (hand carried) by knowledgeable personnel from

the distributing or receiving facility, product temperature at the receiving facility should be documented regardless of the distance traveled.

STANDARD:

D10.5.2.2 The shipping facility shall maintain a record of the temperature over the period of travel.

Explanation:

Continuous monitoring that creates a record typically utilizes a thermometer with data logging capability. The frequency of data capture is not specified but should be sufficient to confirm that the proper temperature was maintained. For external transportation, it is recommended that a copy of the data logger printout be shared with the receiving facility for their records; however, documentation from the distributing facility of the temperature conditions during transport would be acceptable.

STANDARD:

D10.5.3 The outer container shall be secured to prevent unauthorized access.

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 A](#) and Applicable Law.

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 A](#).

D10.5.6 The outer container shall be labeled in accordance with Applicable Law regarding the cryogenic material used and the transport or shipment of biological materials.

Explanation:

Labeling that must be affixed to the outer container or accompanying the cellular therapy product is specified in [Appendix III](#).

Appropriate biohazard and warning statements must be present on the documentation inside the container. Outer containers bearing biohazard and warning statements on the exterior of the container will be refused by some carriers.

Information regarding shipping and receiving facilities and responsible individuals at those centers is required for contact in the event of delay or emergency during transit or if questions about the cellular therapy product arise after it reaches its destination. Having this information attached to

the container safeguards that the product can be delivered in the event that the accompanying paperwork is lost or destroyed. To safeguard anonymity of donors and recipients of unrelated transplants, neither the donor nor recipient name shall be on the transport or shipping label; however, unique identifiers are appropriate.

The Processing Facility personnel are responsible for verifying the labeling requirements of any courier services utilized.

The courier should be able to contact the receiving facility on a 24-hour basis in case of emergency or delay during transit. Shipping instructions, contact names, and phone numbers should be printed or, if handwritten, clearly legible.

Evidence:

The inspector should review transportation and shipping records and inspect outer containers to confirm that the elements in this section are met and documented.

Example(s):

EU regulations also require the time at the start of transportation or shipping and specification of the conditions of transportation or shipping relevant to the quality and safety of the tissues and cells. Examples include "Keep Cool," "DO NOT FREEZE," and "Keep Upright."

STANDARD:

D10.6 Cellular therapy products transported or shipped over an extended period of time shall be transported or shipped in a container within a temperature range defined in a Standard Operating Procedure or written agreement and according to manufacturer instructions.

Explanation:

The cellular therapy product temperature during transit is dependent upon a number of variables, including transport time, ambient temperature ranges, initial temperature, size of the product, and characteristics of the specific container system, and these must be defined in SOPs. The ideal transport temperature of non-cryopreserved products may range from 1–24°C. There must be a prospective agreement among the collecting, processing, and receiving facilities regarding transport and shipping conditions based on intended use of the product upon receipt and other factors. Most products should not be transported or shipped at temperatures above 24°C. Non-cryopreserved products should never be allowed to cool to temperatures below freezing. The use of additives in the product is to be determined by the program and validated for the conditions of shipping and transport.

For cellular therapy products transported between sites of a single cellular therapy program, the distance between the facilities varies widely. Transport between facilities, where the product remains in the control of trained personnel, usually requires the use of an outer container that protects the product from adverse conditions encountered during transport (e.g., air pressure changes, rough

handling, exposure to extreme temperatures, unexpected delays) and that has been validated to maintain the agreed transport temperature for the expected transit time and conditions.

For situations where transport to and from the Processing Facility requires only minutes, such as between adjacent facilities, a controlled temperature environment is optional, provided the product is transported securely, safely, and remains in the control of trained personnel. However, for extended periods of transport time within a facility or outside of a building, a controlled temperature environment should be maintained using a validated outer container and shall remain in the control of trained personnel.

Validation and periodic quality control must be performed on all dry shippers used for cryopreserved cellular therapy products and for containers used for non-cryopreserved products, specific to the transit conditions expected and the design and characteristics of the containers or shippers in use. Validation must be performed prior to use and when changes to the container system are made. Containers should be monitored to safeguard continued performance and verified or re-validated periodically per Processing Facility-defined SOPs. Calibration and verification of function of data loggers per manufacturers' recommendation is required.

Facilities using shipping containers from a third-party manufacturer should verify that shipping containers are validated for conditions of use.

Example(s):

Refrigerated cellular therapy products shall be insulated from direct contact with frozen materials during transportation or shipping. Frozen products may be placed in the dry shipper surrounded by material such as Styrofoam to absorb impacts during shipping.

TNC and product viability are examples of data for which temperature ranges should be established.

STANDARD:

D10.6.1 Additives to the cellular therapy product should be used for shipping or transporting over an extended period of time.

Explanation:

Guidelines for shipping and transportation shall utilize validated processes. Shipping and transportation orders including the use of additives, if applicable, shall be provided by the Clinical Program or manufacturer. Additives may be combined with the product when shipping cellular therapy products over a long duration of time for further manufacturing is anticipated.

Example(s):

If products are shipped over a long period of time, the facility should use additives, such as Anticoagulant Citrate Dextrose Solution, Solution A (ACD-A). Additionally, the Processing Facility may consider adding Heparin or autologous plasma.

STANDARD:

D10.7 There shall be a risk assessment to evaluate the need for continuous temperature monitoring during transportation or shipment of cellular therapy products.

Explanation:

The objective of this Standard is to confirm that products are continuously maintained at the target temperature, as required. The integrity of cellular therapy products needs to be safeguarded during transport or shipping, and a risk assessment may be needed. Validation studies may be especially important to determine whether continuous temperature monitoring is appropriate for the transport or shipping conditions. Factors which can impact the quality of the product and need to be considered include distance and length of transport.

STANDARD:

D10.8 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.

Explanation:

If a patient has undergone high-dose marrow ablative treatment in preparation for transplant, the cellular therapy product is essential for the patient's survival since it may not be possible to obtain additional marrow or blood from the original donor or a second donor in time to prevent complications from aplasia. For this reason, it is important that the product be entrusted to a knowledgeable individual who accompanies it from the distributing facility to the receiving facility. See [A4](#) for the definition of "transport."

STANDARD:

D10.9 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.

D10.10 There shall be contingency plans for alternative means of transport or shipping in an emergency.

D10.11 The cellular therapy product shall be transported or shipped with required accompanying records as defined in Standard Operating Procedures and in compliance with [D7.4](#) as applicable.

D10.12 There shall be a record of the date and time of cellular therapy product distribution.

STANDARD:

D10.13 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.

Explanation:

Outer containers should not be exposed to gamma irradiation or X-ray devices designed to detect metal objects to prevent potential damage that may compromise progenitor cell repopulating capacity. Circumstances may require X-ray by airport security personnel. Those situations should be avoided, if possible, but complied with as required.

Evidence:

SOPs should address alternative emergency transport and provide direction to request a manual inspection of cellular therapy products rather than X-ray exposure. Inspectors should review the process for qualification of couriers appropriate for the transportation or shipping methods provided. It is suggested to validate the alternative emergency transport plan.

D11: RECEIPT AND DISTRIBUTION

STANDARD:

D11.1 RECEIPT OF CELLULAR THERAPY PRODUCTS

D11.1.1 Standard Operating Procedures shall be established and maintained for acceptance, rejection, and quarantine of cellular therapy products.

Explanation:

Processing Facilities must have established SOPs for receipt to verify that the appropriate cellular therapy product has been received and that it is acceptable for administration to the intended recipient. This Standard applies to the receipt of cellular therapy products from a Collection Facility within the Processing Facility's institution, from an external facility, or from the clinical unit that returned the product after it was distributed for administration.

The cellular therapy product receipt SOP must minimally describe the criteria for product acceptance, rejection, and quarantine. Documentation of the receipt process must include the integrity of the primary product container and confirmation that the label information meets the requirements specified in [Appendix II](#). There must also be a visual examination of the appearance of the cellular therapy product for evidence of microbial contamination (excess hemolysis or inappropriate cloudiness, or other unusual appearance). Any samples that accompany the product must be labeled so as to be clearly identified with the donor and date of collection. In many cases donor screening and test results will have been received into the Processing Facility prior to product

receipt. The minimum requirements for a summary of documents used to determine allogeneic donor eligibility, to which the Processing Facility shall have ready access, are defined in [Appendix IV](#).

A process to store cellular therapy products in quarantine until they have been determined to meet all predetermined release criteria must be in place. Management of the return of products must be addressed in SOPs.

Evidence:

The inspector should review documentation of cellular therapy product receipt into the Processing Facility to confirm compliance with the facility's SOPs and the Standards. Documentation must verify that the quarantine process is defined in SOPs and physical or electronic systems are in place to support quarantine functions.

Example(s):

EU requirements for documents that should be available to the Processing Facility that are not addressed by FACT-JACIE Standards are defined in EU Directives [2006/17/EC](#) and [2006/86/EC](#) and include the identification of the person responsible for the procurement, the SOP that was used, a listing of batch numbers of reagents and solutions used. Other specified EU requirements are present on the label, including the collection date and time and identity of the Collection Facility; however, all of this required information may be part of the label or the accompanying documents that serve as an extension of the label. For inspections performed in EU member states, the access to such documentation containing the required information should be confirmed.

STANDARD:

D11.1.2 The receipt of each cellular therapy product shall include inspection to verify:

D11.1.2.1 The integrity of the cellular therapy product container.

D11.1.2.2 The appearance of the cellular therapy product for evidence of mishandling or microbial contamination.

D11.1.2.3 Appropriate labeling.

Explanation:

When a cellular therapy product is received from a third-party manufacturer with missing or unclear labeling information, the facility should take action and complete an investigation, which may result in adding accompanying labeling documentation.

STANDARD:

D11.1.3 There shall be Standard Operating Procedures to verify that the cellular therapy product was appropriately transported or shipped.

D11.1.3.1 The receiving facility shall document the temperature inside the container upon arrival if shipped or transported on public roads.

D11.1.3.2 For cryopreserved cellular therapy products, the receiving facility records shall include documentation of the container temperature during shipping.

D11.1.4 The receiving facility shall review and verify cellular therapy product specifications provided by the manufacturer, if applicable.

D11.1.5 The receiving facility shall have readily available access to a summary of documents used to determine allogeneic donor eligibility.

D11.1.5.1 For cellular therapy products received from an external facility, there shall be documented evidence of donor eligibility screening and testing in accordance with Applicable Law.

Explanation:

The Processing Facility is responsible for all activities performed by external facilities, especially the manufacture of those cellular therapy products that the facility will ultimately distribute for administration to a recipient. When the Processing Facility or external facility performs more than minimal manipulation, the external facility must be qualified to demonstrate that it follows current GMPs to protect product integrity, recipient safety, and regulatory compliance, including requirements of an IND or BLA.

In the Standards, “manufacturer” refers to whoever produced the cellular therapy product, such as a laboratory or a pharmaceutical company. This Standard does not require the receiving facility to establish cellular therapy product specifications for products received from a third-party; rather, if the manufacturer provides specifications, the facility must verify the specifications are met. If not, this could be evidence of damage to the product’s integrity.

STANDARD:

D11.1.6 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.

D11.1.6.1 The Processing Facility Director shall consult with the recipient's physician regarding reissue or disposal of the returned cellular therapy product.

Explanation:

The return of any cellular therapy product issued for administration is always a deviation from standard procedures and requires a detailed report as to the cause and action taken by the Processing Facility to safeguard the product.

Should a cellular therapy product need to be returned to the facility, it should be stressed to the medical staff that this be done as soon after issue as possible. All events surrounding the release and return of the product must be documented in the facility records, including the reason for return. The facility personnel are responsible for examination of the product and documentation of the outcome of that examination, including the length of time the product was removed from a monitored temperature-controlled environment and the temperature of the product upon return to the facility.

Cellular therapy products cannot be reissued or disposed of without authorization by a responsible individual, such as the Processing Facility Director or Processing Facility Medical Director, and must always be done in collaboration with the recipient's physician. Records for both the initial distribution and any subsequent distribution must be maintained in the Processing Facility record. Return of products and conditions of re-storage, reissue, or disposal shall be described in an SOP for release and exceptional release.

The Standards require an SOP for product recall, which may include elements of product return and reissue, but must additionally address situations in which the Processing Facility must recall a distributed product. For academic centers that primarily distribute products for direct administration, such an event would be very rare. For laboratories that process products for multiple centers and distribute products in advance of the administration day, such a situation may be more likely to occur.

Evidence:

The inspector should verify the Processing Facility SOP for cellular therapy product return and ask to review the records of one or more products that were returned and reissued, if this situation has occurred.

Example(s):

There are a variety of reasons why a cellular therapy product may be returned to the Processing Facility, such as cases in which a scheduled treatment is delayed or a recipient has an anaphylactic reaction to DMSO.

STANDARD:

D11.1.6.2 If the temperature of the cellular therapy product has been compromised, the Processing Facility Director shall give specific authorization to return the product to inventory.

Explanation:

Cellular therapy products are highly sensitive to temperature fluctuations, which can directly affect cell viability, potency, and overall safety. Proper temperature control must be maintained throughout all stages of storage, transport, and handling. Any deviation from validated temperature ranges, whether during cryogenic storage, refrigeration, or transport may compromise product integrity.

This Standard requires that if such a temperature variation occurs, the product may not be automatically returned to inventory. Instead, the Processing Facility Director must conduct a formal assessment and provide specific, documented authorization before the product is deemed acceptable for reintegration into usable stock.

The Director's decision must consider:

- Duration and extent of the temperature deviation.
- Product type (e.g., fresh vs. cryopreserved).
- Results of any available viability or potency testing.
- Risk to patient safety if the product were to be used.

This Standard is critical for ensuring that no potentially compromised product is used in a clinical setting without a risk-based evaluation by qualified personnel. It also supports regulatory compliance with GMP principles and enhances traceability and accountability in cellular therapy product management.

STANDARD:**D11.2 DISTRIBUTION CRITERIA**

D11.2.1 The processing, collection, and transport or shipping records for each cellular therapy product shall be reviewed by the Processing Facility Director for compliance with Standard Operating Procedures and Applicable Law prior to product release or distribution.

D11.2.1.1 Records shall demonstrate traceability from the donor to the recipient and from the recipient to the donor.

Explanation:

Distribution is the time at which the cellular therapy product leaves the control of the Processing Facility. This includes both distribution of the product within the institution for administration and release of the product to an outside facility for additional processing or administration. In both cases, review of the product's processing and tracking records by the Processing Facility Director is required to confirm that the product meets all predetermined criteria for release, including those required by the Standards, the Processing Facility's own SOPs, and applicable regulations. Documentation of specific areas of review must include:

- Allogeneic donor test results to confirm that the relevant communicable disease agent tests were performed within the required time span.
- Review that donor eligibility determination was completed.
- Confirmation that the unique product identifier on the label matches the identifier in the facility records and can be traced to the donor records. Tracking and tracing must be bi-directional from donor to recipient and from recipient to donor.
- Review of the entire processing record for completeness and accuracy per SOPs.

Non-conforming cellular therapy products that are used under regulatory approval or licensure (e.g., INDs or BLAs in the U.S.) may require regulatory approval for use or even a separate IND.

STANDARD:

D11.2.2 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.

D11.2.2.1 The Processing Facility Director shall give specific authorization for release when the cellular therapy product does not meet technical release criteria.

STANDARD:

D11.2.2.2 The Processing Facility Medical Director shall give specific authorization for release when the cellular therapy product does not meet clinically relevant release criteria.

D11.2.2.3 Documentation of agreement between the Processing Facility Medical Director and the recipient's physician to use any non-conforming product shall be retained in the processing record if such release is allowed by policies, Standard Operating Procedures, or package inserts of licensed products.

Explanation:

The Standards require that there be predefined release criteria for distributed products and that there be provisions for exceptional release when a given cellular therapy product does not meet established criteria.

There may be situations when testing results are not available at the time a recipient needs a cellular therapy product. In these cases, the Processing Facility must follow urgent medical need or exceptional release processes. However, preliminary review of some test results (e.g., microbiology) may be informative.

While the Processing Facility Director may approve the release of products that meet all release criteria, the Processing Facility Medical Director or another acceptable designee with the appropriate medical background must authorize exceptional release when the failed criteria might affect the clinical efficacy of the product. It is left to the Processing Facility to define who the "designee" would be that meets the knowledge requirement for approval for release of a product under exception, and this should be clearly defined in the facility SOP for product approval for release.

Evidence:

The inspector should review documentation that release criteria are defined and are met for given cellular therapy product types issued by the Processing Facility. Additionally, the inspector should specifically review records of products released under exception to confirm that the required documentation of Processing Facility Director or Processing Facility Medical Director approval and physician notification is present.

Example(s):

For failed release criteria that are technical or clerical in nature, the Processing Facility Director may approve the cellular therapy product for release. Examples may include a review of the processing record that shows a missing signature, or a product with an adequate cell dose but a below-expected cell recovery (assuming that cell recovery was considered to be a release criteria).

In the U.S., when cellular therapy products do not meet release criteria, the Processing Facility Director or Medical Director, as appropriate, must give specific authorization for release. In the case of investigational products regulated by the FDA under IND applications, the FDA expects that products will not be administered if they fail to meet the release criteria listed in the IND. The FDA recognizes that there may be situations when administration of a failed lot may be in the best interest of the patient, but the FDA must be involved in that decision. To comply with the FACT Standards, both this Standard and the regulatory requirements of the FDA must be met. Facilities outside of the U.S. must follow their national regulations.

STANDARD:

D11.2.3 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.

D11.2.3.1 A cellular therapy product shall not be released when the container is compromised or recipient or donor information is not verified unless the Processing Facility Director gives specific authorization for the product's release.

Explanation:

The release process includes the requirement for two trained individuals to inspect the final product to confirm that the product is properly labeled, is intact, and is normal in appearance. The individuals may be members of the patient care team, or the Processing Facility staff.

Evidence:

The inspector should review the release documentation to verify that all the requirements were met and the signatures of two trained individuals exist. The cellular therapy product identity verification can be made when the product is documented to be properly labeled unless other testing is required by the IND, IDE, or other regulatory approval.

STANDARD:

D11.2.4 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:

D11.2.4.1 The use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

D11.2.4.2 Instructions for handling the cellular therapy product to minimize the risk of contamination or cross-contamination.

STANDARD:

D11.2.4.3 Appropriate warnings related to the prevention of the transmission or spread of communicable diseases.

Explanation:

The frequency with which individuals are involved in administration of a given type of cellular therapy product may vary. Information regarding the product should be made available to the medical staff within the Clinical Program to provide a full description of the product and the way in which the product should be handled and administered based on the current protocols and practices of the institution. Instructions for administration must include information to prevent the introduction, transmission, or spread of communicable diseases.

The instructions for administration may contain cell types that are not currently being used at the Processing Facility, but they must include all cell types that are in use. The facility will need to generate instructions for administration for cellular therapy products not included in this document and may create their own documents for all products as long as they meet the criteria specified in this section of the Standards. The facility may wish to issue the Circular of Information with each administration, although this is not required by the Standards. The circular must be available to personnel at the sites where administrations are performed. However, EU regulations require that instructions for opening the container, package, and any required manipulation or reconstitution be included as a document accompanying the product. Like controlled documents, these documents should be reviewed at least every two years and must reflect the current practices in the facility.

Cellular therapy products licensed in the U.S. must contain much of this information in the package insert to accompany the product. Information required to be included on the package insert is defined within the BLA approved by the FDA. If all information required by these Standards is within the package insert, the insert will satisfy these requirements.

Evidence:

The inspector should review the current version of the instructions for administration and its availability at the sites of administration.

Example(s):

A [Circular of Information for the Use of Cellular Therapy Products](#) document has been prepared jointly by multiple organizations, including FACT and JACIE. This document provides the information for commonly used hematopoietic cellular therapy products and may be used to satisfy the requirements of this standard. Please note, when a FACT Standard is stricter than the Circular of Information, the Standard must be followed.

A method of circulating this information is via an SOP for administration that describes all elements listed in this Standard.

STANDARD:**D11.3 DISTRIBUTION RECORDS**

D11.3.1 The cellular therapy product distribution records shall permit tracking and tracing of the cellular therapy product and shall contain the following information at a minimum:

D11.3.1.1 The proper product name and identifier.

D11.3.1.2 Unique identifier of the intended recipient.

D11.3.1.3 Documentation of allogeneic donor eligibility determination, as appropriate.

D11.3.1.4 Identification of the facilities that requested and distributed the product.

D11.3.1.5 Identity of the receiving facility.

D11.3.1.6 Date and time the cellular therapy product was distributed.

D11.3.1.7 Date and time the cellular therapy product was received.

D11.3.1.8 Identity of the transporting or shipping facility.

D11.3.1.9 Identity of personnel responsible for cellular therapy product transportation or shipping and of personnel responsible for receiving the product.

D11.3.1.10 Identity of the courier.

D11.3.1.11 Documentation of any delay or problems incurred during transportation or shipping.

Explanation:

The distribution records must include, at a minimum, the distribution date and time, recipient name and identifier, product identifier(s), the proper product name(s) and any attributes of the product(s), the identity of the distribution facility, as well as documentation of allogeneic donor eligibility, if applicable. If the cellular therapy product is distributed for administration, the distribution records must also document receipt of the product by the medical staff responsible for administration, including the date and time of receipt. Clinical standards additionally require documentation in the recipient's medical record of the administered product unique identifier, initiation and completion times of administration, and any adverse events related to administration. This requirement may be met using a tracking document which contains all of the elements in the Standard. If the product is distributed to an external facility, the distribution records must include documentation of receipt by

a responsible individual at that facility. Documentation of receipt can be by signature or initials. The recipient information in the distribution records must match that on the product label.

Transport and shipping records must be complete to allow tracking and tracing of the cellular therapy product from one facility to another. Records must document the identity of all responsible personnel, including the courier, and any delays or problems occurring during product transit. Key steps in receipt, quarantine, release, and return must be traceable to the cellular therapy product, including responsible staff and date and time, where applicable.

Evidence:

The inspector should verify the presence of cellular therapy product distribution records in the Processing Facility files for each product that is released for distribution. The inspector should confirm that identification checks and product receipt are documented in the distribution records. An SOP should state that the facility should keep signed product distribution and administration records in the processing record.

The inspector should ask to review transportation and shipping records for cellular therapy products distributed between facilities for compliance with this section of the Standards.

D12: DISPOSAL

STANDARD:

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.

Explanation:

The control of the disposal of cellular therapy products must be clearly defined to protect both the recipient from inadvertent destruction of potentially life-saving products and the need of the Processing Facility storage unit to operate efficiently. Written SOPs are required that detail the conditions under which product disposal may occur and the process to be followed for the disposal of products. The limits for storage and reasons for disposal must be defined prior to the collection of the product and be contained in the consent for the collection of products.

In the case of autologous or related donations, donors, recipients, and associated clinical programs should be informed of the conditions of storage and storage duration, preferably before product collection.

When a cellular therapy product is received by the Processing Facility from an external manufacturer for recipient administration, there may be additional requirements beyond what exists for products manufactured in house. For example, a manufacturer may have a return policy instead of allowing the facility to dispose of a product. Any additional requirements for these products must be included as part of the pre-collection written agreement.

The most common reasons for disposal are the following:

- Death of the recipient: This must be documented by the storage facility following their policies and SOPs before the product can be discarded.
- No further need for the cellular therapy product: Under certain circumstances, the physician responsible for the recipient may determine there is no further need for the product. If the recipient is alive at the time, the recipient or legal guardian must be offered an opportunity to move the product to an alternative facility for storage. In the countries or areas where private storage is available, the possibility to move the product should be included in the informed consent. This situation has potential legal liability to the institution, and many institutions may decide to store products for the life of the intended recipient rather than expose themselves legally by disposing of potentially life-saving products.
- Discard to comply with written agreements with donor registries: Donor registries may have their own specific standards on product cryopreservation and disposal that will be agreed upon between the Processing/Storing Facility and the registry. The Processing/Storing Facility must adhere to these standards and to the FACT-JACIE Standards. The most stringent requirement is to be followed.

For medical and legal reasons, it is essential to document that the conditions for disposal have been met and that the current processing procedures are not in contradiction with consent forms signed at the time of collection.

Processing Facilities are not required to directly contact the recipient; however, they must require that the transplant physician obtain an agreement on the length of storage and circumstances for disposal of cellular therapy products.

Evidence:

The inspector should ask to review records of cellular therapy products that have been disposed and should be able to trace all steps of notification of product discard, method of destruction or transfer, and documentation of the action in the recipient's records.

Example(s):

FACT and JACIE strongly advise that SOPs for disposal and consents for collection be reviewed by the institution's legal advisors, since the ownership of cellular therapy products vary depending on whether the product is autologous or allogeneic and can also vary between nations, states, provinces, or other governmental units that regulate Processing Facilities.

STANDARD:

D12.1.2 The option, if in accordance with Applicable Law, to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.

Explanation:

If the recipient is alive after the agreed upon storage interval, the recipient or legal guardian must be offered an opportunity to move the product to an alternative facility for storage. Transfer of cellular therapy products should comply with Applicable Law.

STANDARD:

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.

Explanation:

The Processing Facility's institution should have a process for documentation of death that is entered into the recipient's medical record outside of the lab.

While not mandated, the clinical team can write a specific note stating that the recipient has died; however, documentation must be a primary piece of evidence and should not conflict with others.

Example(s):

Proof of death includes an autopsy report, a signed statement by the treating physician, or the Social Security Death Index in the U.S. The institutional registry or the governmental regional registries are also adequate sources. Secondary sources of information, such as newspaper articles, do not satisfy this requirement.

STANDARD:

D12.1.4 Approval by the Processing Facility Medical Director in consultation with the recipient's physician for cellular therapy product discard or other disposition and method of disposal.

Example(s):

If the Medical Director of the Processing Facility approves of cellular therapy product disposal, it is recommended that they consult with the recipient's physician, and the two parties are in agreement on the vital status of the patient, the disposition of the product, and method of disposal. This can be accomplished with an exchange of documents between the Processing Facility Medical Director

and the recipient's physician. Documented approval for disposal given to the Processing Facility by the recipient's physician is also acceptable.

STANDARD:

D12.1.5 A method of disposal and decontamination that meets Applicable Law for disposal of biohazardous materials or medical waste.

Explanation:

Cellular therapy products derived from human tissue are considered to be a potential biohazard, and adherence to universal precautions is required during the disposal process.

Evidence:

The applicant must present evidence to the inspector that the Processing Facility is in compliance with standards of biohazard waste disposal.

Example(s):

Disposal can be by ultra-high temperature incineration, autoclaving, or decontamination with freshly prepared hypochlorite solution followed by, if permitted by local law, discard in a landfill or other institutionally approved method.

STANDARD:

D12.2 Processing Facilities, in consultation with the Clinical Program, shall establish policies or Standard Operating Procedures for the duration and conditions of storage and indications for disposal.

D12.2.1 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.

Explanation:

Two problems faced by older cellular therapy programs are the disposition of cellular therapy products collected when there was no pre-existing agreement describing conditions for product storage or disposal, and when recipients are lost for follow-up and their survival cannot be confirmed. Each institution must establish its own policy on discarding such products. The definition of a good faith effort to contact the recipient or family likewise is a decision left to the individual center. The rights of the donor should be protected according to local laws and the standards of donor registries.

STANDARD:

D12.3 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.

D13: RECORDS

STANDARD:

D13.1 There shall be a records management system for cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

Explanation:

A record is defined as documented evidence that activities have been performed or results have been achieved. A record does not exist until the activity has been performed. Each Processing Facility has the flexibility to develop an individualized system of organizing and maintaining records as long as certain objectives are achieved. The record keeping system must be documented and should include at a minimum:

- Location of new and completed forms.
- Method of error correction that prevents obscuring the original entry and indicates the identity and date of the individual modifying the record.
- Method to prevent destruction or loss of the record.
- Method of documenting modifications and distribution.
- Time of retention and proper storage location.
- System to secure confidentiality of records.
- Methods for filing and transfer of records to archival storage.

Each Processing Facility has the flexibility to develop individualized systems of maintaining and organizing records as long as the objectives of the Standards are achieved. The methods for filing and transferring records to archival storage should be specified in the Quality Manual.

STANDARD:

D13.1.1 A records management system shall be established and maintained to facilitate the review of records.

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.

STANDARD:

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.

Explanation:

The intent of this Standard is to track the identity of the product to the final recipient. The Processing Facility must inform the receiving institution of the identifiers necessary to complete the tracking.

STANDARD:

D13.1.4 Records shall be maintained to ensure their integrity, preservation, and retrieval.

Explanation:

Records may be maintained in more than one location, provided that the records management system is designed to safeguard prompt identification, location, and retrieval of all records. The methods for filing and transfer of records to archival storage should be specified in a policy or in the SOP manual.

Evidence:

Records related to products processed in the Processing Facility under IRB-approved research protocols should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information.

Example(s):

It is recommended that recent records be kept on-site and archived records are readily accessible within a reasonable time frame.

Records may be maintained as original paper records, electronic files, photocopies, digital images, or on microfiche or microfilm. Electronic records must be backed up on a regular basis and stored to prevent their loss when records are maintained in common electronic portable formats. Examples of common formats include but are not limited to portable document format (PDF), extensible markup language (XML), or standard generalized markup language.

STANDARD:

D13.1.5 Records shall be accurate and legible.

D13.1.6 Written records shall be indelible.

STANDARD:

D13.1.7 Safeguards to secure the confidentiality of all records and communications among the clinical, collection, and processing staff and with donors and recipients shall be established and followed in compliance with Applicable Law.

Example(s):

Breaches in policy that might compromise confidentiality include the following:

- Unsecured patient records.
- Patient charts left unattended in areas where unauthorized personnel or visitors may have access or unattended computer screens displaying patient information in such areas.
- Patient charts or records, in hard copy or electronic format, involuntarily displayed during video conference or video calls.
- Indiscriminate discussions using patient-specific identifiers in the presence of unauthorized personnel or visitors.
- Patient information posted on chalk or bulletin boards that is potentially visible to unauthorized personnel or visitors.
- Release of confidential information without appropriate consent and approval.

Confidential storage may consist of maintaining the records in a locked room with access restricted to authorized personnel or the use of locked file cabinets. The Processing Facility must have SOPs describing the maintenance of donor and recipient confidentiality.

STANDARD:

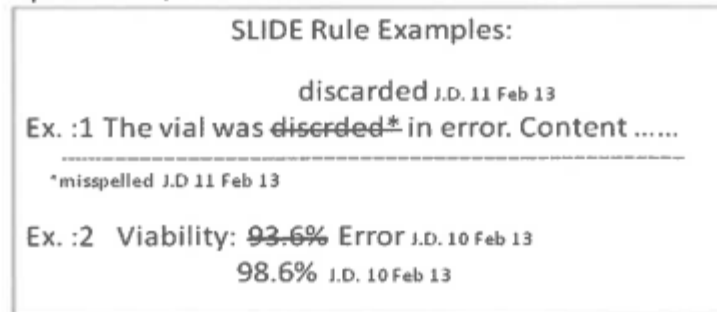
D13.2 The Processing Facility shall define and follow good documentation practices.

Explanation:

Good documentation practices are the guidelines that ensure records are created and maintained in a consistent manner, legible, indelible, accurate, and allow traceability to the person, date, and if applicable, time, of each event and entry. Good documentation practices should be used for all controlled documents and facility records, including forms, worksheets, training records, calibration logs, and cleaning logs. Examples of good documentation practices include:

- Data entry must be clear and legible.
- Use indelible blue or black ink. Avoid gel pens, felt tip pens, or pencils.
- Make record entries at the time the task was performed (concurrently).
- Do not use ditto marks or continuation lines to include several data entry fields.

- Do not use correction fluid, correction tape, or overlay of labels.
- Use the example below as a method to correct errors:
 - **Single Line** – Draw a single line through the error. The cross-out must permit the reading of the original information.
 - **Initial and Date** – Add initial of person making correction and date of correction.
 - **Errors** – Explain errors, if reason is not obvious.



Each facility should have an SOP that describes the details of the expected practices. Facility-specific SOPs may include such issues as a standardized format for date and time, expectations for attaching a label or printout to records, or other details.

STANDARD:

D13.3 RECORDS TO BE MAINTAINED

D13.3.1 Processing Facility records related to quality control, investigational protocols, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years after the creation of the cellular therapy product record, date of the cellular therapy product's distribution, disposition, or expiration, whichever is latest, or according to Applicable Law.

Explanation:

Because QM documents provide evidence of compliance with the QM requirements, they should be maintained for as long as they are applicable to the processes, equipment, supplies, and reagents currently being used. Archived records do not need to be immediately available.

Evidence:

Processing Facilities must identify Applicable Law, and applicable regulatory authorities, in pre-inspection documentation for FACT or JACIE inspectors to reference when preparing for the inspection.

The inspector should review the Processing Facility's records related to QM, including documentation of periodic personnel training and cellular therapy product characteristics, and

inspect the QM documents to confirm compliance with the facility's requirements. Likewise, the inspector should examine paperwork to determine if adequate records are maintained that identify the processes, equipment, supplies, and reagents currently being used for all significant steps of processing.

STANDARD:

D13.3.2 Records of validation studies for a processing procedure shall be retained at a minimum until the procedure is no longer in use and no products remain in storage that were processed using that procedure.

Explanation:

The validation study for a current processing procedure needs to be maintained as long as the procedure is still being utilized in order to demonstrate compliance with validation requirements.

STANDARD:

D13.3.3 Employee records shall be maintained in a confidential manner, as required by Applicable Law.

D13.3.4 Cleaning and sanitation records shall be retained for at least three (3) years or longer in accordance with Applicable Law or by a defined program or institution policy.

Explanation:

An exception to the 10-year requirement for retention of Processing Facility records is for the documentation of cleaning and sanitation. These records only need to be retained for at least three years after creation but should include cleaning schedules, methods, and identification of personnel responsible for cleaning. There should also be documentation for the initial training and retraining of personnel as needed.

Evidence:

If documentation of cleaning and sanitation is performed directly by the Processing Facility's institutional environmental services department, then the Clinical Program should have knowledge of this documentation and the ability to show that it is complete.

STANDARD:

D13.3.5 Records to allow tracking and tracing of cellular therapy products shall be maintained in a confidential manner for a minimum of ten (10) years after administration, distribution, disposition, or expiration of the cellular therapy product, or as required by Applicable Law, whichever is latest.

Explanation:

Records related to cellular therapy products should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for collection is critical for tracing purposes in the event of a problem, recall, or adverse event.

Evidence:

The inspector should ask who is responsible for records and where these records are maintained and determine if an organized system is in place that allows timely retrieval.

Example(s):

In the U.S., NMDP requires that records pertaining to the traceability and tracking of all aspects of the manufacture of the products managed by them to be retained indefinitely, as should records of adverse reactions and post-donation complications, treatment interventions, and recovery.

Per the EU [Directive 2004/23/EC](#), tissue establishments must keep the data necessary to ensure traceability at all stages. Data required for full traceability must be kept for a minimum of 30 years after clinical use.

STANDARD:

D13.3.5.1 These records shall include the identities of the Collection and Processing Facilities, unique numeric or alphanumeric identifier, collection date and time, product code, and donor and recipient identification as found on the original container.

Explanation:

In order for the records to allow tracking and tracing of cellular therapy products, it is required that the Collection Facility will keep all the required elements in the standard as part of the record.

STANDARD:

D13.3.6 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, ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, or the creation of the cellular therapy product record, whichever is most recent, or according to Applicable Law or institutional policy, whichever is latest.

Explanation:

The Standards in this section detail which records must be maintained and the minimum time period of retention. Where institutional or governmental policies differ, the longer retention period must be observed. Records must be retrievable within a reasonable time frame but need not be immediately available in the Processing Facility.

Records that are to be maintained for at least ten years after their creation include:

- QM records: validation and qualification studies; equipment maintenance reports; the results of audits; errors, accidents and adverse reactions reports; and outcome analysis. Because QM documents provide evidence of compliance with the QM requirements, they should be maintained for as long as they are applicable to the processes, equipment, supplies, and reagents currently being used. For example, the validation study for a current processing procedure needs to be maintained regardless of how long ago the study was performed in order to demonstrate compliance with validation requirements.
- Investigational protocols: reference vials for genetically modified cellular therapy products must be retained throughout the duration of required follow-up. Some protocols may have longer retention requirements.
- Personnel training and competency records: job qualification records; records of orientation; initial training; safety training for biological, chemical and radiation exposure or disposal; continuing education; and annual competency assessments.
- Processing Facility maintenance management and general facility issues: dates and extent of renovations and new construction; dates and extent of repairs on mechanical systems; preventive maintenance on equipment; agreements or contracts with any entity served by the facility; sterilization records; disposition of supplies and reagents; and the outcome of any building and/or facility inspections for safety and/or compliance with governmental and/or other agencies.
- Processing Facility management records should include a list of responsible individuals with job titles and areas of oversight and resolution of facility problems.

General Processing Facility records may include global policies for the institution of which the facility is a part. Examples include:

- Disaster plans.
- Fire response and safety.
- Biological, chemical and radiation disposal policies.
- Confidentiality and data protection requirements.

Evidence:

The inspector should look for evidence of 10-year retention of representative records, including some older and some more recent documents. Each Processing Facility should maintain a comprehensive list of all relevant faculty and support staff associated with that facility for the immediate previous 10-year period. The inspector may ask to review the personnel list and then ask to see dated training or competency records for a specific individual. Likewise, the inspector may ask to see the original records of validation of the controlled rate freezers, shipping containers, or cryopreservation technique, assuming the facility is less than ten years old.

The inspector should take into account during the inspection that the Processing Facility is only responsible for compliance from the time of its initial FACT or JACIE accreditation. Some Processing Facilities have not been accredited by FACT or JACIE for a full ten years. In these cases, the facilities are only held responsible for retaining records for as long as they have been accredited and required to comply with the Standards.

Example(s):

Cellular therapy products processed years ago for a recipient may have a complex history. It might be possible that some of the products could not be released because of out-of-specification parameters, some were administered, some are still stored, or some might have been discarded because they were no longer needed for the recipient.

NMDP requires that records from unrelated donor eligibility determination and HPC, Apheresis product records pertaining to collection, processing, labeling, packaging, storage, distribution and final disposition be maintained indefinitely. NMDP further requires indefinite retention of records pertaining to the traceability and tracking of all aspects of the manufacture of the HPC product, along with records of adverse reactions and post-donation complications, treatment interventions, and recovery.

STANDARD:

D13.3.7 Research records shall be maintained in a confidential manner as required by Applicable Law or for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

Explanation:

Records related to cellular therapy products processed under IRB-approved research protocols should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. If research records are stored independently of patient records, the same considerations regarding confidentiality apply. The sponsor of the research, IRB, and governmental authorities may place specific requirements for long-term maintenance of research records.

Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for processing is critical for tracing purposes in the event of a problem, recall, or adverse event.

Evidence:

The inspector should ask who is responsible for records and where these records are maintained and determine if an organized system is in place that allows timely retrieval of research records.

STANDARD:

D13.4 ELECTRONIC RECORDS

D13.4.1 The Processing Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures. For all critical electronic record systems:

Explanation:

The definition of an electronic record is, "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." This Standard requires Processing Facilities to establish and maintain a current listing of all critical electronic record systems specific to cell processing. As facilities utilize more electronic systems, it is important that they maintain a list of which ones are critical.

Electronic record systems are considered critical when they are used in any of the following manners:

- As a substitute for paper.
- To make decisions based upon the data stored or created by the electronic record system (including outcome analysis).
- To make calculations via automated functions.
- To create or store pieces of information that are inputs into critical processes (whether the electronic record system is used during critical processes or used as source data for critical procedures).

Critical procedures include processing techniques, cryopreservation procedures, labeling, storage conditions, and distribution.

It is not the intent of the Standards to include hospital-based systems and clinical medical records. These systems are typically inspected by hospital-based regulatory and accrediting organizations. Furthermore, Processing Facilities may not have the authority to direct validation studies on these systems.

Evidence:

Inspectors should assess the Processing Facility's list of critical electronic record systems to confirm it includes all electronic record systems used by the facility that meet the criteria in this Standard.

Example(s):

Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

When computers are used to generate paper printouts of electronic records, and the printouts are the "official" records used for the performance of further activities, the electronic records are not considered to be used as a substitute for paper records. For example, an electronic record of the location of a cellular therapy product in liquid nitrogen storage is printed for the processing chart, and the information is verified by a signature or initials. This printed record is then used by personnel to retrieve the product at the time of administration. The electronic record is not considered to have been used in lieu of a paper record and may not be critical based on that criterion. If, however, the electronic system performed one or more calculations on the entered data prior to making the final printout, then the system is critical, and the Standards in this section would apply. Similarly, if the electronic system formats data that is entered into a specific format for printing for retention, then that data is also processed, and validation that the data is being correctly reproduced is necessary.

If a computerized system is used to generate SOPs, validation is not required since the quality and safety of a cellular therapy product would not be directly affected. However, if a computerized system is used to make a critical calculation (e.g., T cell dose, DMSO concentration, CD34 cell

recovery) and the electronic calculation is the only calculation performed, validation is required to assure that the calculation is always performed correctly under any circumstances. However, if the computerized calculation is used to confirm a manual calculation, and the manual calculation is used for manufacturing purposes, the extent of validation need not be as extensive as in the previous example.

In the U.S., for electronic records used as a substitute for paper, the inspector should refer to the FDA document [Part 11, Electronic Records; Electronic Signatures - Scope and Application](#) (2003), for guidance to assess the validation procedures, as well as the applicable requirements of HIPAA. In the EU, the inspector should refer to the Modular Requirements for Electronic Records and Document Management ([MoReq](#)).

STANDARD:

D13.4.1.1 There shall be policies, Standard Operating Procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

D13.4.1.2 There shall be a means by which access is limited to authorized individuals.

D13.4.1.3 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

Explanation:

In case of error or ambiguity, a method must exist to allow traceability of data entered into the electronic record system to the staff member who performed the entry. This may take the form of an audit trail maintained internally by software, or it may take the simple form of a login sheet on which staff members record their session with the electronic record system and identify what data was entered in that session.

Example(s):

To identify individuals responsible for record entries, several options exist. Examples include using a sign-in sheet when using the system or using a worksheet to create an audit trail of each data element. More sophisticated systems usually have an automated system that tracks record entry based upon an individual's login credentials.

STANDARD:

D13.4.1.4 There shall be written policies and Standard Operating Procedures for record entry, verification, and revision.

D13.4.1.5 A method shall be established or the system shall provide for review of data before final acceptance.

Explanation:

The final review and acceptance of entered data do not require a second individual to verify the data. Nor does the identification of individuals responsible for record entries need to be automated. The intent of the Standard is to be certain that all data is verified to be correct and to maintain documentation of who has entered pieces of information.

STANDARD:

D13.4.1.6 There shall be documented training of personnel in the system's use.

D13.4.1.7 There shall be a defined process for continued competency of personnel in the system's use.

Explanation:

Personnel must be trained to appropriately use all critical electronic record systems (including record entry, verification, and revision) and backup processes when the critical systems are not available. This training must be continuous, including initial training and ongoing training as SOPs are revised and issues with the use of critical electronic record systems are identified.

As with all other cellular therapy processing activities, the staff members who utilize the electronic record system must be trained for such use. Moreover, just as SOPs are required for cell processing, SOPs must also be in place to describe how to enter, process, and retrieve data using the electronic record system. Competency of staff using the system must be documented on a regular basis (annually at a minimum) and must also be documented with changing versions of the systems in use.

STANDARD:

D13.4.1.8 There shall be a defined process for the use of electronic signatures.

Explanation:

The term "electronic signature" shall be clearly and precisely defined. The definition shall specify what constitutes a valid electronic signature and delineate how the electronic signature will be used and interpreted. The policy defining electronic signature shall include the following elements: the method of creating the signature (e.g., typing a name, using a mouse to draw, clicking an "accept" button), the elements included (e.g., first and last name, role/title, time and date stamp), a statement

that the electronic signature is legally binding, and the type of records to which the signature applies (e.g., manufacturing batch records, regulatory documents, audits, validations review, contracts and agreements). The method of creating a signature and the intended use may vary among Processing Facilities.

The Processing Facility needs to define when, under what conditions, and for which programs it is appropriate to utilize electronic signatures.

STANDARD:

D13.4.1.9 Unique identifiers shall be maintained.

D13.4.1.10 There shall be the ability to generate true copies of records in both human readable and electronic format suitable for inspection and review.

D13.4.1.11 There shall be protection of records to enable their accurate and ready retrieval throughout the period of record retention.

D13.4.1.12 All system modifications shall be authorized, documented, and validated prior to implementation.

D13.4.2 For all critical electronic record systems under the control of the Processing Facility, there shall be processes for and documentation of.

Explanation:

Establishment of an electronic record keeping system that meets one or more of the criteria for a critical electronic record system requires validation. The extent of validation is somewhat dependent upon whether the computerized system was developed in-house, custom-built by an outside vendor or consultant, or developed from off-the-shelf software.

Validation procedures of critical electronic systems include, as appropriate, such elements as:

- Documentation of development requirements and function.
- Verification that calculations are performed correctly.
- Evidence that records reproducibly contain the desired information.
- Tests of system functions under "worst case" scenarios such as system overloads (e.g., too many simultaneous users, too many simultaneous processes being performed [such as too many programs open on a Windows desktop]), and power failures.
- A method for data verification before final entry.
- Internal consistency checks to verify that values are within defined ranges.
- Restricted entry of data to match predefined value limits.
- Required entry of data with field information limited with choices for data consistency.

- Source data is derived from pre-defined sources such as fixed forms. "Monitoring for data integrity" means establishing assurances that data has not been changed either by accident or by intent, and this requires access to original documents whenever possible, along with a plan for verification of the electronic system data by comparison to original data.
- Evidence of a schedule of regular backups that include storage of backup data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the backup copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include the information entered into the database, acceptable sources of the entered data, and a description of system maintenance and development history.
- Formal and documented training in system use requirements for all personnel.
- Evidence of SOPs in place for computer record-keeping systems.
- Regular quality audit trails.
- A mechanism to report deviations and to ensure that problems are reported and resolved.
- Evidence that changes to records do not obscure previously entered information.
- Documentation that deleted electronic files have been converted to non-electronic media such as microfilm, microfiche, or paper in a manner that preserves the content and meaning of the record.

Evidence:

While details of the validation system may be located in an institutional department of information services or elsewhere, the Processing Facility shall have a summary of the validation available to the inspector.

If electronic records are used in addition to paper records, the inspector should evaluate the electronic record system to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.
- The system has access limited to authorized individuals and that documentation is generated to identify which individuals have accessed the system and made record entries.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.

- Documentation that the individuals performing the development, maintenance or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- Procedures are in place to provide for record keeping in the event of failure of the electronic record system, and that the staff members who may have to follow these procedures are trained in their use.
- A process for generating backups of records maintained electronically is in place.

STANDARD:

D13.4.2.1 Prospective validation of systems, including hardware, software, and databases.

D13.4.2.2 Installation of the system.

D13.4.2.3 Numerical designation of system versions, if applicable.

D13.4.2.4 Authorization and validation of all system modifications prior to implementation.

D13.4.2.5 Systems development including the verification of calculations and algorithms.

D13.4.2.6 System maintenance and operations.

D13.4.2.7 Monitoring of data integrity.

D13.4.2.8 Backup of the electronic records system on a regular schedule.

D13.4.3 For each critical electronic record system, there shall be an alternative system to allow for continuous operation of the Processing Facility if the critical electronic record system is not available. The alternative system shall be validated, and processing staff shall be trained in its use.

STANDARD:**D13.5 RECORDS IN CASE OF DIVIDED RESPONSIBILITY**

D13.5.1 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.

Explanation:

Most, but not all, Processing Facilities will have some of the activities or services covered by the Standards performed by another entity in the same institution or in another institution. In such cases, the conditions under which the activity or service is performed must be documented through written agreements. When the facilities are within the same institution, the responsibilities may be written in a policy or other type of document.

These agreements should clearly define roles and responsibilities for critical tasks. All such agreements should be dated, reviewed and renewed on a regular basis, and include provision for the maintenance of records following termination of the agreement. How such agreements are executed is a function of the type of Processing Facility.

The agreements must clearly define the role and responsibility of the contracted facility to comply with all governmental regulations and Standards that are applicable to the performed services. The contracted facility must also adhere to critical processing, storage, and distribution standards defined by the contracting facility, although the contracted facility does not have to be accredited by FACT or JACIE. The contracting facility must have implemented a process to verify that regulated services are performed in compliance with all applicable Standards and regulations.

The Processing Facility's records should include relevant contracts and agreements, and the Processing Facility is responsible for compliance with the Standards. The entire record of the outside facility(ies) need not be duplicated for the facility record. However, the facility record should allow tracing and tracking of relevant information to the correct source. For example, the facility may manufacture products for multiple clinical programs.

The facility record should indicate where the product was collected, stored, and/or administered but does not need to contain a record of the supply and reagent lot numbers used for steps performed at the Collection Facility or Clinical Program. The facility should verify that such relevant and appropriate records will be maintained by the facility that performs the work. Records of allogeneic donor eligibility screening and testing must be provided to the facility.

Maintenance of records must be specified in the SOPs, and it must be clear who is responsible for maintaining records. In general, records should be sufficiently detailed to enable tracking and tracing from a donor to a recipient or final disposition and vice versa.

Donor and recipient confidentiality must be maintained through the use of identifiers whenever the identity of the unrelated donor must remain anonymous. The location of each facility must be known to the relevant personnel at each facility but should not be known to the recipient. To that end, the Processing Facility may not know the identification or location of the Collection Facility in the case of a product obtained through an unrelated donor registry. Facilities that participate in programs such as NMDP or other donor registries will have well-defined procedures for divided responsibility. Applicable rules and regulations regarding the sharing of confidential information must be followed.

QM Plans must include the concept of written agreements even if no agreements are currently in place at the Processing Facility. The purpose is to outline the general process for establishing agreements should the need arise. Extensive detail is not required, but the plan must minimally describe who is responsible for reviewing and approving agreements and require that agreements include the external facility's responsibility to comply with the Standards in their activities relating to the Processing Facility.

In the event the Processing Facility (or entities with which the facility has agreements) terminates its activities, it is essential that traceability data and material concerning the quality and safety of the cellular therapy products be provided to the relevant parties.

Evidence:

The inspector should review the process for establishing agreements or contracts with entities outside of the Processing Facility that participate in product collection, testing, storage, transport or other critical services that might affect the quality of the product. In the case of donor registries, they should be accredited by the WMDA. If agreements exist, examples should be reviewed by the inspector for adherence to the facility's established process. In all cases, a process must exist for the development and implementation of such agreements. The inspector should verify that there is a process in place to assess compliance with the requirements and that this process is effective. Copies of those agreements should be available to the inspector on the day of the inspection.

Example(s):

Written agreements should be reviewed every two years, similar to SOPs, although a greater or lesser time interval may be appropriate under some conditions. The effective dates of an agreement could be specified within the agreement itself. It would be helpful to have a list of written agreements to inventory whether each one is reviewed and renewed appropriately.

For services provided with the same institutions, shared policies or procedures that address expectations and performance quality can be interpreted as agreements. For Processing Facilities receiving products facilitated through donor registries, agreements may be through those registries.

Such agreements may include, but are not limited to donor qualification, determination of donor suitability and eligibility (allogeneic donors only), collection of the product, donor or product testing, and long-term storage.

Stand-alone facilities may execute agreements directly with the service providers (or institutions for which they provide services), whereas agreements involving Processing Facilities in academic institutions may be between the institution and the service provider.

Audits of external facilities may be accomplished by reviewing the Processing Facility's internal and external audit reports, performing on-site inspections for compliance, receiving period performance reports from the facility, or the Processing Facility can audit its experience with the contracted facility using data that it defines and collects. There may be other alternatives, but the contracting facility must verify that their contracted services are meeting requirements.

STANDARD:

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

Explanation:

The Processing Facility shall have an applicable SOP that describes the dissemination to other Collection Facilities or Clinical Programs of summary records that concern safety, purity, and potency of the cellular therapy product.

Evidence:

The inspector should determine if divided responsibility occurs regarding any aspect of the cellular therapy process and ask to review a relevant recipient file to confirm that an appropriate mechanism is in place to track the process from beginning to end and trace the process from the end to the beginning.

Example(s):

The processing and the storage of a cellular therapy product might be located in different departments of the same institution or different institutions. There should be a written policy or agreement between both departments or institutions that clearly defines the responsibilities and the documents to be handed over between both departments or institutions. It must be possible to identify these responsibilities when reviewing the documents.

STANDARD:

D13.5.3 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.

Explanation:

The entire record of the outside facility(ies) need not be duplicated for the facility record. However, the facility record should allow tracing and tracking of relevant information to the correct source. For example, the facility may manufacture products for multiple clinical programs.

APPENDIX I

MINIMUM NUMBER OF NEW PATIENTS FOR ACCREDITATION

Clinical Programs shall transplant at least the following number of new patients¹ before initial accreditation and annually thereafter:

Patient Population	Clinical Site(s)	Type of Cellular Therapy	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
		IEC	• Within a transplant program: 3	• Within a transplant program: 3
	Multiple Clinical Sites	Autologous only	• 5 autologous recipients at each site	• 5 autologous recipients at each site
		Allogeneic and Autologous	• 10 allogeneic recipients at each applicable site ² • 5 autologous at each applicable site ²	• 10 allogeneic recipients at each applicable site ² • 5 autologous at applicable each applicable site ²
		IEC	• Within a transplant program: 3 at each applicable site	• Within a transplant program: 3 at each applicable site
Combined Adult AND Pediatric	Single Clinical Site	Autologous only	• 5 adult autologous • 5 pediatric autologous recipients	• 5 adult autologous • 5 pediatric autologous recipients
		Allogeneic and Autologous	• 5 adult allogeneic recipients • 5 pediatric allogeneic recipients	• 5 adult allogeneic recipients • 5 pediatric allogeneic recipients
		IEC	• Within a transplant program: 6 patients total; at least one in each applicable population	• Within a transplant program: 3 pediatric and 3 adults
	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 and 5 pediatric allogeneic • 5 adult autologous at each applicable site ² • 5 pediatric autologous at each applicable site ²	• 5 adult allogeneic recipients at each site • 5 pediatric allogeneic recipients at each site • 5 adult autologous at each applicable site ² • 5 pediatric autologous at each applicable site ²
		IEC	• Within a transplant program: 3 pediatric and 3 adults at each applicable clinical site	• Within a transplant program: 3 pediatric and 3 adults at each applicable clinical site

¹The term “new allogeneic patient” or “new autologous patient” includes only a patient who received their first transplant of that type during the period of time in question.

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

Explanation:

For a Clinical Program to demonstrate continued proficiency, a minimum number of patients must be treated in the 12-month period preceding accreditation and annually thereafter (the number of patients between inspections is submitted to FACT and JACIE in the interim/annual report). If the Clinical Program is requesting accreditation for allogeneic or allogeneic and autologous transplant, at least ten new allogeneic patients must have been transplanted. The term “new allogeneic patient” or “new autologous patient” includes a patient who will be receiving their first transplant of each type. Patients receiving second or subsequent transplants of the same type will only be counted towards a Clinical Program’s minimum number of patients if there has been at least one year between transplants. Cellular therapy in this table refers to both transplant and other types of cellular therapies such as IECs.

DLIs are considered part of the initial transplant because they generally follow a transplant when a recipient does not demonstrate tri-lineage engraftment (i.e., red cells, neutrophils, and platelets) when engraftment would have been expected. The recipient may experience a relapse after transplant or rejection of the cellular therapy product. When a recipient does not receive enough viable stem cells, the DLI provides more cells from the same donor into what is conceived of as an “empty marrow space” to achieve engraftment.

There is no minimum requirement for autologous transplant for centers performing allogeneic transplants, as it is felt that proficiency in allogeneic transplant is a sufficient criterion for performing autologous transplant. If one site of a program that performs allogeneic and autologous transplants performs autologous transplants alone, it must meet the criteria of a minimum average of five autologous transplants per year.

The age definition for a pediatric patient varies in different countries, but there would be general consensus that a child aged 12 or younger should be treated in a pediatric unit. A combined pediatric and adult Clinical Program should have a policy on how they distribute adolescents and young adults between the two components of the Clinical Program.

Evidence:

The inspector will review the number of transplants in the previous year (initial accreditation) or the yearly average throughout the accreditation cycle (renewal accreditation) and may also ask how patients are allocated to each site if warranted.

Example(s):

The following examples illustrate the criteria used to determine if a given recipient would be considered to be a “new patient:”

- A patient who received two autologous transplants two months apart would count as one new autologous patient.

- A patient who received an autologous transplant and subsequently received an allogeneic transplant four months later would count as one new autologous patient and one new allogeneic patient.
- A patient receiving an allogeneic transplant who failed to engraft and received a second allogeneic transplant two months later would count as one new allogeneic patient.
- A patient who received an allogeneic transplant then relapse and received a second allogeneic transplant from the same or a different donor 18 months later would count as one new allogeneic patient in each year.
- A patient who received an autologous transplant for myeloma with a good response who subsequently progressed and received a second transplant five years later would count as a new autologous transplant on each occasion.
- A "boost" for an aplastic patient 35 days after initial transplant is considered part of the initial transplant (one transplant).

FACT and JACIE will use the average number of transplants over the accreditation cycle to determine if a Clinical Program meets the minimum transplant volume per year as described in this appendix.

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APPENDIX II

CELLULAR THERAPY PRODUCT LABELING

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

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

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

¹Container and full package labeling requirements for licensed products or products under IND application shall follow Applicable Law. In the U.S., see [21 CFR 312.6\(a\)](#).

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

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

⁴A partial label is a label used at the end of collection or at distribution for administration due to the limitations of the size of the product container or other constraints.

⁵Product proper names and attributes must also be identified in words and are listed in Chapter Three of the [ISBT 128 Standard Terminology for Medical Products of Human Origin](#). This includes all potential attributes, in addition to the core attributes referenced in this table (Anticoagulant, Volume, Storage Temperature): Intended Use, Manipulation, Cryoprotectant, Blood Component from 3rd Party Donor, Other Additives, Genetically Modified, Irradiation, Modification, Mobilization, Pooled Single Donor, Cultured, Enrichment, Reduction, Fluid Source Location.

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

Explanation:

Full implementation of ISBT 128 or Eurocode is required, and this table reflects the requirements of those systems. In addition to the correct labeling content, the labeling elements must be in the appropriate quadrants of the label when using ISBT 128. Eurocode is a coding system and does not have specific labeling requirements; therefore, users of Eurocode must still comply with this table to meet the intent of consistent labeling practices to facilitate product identification and information exchange. Chapter Three of the ISBT 128 document [*Standard Terminology for Medical Products of Human Origin*](#) is useful and review is strongly encouraged.

At the time of completion of collection, completion of processing, and distribution for administration, three pieces of information must be affixed per ISBT 128 requirements: the unique numeric or alphanumeric identifier (i.e., ISBT 128 DIN), the proper name of the product (referred to by ISBT 128 as the class name), and the product code (which reflects to proper product name and product attributes).

When ISBT 128 is fully implemented, all data elements on the table should be affixed to the cellular therapy product. However, there may be times when the product container used at the time of distribution for administration is too small to fit all of the information. The label elements in the column titled, "Partial label at distribution for administration," is the absolute minimum information that must be included at the time of administration, and the column titled, "Label at distribution for administration," is the minimum required when the container is a size large enough to include all of the elements. Products thawed at the bedside do not require a new label unless repackaged into a new container.

An in-process label may be used within each facility during the time of collection or processing. At a minimum, this label must include the proper name of the product and the unique numeric or alphanumeric identifier. A partial label is not acceptable at the time of distribution from collection to processing. All of the elements listed in the column titled, "Label at completion of collection," must be included.

The differences between the columns, "Label at completion of processing," and "Label at distribution for administration," are mostly in consideration of non-cryopreserved cellular therapy products. When a product will be cryopreserved, it is prudent to affix all information as required at distribution for administration.

Product attributes can be displayed in two formats in the ISBT 128 labeling system: as part of the product code and spelled out in words. FACT and JACIE require that attributes be communicated on the label in both formats (i.e., inclusion of attributes via only the alphanumeric product code is insufficient). If a cellular therapy product is thawed at the bedside, relabeling to include the attribute "thawed" is not required unless the product is repackaged into a new container.

APPENDIX III

A: 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 ¹ 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 C7.4 , D7.4)	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

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

B: CELLULAR THERAPY PRODUCT LABELS FOR INTERNAL TRANSPORT

Each container for internal transport shall be labeled with at least the elements detailed in the following table:

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

AF=Affix

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APPENDIX IV

ACCOMPANYING DOCUMENTATION

Products collected in or designated for use in the U.S. shall be accompanied upon leaving the control of the Collection or Processing Facility with at least the elements detailed in the following table¹:

Documentation	Allogeneic Donor-Eligible	Allogeneic Donor-Ineligible ²	Allogeneic Donor-Incomplete ²
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 ³	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 ⁴	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 administered 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 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 ¹	X	X	X
Instructions for reporting serious adverse reactions or events to the distributing facility ^{1,5}	X	X	X

¹For 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. Autologous donor eligibility determination is not required by the U.S. FDA; however, if any donor screening or testing is performed and risk factors or reactive test results are identified, accompanying documentation shall be provided.

²May 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.

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

⁴This includes laboratories certified to perform such testing on human specimens under CLIA (1988) or those laboratories that have met equivalent requirements as determined by CMS, or those that have met equivalent non-U.S. requirements. If communicable disease testing is not performed by a laboratory that meets regulatory requirements, the donor is ineligible. If a donor is ineligible for other reasons, but the testing was performed in a compliant laboratory, this statement must be included in the documentation.

⁵Access to the Clinical Program Standard Operating Procedures and forms could suffice when the distributing and clinical facilities are within the same institution.

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APPENDIX V**MINIMUM NUMBER OF CELLULAR THERAPY PRODUCT COLLECTIONS**

Number of procedures	Apheresis	Marrow	Other Tissues
Performed in the twelve-month period immediately preceding initial accreditation	10	1	1
Minimum average performed per year within each accreditation cycle	10	1	1

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APPENDIX VI

NINTH EDITION – VERSION HISTORY

The table below outlines changes made to the ninth edition of the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration Accreditation Manual*, from its initial publication to its current version.

Version Number	Publication Date	Description of Change	Effective Date	Archival Date
9 th Edition	10/28/2025	Initial publication.	2/2/2026	12/17/2025
9.1	12/17/2025	B2.11/C2.10: Removed inapplicable guidance from Explanation.	2/2/2026	N/A
		B/C/D4.11.4.1: Added “to” before “other facilities...” for readability.		
		B4.15.2.7/D4.14.4: Corrected Standard text (“Director” missing from end).		
		B7.11: Reinstated guidance from eighth edition HCT Accreditation Manual, updated references to be inclusive of other cellular therapies.		
		B7.11.3.7: Removed duplicative guidance.		
		B10.3.3: Removed “by the Clinical Program” to harmonize with Part D and clarify intent of Standard.		
		C1.5: Edited guidance to clarify Evidence the Collection Facility can provide to demonstrate compliance with the Standard.		
		C4.8.5.1: Rearranged Standard for greater accuracy.		
		C4.8.5.2: Reworded Standard, added “daily,” and linked to activity being audited to clarify intent, updated guidance accordingly.		
		C4.8.5.5/D4.8.5.3: Updated guidance with link to the activity being audited.		
		C4.10.1: Added “Processing Facility” to harmonize with the third edition IEC Standards.		
		C11.11/D10.11: Edited to reference applicable section in the Standards.		
		C12.3.3: Removed “by the Collection Facility” to harmonize with Part D and clarify intent of Standard.		
		D6.1: Added “or store” to clarify intent of Standard.		
		D7.4.4: Standard was omitted in error, added to harmonize with the third edition IEC Standards.		
		Crosswalk: Updated to reflect renumbered and/or reorganized Standards.		

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CROSSWALK

The crosswalk below details the relationship between Hematopoietic Cellular Therapy Standards from the eighth edition to the ninth edition. Standards from the eighth edition (lefthand column) are listed chronologically to preserve their structure and order as published. The ninth edition Standards (righthand column) are paired with the corresponding eighth edition Standards, and as a result many of these do **not** appear in chronological order. The Collection section has an additional (middle) column representing the eighth edition Part CM: Marrow Collection Facility Standards. In the ninth edition, all Standards relating to the collection of cellular therapy products—whether by apheresis, bone marrow harvest, or other methods—were consolidated into a single, comprehensive Collection section.

The following key will assist with interpreting how revisions are represented:

1. A dash (–) represents that there is not a correlating Standard in the compared edition.

B2.16	B2.8
–	B2.9.1

2. **Bolded font** represents ninth edition Standards that have changed sections (e.g., **B10.1**), indicating that there was a significant move.

B4.5.3.8	B4.5.3.8
B4.5.3.9	B10.1

3. Ninth edition Standards that were consolidated but contain elements of or correspond to multiple eighth edition Standards are marked as *1 of 2*, *2 of 2*, etc. They are repeated for mapping purposes.

B10.6.4	B10.4.1.9 <i>1 of 2</i>
B10.6.5	B10.4.1.11

FACT-JACIE Hematopoietic Cellular Therapy Standards Crosswalk

Edition 8 to Edition 9

PART B: CLINICAL PROGRAM STANDARDS

8th Edition	9th Edition
B1	B1
B1.1	B1.1
B1.1.1	B1.1.1
B1.1.2	B1.1.2
–	B1.4
B1.2	B1.5
B1.2.1	B1.6
B1.2.1.1	B1.6.1
B1.2.1.2	B1.6.2
	B1.6.3
B1.2.1.3	B1.6.4
B1.2.1.4	B1.6.5
B1.2.1.5	B1.6.6
B1.2.1.6	B1.6.7
B1.3	B1.2
B1.3.1	B1.2.1
B1.4	B1.3
B1.5	B1.7
–	B1.8
–	B1.8.1
–	B1.9
B2	B2
B2.1	B2.1
B2.2	B2.2
B2.3	B2.3
B2.4	B2.5
B2.5	B2.10
B2.6	B2.4
B2.7	B2.11
B2.7.1	B2.11.1
B2.8	B2.15
B2.9	B2.12
B2.9.1	B2.12.1

8th Edition	9th Edition
B2.10	B2.13
B2.11	B2.14
–	B2.16
B2.12	B2.17
	B2.17.1
B2.13	B2.18
–	B2.18.1
B2.14	B2.6
B2.15	B2.7
B2.16	B2.8
–	B2.9.1
B2.17	B2.9.2
	B2.9.3
B3	B3
B3.1	B3.1
B3.1.1	B3.1.1
B3.1.2	B3.1.1.1
B3.1.3	B3.1.2
B3.1.4	B3.1.3
B3.1.5	B3.1.4
B3.1.5.1	B3.1.4.1
B3.1.6	B3.1.5
B3.1.6.1	
B3.2	B3.2
B3.2.1	B3.2.1
	B3.2.1.1
–	B3.2.1.2
B3.2.1.1	B3.2.2
B3.2.1.2	B3.2.3
B3.2.2	B3.2.4
B3.2.3	B3.2.5
B3.2.3.1	
B3.3	B3.3

8th Edition	9th Edition
B3.3.1	B3.3.1
B3.3.2	B3.3.2
B3.3.3	B3.3.3
B3.3.4	B3.3.4
B3.3.4.1	B3.3.4.1
–	B3.3.4.2
B3.3.4.2	B3.3.4.3
B3.3.4.3	B3.3.4.4
B3.3.4.4	B3.3.4.5
B3.3.4.5	B3.3.4.6
B3.3.4.6	B3.3.4.7
B3.3.4.7	B3.3.4.8
B3.3.4.8	B3.3.4.9
–	B3.3.4.10
B3.3.4.9	B3.3.4.11
B3.3.4.10	B3.3.4.12
B3.3.4.11	–
B3.3.4.12	B3.3.4.13
B3.3.4.13	B3.3.4.14
B3.3.4.14	B3.3.4.15
B3.3.4.15	B3.3.4.16
B3.3.4.16	B3.3.4.17
B3.3.4.17	B3.3.4.18
B3.3.4.18	B3.3.4.19
B3.3.4.19	B3.3.4.21
–	B3.3.4.22
B3.3.4.20	B3.3.4.24
B3.3.4.21	B3.3.4.25
B3.3.4.22	–
B3.3.4.23	B3.3.4.26
B3.3.4.24	B3.3.4.27
B3.3.4.25	B3.3.4.28
B3.3.4.26	B3.3.4.29

FACT-JACIE Hematopoietic Cellular Therapy Standards Crosswalk

Edition 8 to Edition 9

PART B: CLINICAL PROGRAM STANDARDS

8th Edition	9th Edition
B3.3.4.27	B3.3.4.20
B3.3.4.28	B3.3.4.30
	B3.3.4.23
B3.3.4.29	B3.3.4.31
B3.3.4.30	B3.3.4.32
B3.3.4.31	B3.3.4.33
B3.3.4.32	B3.3.4.34
B3.3.4.33	B3.3.4.35
B3.3.5	B3.3.5
B3.3.5.1	B3.3.5.1
B3.3.5.2	B3.3.5.2
B3.3.5.3	B3.3.5.3
B3.3.5.4	B3.3.5.4
B3.3.5.5	B3.3.5.5
B3.3.5.6	B3.3.5.6
B3.3.6	B3.3.6
B3.3.6.1	B3.3.6.1
B3.3.6.2	
B3.3.6.3	B3.3.6.2
–	B3.3.6.3
B3.3.6.4	B3.3.6.4
B3.3.6.5	–
B3.3.6.6	B3.3.6.5
–	B3.3.6.6
B3.4	B3.4
B3.4.1	B3.4.1
B3.4.2	B3.4.2
B3.5	B3.5
B3.5.1	B3.5.1
B3.5.2	B3.5.2
B3.5.3	B3.5.3
B3.5.3.1	
B3.6	B3.6

8th Edition	9th Edition
B3.6.1	B3.6.1
B3.6.1.1	B3.6.1.1
B3.6.1.2	B3.6.1.2
B3.6.2	B3.6.2
B3.6.2.1	B3.6.2.1
B3.6.2.2	B3.6.2.2
B3.6.2.3	B3.6.2.3
B3.6.2.4	B3.6.2.4
B3.6.2.5	B3.6.2.6
B3.6.2.6	B3.6.2.5
B3.6.2.7	B3.6.2.7
B3.6.3	B3.6.3
B3.6.4	B3.6.4
B3.7	B3.7
B3.7.1	B3.7.1
B3.7.2	B3.7.2
B3.7.2.1	B3.7.2.1
B3.7.2.2	B3.7.2.2
B3.7.2.3	B3.7.2.3
B3.7.2.4	B3.7.2.4
B3.7.2.5	B3.7.2.5
B3.7.3	B3.7.3
B3.7.4	B3.7.4
B3.7.4.1	
B3.8	B3.8
B3.8.1	B3.8.1
B3.8.1.1	B3.8.1.1
B3.8.1.2	B3.8.1.2
B3.8.1.3	B3.8.1.4
B3.8.1.4	B3.8.1.5
B3.8.1.5	B3.8.1.6
B3.8.1.6	B3.8.1.7
B3.8.1.7	B3.8.1.8

8th Edition	9th Edition
B3.8.1.8	B3.8.1.9
–	B3.8.1.3
B3.8.1.9	B3.8.1.10
B3.8.1.10	B3.8.1.11
B3.8.1.11	B3.8.1.12
B3.8.1.12	B3.8.1.13
B3.8.1.13	B3.8.1.14
B3.8.1.14	B3.8.1.15
B3.8.1.15	B3.8.1.16
B3.8.1.16	B3.8.1.17
B3.8.1.17	B3.8.1.18
–	B3.8.1.19
B3.8.2	B3.8.2
B3.9	B3.9
B3.9.1	B3.9.1
B3.9.2	B3.9.2
B3.9.3	B3.9.3
B3.9.3.1	
B3.10	B3.10
B3.10.1	B3.10.1
B3.10.2	B3.10.2
B3.11	B3.11
B3.11.1	B3.11.1
B3.11.1.1	B3.11.1.4
B3.11.1.2	B3.11.1.1
B3.11.1.3	B3.11.1.2
B3.11.1.4	B3.11.1.3
B4	B4
B4.1	B4.1
B4.1.1	B4.1.1
B4.2	B4.2
B4.2.1	B4.2.1
B4.3	B4.3

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PART B: CLINICAL PROGRAM STANDARDS

8th Edition	9th Edition
B4.3.1	B4.3.1
B4.4	B4.4
B4.4.1	B4.4.1
B4.4.2	B4.4.2
B4.4.2.1	B4.4.2.1
B4.4.2.2	B4.4.2.2
B4.4.2.3	B4.4.2.3
B4.4.2.4	B4.4.2.4
–	B4.4.2.5
B4.4.2.5	B4.4.2.6
B4.5	B4.5
B4.5.1	B4.5.1
B4.5.1.1	B4.5.1.1
B4.5.1.2	B4.5.1.2
B4.5.1.3	B4.5.1.3
B4.5.1.4	B4.5.1.4
B4.5.2	B4.5.2
B4.5.3	B4.5.3
B4.5.3.1	B4.5.3.1
B4.5.3.2	B4.5.3.2
B4.5.3.3	B4.5.3.3
B4.5.3.4	B4.5.3.4
B4.5.3.5	B4.5.3.5
B4.5.3.6	B4.5.3.6
B4.5.3.7	B4.5.3.7
B4.5.3.8	B4.5.3.8
B4.6	B4.6
B4.6.1	B4.6.1
B4.6.2	B4.6.2
B4.6.2.1	
B4.6.3	B4.6.3
B4.7	B4.7
B4.7.1	B4.7.1

8th Edition	9th Edition
B4.7.2	B4.7.2
B4.7.3	B4.7.3
B4.7.3.1	B4.7.3.1
B4.7.3.2	B4.7.3.2
B4.7.3.3	B4.7.3.3
B4.7.3.4	B4.7.3.4
B4.7.3.5	B4.7.3.5
B4.7.3.6	B4.7.3.6
B4.7.3.7	B4.7.3.7
B4.7.4	B4.7.4
B4.7.5	B4.7.5
B4.7.5.1	B4.7.5.1
B4.7.6	B4.7.6
B4.8	B4.8
B4.8.1	B4.8.1
–	B4.8.2
–	B4.8.2.1
–	B4.8.2.2
–	B4.8.2.3
–	B4.8.2.4
–	B4.8.2.5
–	B4.8.3
–	B4.8.3.1
–	B4.8.3.2
–	B4.8.3.3
–	B4.8.3.4
–	B4.8.3.5
–	B4.8.3.6
–	B4.8.3.7
B4.8.2	B4.8.4
B4.8.3	B4.8.5
B4.8.3.1	B4.8.5.1
B4.8.3.2	

8th Edition	9th Edition
B4.8.3.3	B4.8.5.2
B4.8.3.4	B4.8.5.3
B4.8.3.5	B4.8.5.4
B4.8.3.6	B4.8.5.5
B4.8.3.7	B4.8.5.6
B4.8.3.8	–
–	B4.8.6
–	B4.9
B4.9	B4.10
B4.9.1	B4.10.1
B4.9.2	B4.10.2
B4.9.3	B4.10.3
B4.9.4	B4.10.4
B4.9.5	B4.10.5
B4.9.6	B4.10.6
B4.10	B4.11
B4.10.1	B4.11.1
B4.10.2	B4.11.2
B4.10.2.1	B4.11.2.1
B4.10.2.2	B4.11.2.2
B4.10.2.3	B4.11.2.3
B4.10.3	B4.11.3
B4.10.3.1	B4.11.3.1
B4.10.3.2	B4.11.3.2
B4.10.3.3	B4.11.3.3
B4.10.4	B4.11.4
B4.10.4.1	B4.11.4.1 1 of 2
B4.10.4.2	B4.11.4.1 2 of 2
	B4.11.4.2
B4.10.5	B4.11.5
B4.10.5.1	B4.11.5.1
B4.10.5.2	B4.11.5.2

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8th Edition	9th Edition
B4.11	B4.12
B4.12	B4.13
B4.13	B4.14
B4.13.1	B4.14.1.1
B4.13.2	B4.14.1
B4.13.3	B4.14.2
B4.13.4	B4.14.3
B4.14	B4.15
B4.14.1	B4.15.1
B4.14.2	B10.3.2
B4.14.3	B4.15.2
B4.14.3.1	B4.15.2.1
B4.14.3.2	B4.15.2.2
B4.14.3.3	B4.15.2.3
B4.14.3.4	B4.15.2.4
B4.14.3.5	B4.15.2.5
B4.14.3.6	B4.15.2.6
B4.14.3.7	B4.15.2.7
B4.14.4	B4.15.3
B4.15	B4.16
B4.15.1	
B4.16	B4.17
B4.16.1	B4.17.1
B4.16.2	B4.17.2
B4.17	B4.18
B4.17.1	B4.18.1
B4.17.2	B4.18.2
B4.17.3	B4.18.3
B4.18	B4.19
B4.18.1	B4.19.1
B5	B5
B5.1	B5.1
B5.1.1	B5.1.2

8th Edition	9th Edition
B5.1.2	B5.1.1
B5.1.3	B5.1.3
B5.1.4	B5.1.4
B5.1.5	B5.1.5
B5.1.6	B5.1.6
B5.1.7	B5.1.7
B5.1.8	B5.1.8
B5.1.9	B5.1.9
B5.1.10	B5.1.10
B5.1.11	B5.1.11
B5.1.12	B5.1.12
B5.1.13	B5.1.13
B5.1.14	B5.1.14
B5.1.15	B5.1.15
B5.1.16	B5.1.16
B5.1.17	B2.9
B5.1.18	B5.1.17
B5.1.18.1	B5.1.18
B5.1.19	B5.1.19
–	B5.1.20
–	B5.1.21
B5.2	B5.2
B5.3	B5.3
B5.3.1	B5.3.1
B5.3.2	B5.3.2
B5.3.3	B5.3.3
B5.3.4	B5.3.4
B5.3.5	B5.3.5
B5.3.6	B5.3.6
B5.3.7	B5.3.7
B5.3.8	B5.3.8
B5.3.9	B5.3.9
B5.3.10	B5.3.10

8th Edition	9th Edition
B5.4	B5.4
B5.5	B5.5
B5.6	B5.6
B5.7	B5.7
B6	B6
B6.1	B6.1
B6.1.1	B6.1.1
–	B6.1.2
B6.2	B6.2
B6.2.1	B6.2.1
B6.2.1.1	B6.2.1.1
–	B6.2.1.2
B6.2.1.2	B6.2.1.3
B6.2.1.3	B6.2.1.4
B6.2.1.4	B6.2.1.6
B6.2.1.5	B6.2.1.5
B6.2.2	B6.2.2.2
B6.2.2.1	B6.2.2.3
B6.2.3	B6.2.2.4
B6.2.4	B6.2.2.5
B6.2.4.1	B6.2.2.6
B6.2.5	B6.2.2
B6.2.5.1	B6.2.2.1
B6.2.6	B6.2.2.7
–	B6.2.2.8
B6.2.7	B6.2.2.9
B6.2.8	B6.2.2.10
B6.2.9	B6.2.2.11
B6.3	B6.3
B6.3.1	B6.3.1
B6.3.1.1	B6.3.1.1
B6.3.1.2	B6.3.1.2
B6.3.1.3	B6.3.1.3

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8th Edition	9th Edition
B6.3.2	B6.3.2
B6.3.2.1	B6.3.2.1
B6.3.2.2	B6.3.2.3
B6.3.2.3	B6.3.2.2
–	B6.3.2.4
–	B6.3.3
B6.3.3	B6.3.6
	B6.3.6.2
–	B6.3.6.1
–	B6.3.4
B6.3.4	B6.3.4.1
B6.3.5	B6.3.5
	B6.3.5.1
–	B6.3.5.2
B6.3.6	B6.3.7
B6.3.7	B6.3.8
B6.3.8	B6.3.9
B6.3.9	B6.3.10
B6.3.9.1	B6.3.10.1
B6.3.10	B6.3.11
B6.3.11	B6.3.12
–	B6.3.12.1
B6.4	B6.4
B6.4.1	B6.4.1
B6.4.2	B6.4.2
B6.4.3	B6.4.3
B6.4.4	B6.4.4
–	B6.4.4.1
B6.4.5	B6.4.5
B6.4.6	B6.4.6
B6.4.7	B6.4.7
B6.4.8	B6.4.8
B6.4.8.1	B6.4.8.1

8th Edition	9th Edition
B6.4.8.2	B6.4.8.2
B6.4.8.3	B6.4.8.3
B6.4.8.4	B6.4.8.4
B6.4.8.5	B6.4.8.5
B6.4.8.6	B6.4.8.6
B6.4.8.7	B6.4.8.7
B6.4.8.8	B6.4.8.8
B6.4.9	B6.4.9
B6.4.9.1	B6.4.9.1
B6.4.9.2	B6.4.9.2
B6.4.9.3	B6.4.9.3
B6.4.9.4	B6.4.9.4
B6.4.9.5	B6.4.9.5
B6.4.10	B6.4.10
B6.4.10.1	B6.4.10.1
B6.4.10.2	B6.4.10.2
B6.4.10.3	B6.4.10.3
B6.4.10.4	B6.4.10.4
B6.4.11	B6.4.11
B6.4.11.1	B6.4.11.1
B6.4.11.2	B6.4.11.2
B6.4.12	B6.4.12
B6.4.13	B6.4.13
B6.4.14	B6.4.14
B6.4.14.1	B6.4.14.1
B6.4.14.2	B6.4.14.2
B6.4.14.3	B6.4.14.3
B6.4.14.4	B6.4.14.4
B6.4.15	B6.4.15
B6.4.16	B6.4.16
B6.4.17	B6.4.17
B6.4.18	B6.4.18
B6.4.19	–

8th Edition	9th Edition
B6.4.19.1	B6.4.19
B7	B7
B7.1	B7.1
B7.1.1	B7.1.1
–	B7.1.2
B7.2	B7.2
B7.2.1	B7.2.1
–	B7.2.2
B7.3	B7.3
B7.3.1	B7.3.1
B7.4	B7.4
B7.4.1	B7.4.1
B7.4.2	B7.4.2
B7.4.3	B7.4.3
B7.4.4	B7.4.4
B7.4.4.1	B7.4.4.1
B7.4.4.2	B7.4.4.2
B7.5	B7.5
B7.5.1	B7.5.1
B7.5.2	B7.5.2
B7.5.3	B7.5.3
B7.5.4	B7.5.4
B7.5.5	B7.5.5
B7.6	B7.6
B7.6.1	B7.6.1
B7.6.2	B7.6.2
–	B7.6.3
B7.6.3	B7.6.4
B7.6.3.1	B7.6.4.1
B7.6.3.2	B7.6.4.2
B7.6.4	B7.6.5
B7.6.5	B7.6.6
B7.6.6	B7.6.7

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8th Edition	9th Edition
B7.6.7	B7.6.8
B7.7	B7.7
B7.7.1	B7.7.1
B7.7.2	B7.7.2
B7.7.3	B7.7.3
B7.7.4	B7.7.4
B7.7.5	B7.7.5
B7.7.6	B7.7.6
B7.7.7	B7.7.7
B7.8	B7.8 <i>1 of 2</i>
B7.8.1	B7.8.1
B7.8.2	B7.8.2
B7.8.3	B7.8.3
B7.8.4	B7.8.3.1
B7.8.5	B7.8 <i>2 of 2</i>
B7.9	–
B7.9.1	–
B7.9.2	–
B7.9.3	–
B7.9.4	B7.9.2.1
B7.10	B7.9
B7.10.1	B7.9.1
B7.10.1.1	B7.9.1.1
B7.10.1.2	B7.9.1.2
B7.10.1.3	B7.9.1.3
B7.10.2	B7.9.2
B7.11	B7.10
B7.11.1	B7.10.1
B7.11.2	B7.10.2
B7.11.3	B7.10.3
B7.11.4	B7.10.4
B7.12	B7.11

8th Edition	9th Edition
B7.12.1	B7.11.1
–	B7.11.2
B7.12.2	B7.11.3
B7.12.2.1	B7.11.3.1
B7.12.2.2	B7.11.3.2
B7.12.2.3	B7.11.3.3
B7.12.2.4	B7.11.3.4
B7.12.2.5	B7.11.3.5
B7.12.2.6	B7.11.3.6
–	B7.11.3.7
–	B7.11.3.8
B7.12.3	B7.11.4
B8	B8
B8.1	B8.1
B8.1.1	B8.1.1
B8.1.2	B8.1.2
B8.2	B8.2
B8.2.1	B8.2.1
B8.2.1.1	B8.2.1.1
B8.2.1.2	B8.2.1.2
B8.2.1.3	B8.2.1.3
B8.2.1.4	B8.2.1.4
B8.3	B8.3
B8.3.1	B8.3.1
B8.3.2	B8.3.2
B8.3.2.1	B8.3.2.1
B8.3.2.2	B8.3.2.2
B8.3.2.3	B8.3.2.3
B8.3.2.4	B8.3.2.4
B8.3.2.5	B8.3.2.5
–	B8.3.2.6
–	B8.3.2.7
–	B8.3.2.8

8th Edition	9th Edition
B8.4	B8.4
B9	B9
B9.1	B9.2
B9.1.1	B9.2.1
B9.1.2	B9.2.2
B9.1.3	B9.2.3
–	B9.1.3.1
B9.2	B9.3
B9.3	B9.1
B10	B10
–	B10.1
–	B10.1.1
–	B10.1.2
–	B10.1.3
–	B10.1.4
–	B10.1.5
–	B10.1.6
–	B10.2
–	B10.3
B10.1	B10.3.1
B10.1.1	B10.3.3
B10.1.2	B10.3.4
–	B10.3.5
–	B10.3.5.1
B10.2	B10.3.6
B10.3	B10.3.7
B10.4	B10.4
B10.4.1	B10.4.1
B10.4.2	B10.4.1.1
B10.4.3	B10.4.1.2
B10.4.4	B10.4.1.9 <i>1 of 2</i>
B10.4.5	B10.4.1.11
–	B10.4.1.12

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8th Edition	9th Edition
B10.4.6	B10.4.3
B10.4.7	B10.4.1.4
B10.4.7.1	B10.4.1.5
B10.4.7.2	B10.4.1.3
B10.4.8	B10.4.1.10
B10.4.9	B10.4.2
–	B10.4.2.1
–	B10.4.2.2

8th Edition	9th Edition
–	B10.4.2.3
–	B10.4.2.4
–	B10.4.2.5
–	B10.4.2.6
B10.4.9.1	B10.4.1.6
	B10.4.1.7
–	B10.4.1.8
B10.4.9.2	B10.4.2.7

8th Edition	9th Edition
B10.4.9.3	B10.4.2.8
B10.4.9.4	B10.4.1.9 <i>2 of 2</i>
B10.5	B10.5
B10.5.1	B10.5.1
B10.5.2	B10.5.2

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PART C: COLLECTION FACILITY STANDARDS

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C1	CM1	C1
C1.1	CM1.1	C1.1
C1.2	CM1.2	C1.4
C1.3	CM1.3	C1.2
C1.3.1	CM1.3.1	C1.2.1
C1.4	CM1.4	C1.3
C1.5	CM1.5	C1.5
–	–	C1.6
–	–	C1.7
C2	CM2	C2
C2.1	CM2.1	C2.1
C2.1.1	–	C2.1.1
C2.1.2	CM2.1.1	C2.1.2
C2.1.3	CM2.1.2	C2.1.3
C2.1.4	CM2.1.3	C2.1.4
C2.2	CM2.2	C2.2
C2.3	CM2.3	C2.3
C2.4	CM2.4	C2.4
C2.4.1	CM2.4.1	C2.4.1
C2.4.2	CM2.4.2	C2.4.2
C2.4.3	–	C2.4.3
C2.5	CM2.5	C2.5
C2.6	CM2.6	C8.2
C2.7	CM2.7	C2.10
C2.8	CM2.8	C2.6
C2.9	CM2.9	C2.7
C2.10	CM2.10	C2.8
–	–	C2.9.1
C2.11	CM2.11	C2.9.2
		C2.9.3
C3	CM3	C3
C3.1	–	C3.1
C3.1.1	–	C3.1.1
C3.1.2	–	C3.1.2

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C3.1.3	–	–
C3.1.4	–	C3.1.3
C3.1.4.1	–	C3.1.3.1
	–	C3.1.3.2
	–	C3.1.3.3
C3.2	CM3.1	C3.2
C3.2.1	CM3.1.1	C3.2.1
–	CM3.1.2.2	C3.2.2 <i>1 of 5</i>
C3.2.2	CM3.1.2	C3.2.2 <i>2 of 5</i>
	CM3.1.2.5	C3.2.2 <i>3 of 5</i>
	CM3.1.2.6	C3.2.2 <i>4 of 5</i>
	CM3.1.2.7	C3.2.2 <i>5 of 5</i>
–	CM3.1.2.1	–
	CM3.1.2.3	
	CM3.1.2.4	
	CM3.1.2.8	
C3.2.3	–	C3.2.1.1
–	CM3.1.3	C3.2.1.2
–	–	C3.2.1.3
C3.2.4	CM3.1.4	C3.2.3
C3.2.4.1	CM3.1.4.1	
C3.3	CM3.2	C3.3
C3.3.1	CM3.2.1	C3.3.1
C3.3.2	CM3.2.2	C3.3.2
C3.3.3	CM3.2.3	C3.3.3
C3.3.3.1	CM3.2.3.1	
C3.4	CM3.3	C3.4
–	CM3.3.1	–
C3.4.1	CM3.3.2	C3.4.1
C3.4.2	CM3.3.3	C3.4.2

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8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C3.4.3	CM3.3.5	C3.4.3
C3.4.3.1	CM3.3.5.1	C3.4.3.1
C4	CM4	C4
–	CM4.1	–
C4.1	–	C4.1
C4.1.1	–	C4.1.1
C4.2	–	C4.2
C4.2.1	–	C4.2.1
C4.3	–	C4.3
C4.3.1	–	C4.3.1
C4.4	–	C4.4
C4.4.1	–	C4.4.1
C4.4.2	–	C4.4.2
C4.4.2.1	–	C4.4.2.1
C4.4.2.2	–	C4.4.2.2
C4.4.2.3	–	C4.4.2.3
C4.4.2.4	–	C4.4.2.4
C4.4.2.5	CM3.3.4	C4.4.2.5
C4.4.2.6	–	C4.4.2.6
C4.5	–	C4.5
C4.5.1	–	C4.5.1
C4.5.1.1	–	C4.5.1.1
C4.5.1.2	–	C4.5.1.2
C4.5.1.3	–	C4.5.1.3
C4.5.1.4	–	C4.5.1.4
C4.5.2	–	C4.5.2
C4.5.3	–	C4.5.3
C4.5.3.1	–	C4.5.3.1
C4.5.3.2	–	C4.5.3.2
C4.5.3.3	–	C4.5.3.3
C4.5.3.4	–	C4.5.3.4
C4.5.3.5	–	C4.5.3.5
C4.5.3.6	–	C4.5.3.6
C4.5.3.7	–	C4.5.3.7

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C4.5.3.8	–	C4.5.3.8
C4.6	–	C4.6
C4.6.1	–	C4.6.1
C4.6.2	–	C4.6.2
C4.6.3	CM4.1.1	C4.6.3
C4.6.4	–	C4.6.4
C4.7	–	C4.7
C4.7.1	–	C4.7.1
C4.7.2	–	C4.7.2
C4.7.3	–	C4.7.3
C4.8	–	C4.8
C4.8.1	–	C4.8.1
–	–	C4.8.2
–	–	C4.8.2.1
–	–	C4.8.2.2
–	–	C4.8.2.3
–	–	C4.8.2.4
–	–	C4.8.2.5
–	–	C4.8.3
–	–	C4.8.3.1
–	–	C4.8.3.2
–	–	C4.8.3.3
–	–	C4.8.3.4
–	–	C4.8.3.5
–	–	C4.8.3.6
–	–	C4.8.3.7
C4.8.2	–	C4.8.4
C4.8.3	–	C4.8.5
C4.8.3.1	–	C4.8.5.1
C4.8.3.2	–	C4.8.5.2
C4.8.3.3	–	C4.8.5.3
C4.8.3.4	–	C4.8.5.4
–	–	C4.8.5.5
–	–	C4.8.6

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8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
–	–	C4.9
C4.9	–	C4.10
C4.9.1	–	C4.10.1
C4.9.2	–	C4.10.3
C4.9.3	–	C4.10.2
C4.9.4	–	C4.10.4
C4.10	–	C4.11
C4.10.1	–	C4.11.1
C4.10.2	–	C4.11.2
C4.10.2.1	–	C4.11.2.1
C4.10.2.2	–	C4.11.2.2
C4.10.2.3	–	C4.11.2.3
C4.10.3	–	C4.11.3
C4.10.3.1	–	C4.11.3.1
C4.10.3.2	–	C4.11.3.2
C4.10.3.3	–	C4.11.3.3
C4.10.4	–	C4.11.4
C4.10.4.1	–	C4.11.4.1 1 of 2
C4.10.4.2	–	C4.11.4.1 2 of 2
	–	C4.11.4.2
C4.10.5	–	C4.11.5
C4.10.5.1	–	C4.11.5.1
C4.10.5.2	–	C4.11.5.2
C4.11	–	C4.12
C4.12	–	C4.13
C4.13	–	C4.14
–	–	C4.14.1
C4.13.1	–	C4.14.1.1
C4.13.2	–	C4.14.2
C4.13.3	–	C4.14.3
C4.13.4	–	C4.14.4
C4.14	–	C4.15

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C4.14.1	–	C4.15.1
C4.14.2	–	C4.15.2
C4.14.2.1	–	C4.15.2.1
C4.14.2.2	–	C4.15.2.2
C4.14.2.3	–	C4.15.2.3
C4.14.2.4	–	C4.15.2.4
C4.14.2.5	–	C4.15.2.5
C4.14.2.6	–	C4.15.2.6
C4.14.2.7	–	C4.15.2.7
C4.14.3	–	C4.15.3
C4.15	–	C4.16
C4.15.1	–	
C4.16	–	C4.17
C4.16.1	–	C4.17.1
C4.16.2	–	C4.17.2
C4.17	–	C4.18
C4.17.1	–	C4.18.1
C4.17.2	–	C4.18.2
C4.17.3	–	C4.18.3
C4.18	–	C4.19
C4.18.1	–	C4.19.1
C5	CM5	C5
C5.1	CM5.1	C5.1
C5.1.1	CM5.1.1	C5.1.1
C5.1.2	CM5.1.2	C5.1.2
C5.1.3	CM5.1.3	C5.1.3
C5.1.4	CM5.1.4	C5.1.4
C5.1.5	–	C5.1.5
C5.1.6	CM5.1.5	C5.1.6
C5.1.7	CM5.1.6	C5.1.7
C5.1.8	CM5.1.7	C5.1.8
C5.1.9	CM5.1.8	C5.1.9
C5.1.10	CM5.1.9	C5.1.10
C5.1.11	CM5.1.10	C5.1.11

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8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C5.1.12	CM5.1.11	C5.1.12
C5.1.13	–	C5.1.21
C5.1.14	CM5.1.12	C5.1.13
C5.1.14.1	CM5.1.12.1	
C5.1.14.2	CM5.1.12.2	–
–	–	C5.1.14
C5.1.15	CM5.1.13	C5.1.15
C5.1.16	–	C5.1.16
C5.1.17	–	C5.1.17
–	–	C5.1.18
C5.1.18	CM5.1.14	C2.9
C5.1.19	CM5.1.15	C5.1.19
C5.1.20	CM5.1.16	C5.1.20
–	–	C5.1.22
–	–	C5.1.23
–	CM5.2	–
C5.2	–	C5.2
C5.3	CM5.3	C5.3
C5.3.1	CM5.3.1	C5.3.1
C5.3.2	CM5.3.2	C5.3.2
C5.3.3	CM5.3.3	C5.3.3
C5.3.4	CM5.3.4	C5.3.4
C5.3.5	CM5.3.5	C5.3.5
C5.3.6	CM5.3.6	C5.3.6
C5.3.7	CM5.3.7	C5.3.9
C5.3.8	CM5.3.8	C5.3.7
C5.3.9	CM5.3.9	C5.3.8
C5.4	CM5.4	C5.4
C5.5	CM5.5	C5.5
C5.6	CM5.6	C5.6
C5.7	CM5.7	C5.7
C6	CM6	C6
C6.1	CM6.1	C6.1
–	–	C6.1.1

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C6.2	CM6.2	C6.2
C6.2.1	CM6.2.1	C6.2.1
C6.2.1.1	CM6.2.1.1	C6.2.1.1
C6.2.1.2	CM6.2.1.2	C6.2.1.2
C6.2.1.3	CM6.2.1.3	C6.2.1.3
C6.2.1.4	CM6.2.1.4	C6.2.1.4
C6.2.1.5	CM6.2.1.5	C6.2.1.5
–	–	C6.2.1.6
C6.2.2	CM6.2.2	C6.2.2
C6.2.2.1	CM6.2.2.1	C6.2.2.1
C6.2.3	CM6.2.3	C6.2.3
C6.2.4	CM6.2.4	C6.2.4
C6.2.4.1	CM6.2.4.1	C6.2.4.1
C6.2.5	CM6.2.5	C6.2.5
C6.2.5.1	CM6.2.5.1	C6.2.5.1
C6.2.6	CM6.2.6	C6.2.6
–	–	C6.2.6.1
C6.2.7	CM6.2.7	C6.2.7
C6.2.8	CM6.2.8	C6.2.8
C6.2.9	CM6.2.9	C6.2.9
C6.3	CM6.3	C6.3
C6.3.1	CM6.3.1	C6.3.1
C6.3.1.1	CM6.3.1.1	C6.3.1.1
C6.3.1.2	CM6.3.1.2	C6.3.1.2
C6.3.1.3	CM6.3.1.3	C6.3.1.3
C6.3.2	CM6.3.2	C6.3.2
–		C6.3.2.2
C6.3.2.1	–	C6.3.2.3
C6.3.2.2	–	C6.3.2.1
–	–	C6.3.2.4
C6.3.3	CM6.3.3	C6.3.6
		C6.3.6.1
C6.3.4	CM6.3.4	C6.3.5
		C6.3.5.1

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8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C6.3.4.1	–	C6.3.5.2
C6.3.5	CM6.3.5	C6.3.7
C6.3.6	CM6.3.6	–
C6.3.7	–	C6.3.10
C6.3.8	–	C6.3.11
C6.3.8.1	–	
–	–	C6.3.8
C6.3.9	CM6.3.7	C6.3.9
C6.3.9.1	CM6.3.7.1	–
C6.3.10	CM6.3.8	C6.3.12
–	–	C6.3.12.1
C6.4	CM6.4	C6.4
C6.4.1	CM6.4.1	C6.4.1
C6.4.2	CM6.4.2	C6.4.2
–	–	C6.4.2.1
C6.4.3	CM6.4.3	C6.4.3
C6.4.4	CM6.4.4	C6.4.4
C6.4.5	CM6.4.5	C6.4.5
C6.4.6	–	C6.4.6
C6.4.7	–	C6.4.8
C6.4.8	–	C6.4.7
C6.4.9	–	C6.4.9
C6.5	CM6.5	C6.5
C6.5.1	CM6.5.1	C6.5.1
C6.5.2	CM6.5.2	C6.5.2
C6.5.3	CM6.5.3	C6.5.3
C6.5.4	CM6.5.4	C6.5.4
C6.5.5	CM6.5.5	C6.5.5
C7	CM7	C7
C7.1	CM7.1	C7.1
C7.1.1	CM7.1.1	C7.1.1
C7.1.2	CM7.1.2	C7.1.2
–	–	C7.1.3
C7.2	CM7.2	C7.2

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C7.2.1	CM7.2.1	C7.2.1
C7.2.2	CM7.2.2	C7.2.2
C7.2.2.1	CM7.2.2.1	C7.2.3
C7.2.2.2	CM7.2.2.2	C7.2.1.1
C7.2.3	CM7.2.3	C7.2.4
C7.2.4	CM7.2.4	C7.2.5
C7.2.4.1	CM 7.2.4.1	C7.2.1.2
C7.2.4.2	CM7.2.4.2	C7.2.5.1
C7.2.5	CM7.2.5	C7.2.6
C7.2.5.1	CM7.2.5.1	C7.2.6.1
C7.2.5.2	CM7.2.5.2	C7.2.6.2
C7.2.5.3	CM7.2.5.3	C7.2.6.3
C7.2.6	CM7.2.6	C7.2.7
C7.2.7	CM7.2.7	C7.2.8
C7.2.8	CM7.2.8	C7.2.9
C7.2.9	CM7.2.9	C7.2.10
C7.2.10	CM7.2.10	C7.2.11
C7.2.11	CM7.2.11	C7.2.12
C7.3	CM7.3	C7.3
C7.3.1	CM7.3.1	C7.3.1
C7.3.1.1	CM7.3.1.1	C7.3.1.1
C7.3.1.2	CM7.3.1.2	C7.3.1.2
C7.3.1.3	–	C7.3.1.3
–	–	C7.3.2
–	–	C7.3.2.1
C7.3.1.4	CM7.3.1.3	C7.3.3
C7.3.1.5	CM7.3.1.4	C7.3.4
–	–	C7.3.5
C7.4	CM7.4	C7.4
C7.4.1	–	C7.4.1
–	–	C7.4.1.1
C7.4.2	CM7.4.2	C7.4.2
–	CM7.4.2.1	C7.4.2.1
C7.4.3	CM7.4.1	C7.4.3

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8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C7.4.4	CM7.4.3	C7.4.4
C7.4.4.1	CM7.4.3.1	–
C7.4.5	CM7.4.4	C7.4.5
C7.4.6	CM7.4.5	C7.4.6
C7.4.7	CM7.4.6	C7.4.7
C7.4.8	CM7.4.7	C7.4.8
–	–	C8
		C8.1
–	–	C8.3.3
–	–	C8.3.4
–	–	C8.3.6
–	–	C8.3.7
–	–	C8.3.8
–	–	C8.5
C8	CM8	C9
C8.1	CM8.1	C9.1
C8.2	CM8.2	C8.3
C8.2.1	CM8.2.1	C8.3.1
C8.2.2	CM8.2.2	C8.3.2
C8.2.2.1	CM8.2.2.1	C8.3.2.1
C8.2.3	CM8.2.3	C8.3.5
C8.3	CM8.3	C8.4
C8.3.1	CM8.3.1	C8.4.1
C8.3.1.1	CM8.3.1.1	
C8.3.1.2	CM8.3.1.2	C8.4.1.1
C8.3.1.3	CM8.3.1.3	
–	–	C8.4.2
C8.3.2	CM8.3.2	C8.4.2.1
C8.3.2.1	CM8.3.2.1	C8.4.2.2
C8.3.2.2	CM8.3.2.2	C8.4.2.3
C8.3.3	CM8.3.3	C8.3.9
C8.4	CM8.4	C9.2
C8.4.1	CM8.4.1	C6.4.10
C8.5	CM8.5	C9.3

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C8.6	–	C9.4.1.1
C8.7	CM8.6	C9.4
–	–	C9.4.1
C8.8	CM8.7	C9.5
–	CM8.8	C6.3.3
C8.9	CM8.9	C6.3.4
C8.9.1	–	C6.3.4.1
C8.10	CM8.10	C9.6
C8.10.1	CM8.10.1	C9.6.1
–	–	C9.7
C8.11	CM8.11	C9.8
C8.12	CM8.12	C9.9
		C9.9.1
–	CM8.13	C9.15.3
C8.13	CM8.14	C9.10
C8.13.1	CM8.14.1	C9.10.1
C8.14	–	C9.11
C8.14.1	–	C9.11.1
C8.14.2	–	C9.11.2
–	–	C9.13
–	–	C9.14
–	–	C9.14.1
–	–	C9.14.2
–	–	C9.15
–	–	C9.15.1
–	–	C9.15.2
–	–	C9.16
–	–	C9.16.1
–	–	C9.16.1.1
–	–	C9.16.2
–	–	C9.16.3
–	–	C9.16.3.1
–	–	C9.16.3.2
–	–	C9.16.3.3

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8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
–	–	C9.16.3.4
C9	CM9	C10
C9.1	CM9.1	C10.1
–	–	C10.2
C9.2	CM9.2	–
C9.2.1	CM9.2.1	C10.2.1
C9.2.2	CM9.2.2	C10.2.2
–	–	C10.3
–	–	C10.3.1
–	–	C10.3.2
–	–	C10.4
–	–	C10.4.1
C10	CM10	C11
C10.1	CM10.1	C11.1
C10.1.1	CM10.1.1	C11.6.1
C10.2	CM10.2	C11.2
–	–	C11.3
–	–	C11.4
–	–	C11.4.1
–	–	C11.5
–	–	C11.5.1
C10.3	CM10.3	C11.6
C10.3.1	CM10.3.1	C11.5.2
–	–	C11.5.3
–	–	C11.5.4
–	–	C11.5.5
C10.3.2	CM10.3.2	C11.7
C10.3.3	CM10.3.3	C11.8
–	–	C11.9
–	–	C11.10
C10.4	CM10.4	C11.11
C10.5	CM10.5	C11.12
–	–	C11.13
C11	CM11	C12

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
–	CM11.1	–
C11.1	–	–
–	–	C12.1
C11.1.1	–	C12.1.1
C11.1.1.1	–	C12.1.2
C11.1.1.2	–	C12.1.3
C11.1.2	–	C12.1.4
C11.1.3	–	C12.1.5
C11.1.4	–	C12.1.6
C11.1.5	–	C12.1.7
C11.2	–	C12.2
–	–	C12.3
C11.3	–	C12.3.1
C11.3.1	–	C12.3.3
C11.3.2	–	C12.3.4
C11.3.3	–	C12.3.2
C11.4	–	C12.3.5
	–	C12.3.5.1
C11.5	–	C12.4
C11.6	–	C12.5
C11.7	–	C12.6
C11.7.1	–	C12.6.1
C11.7.2	–	C12.6.1.1
C11.7.3	–	C12.6.1.2
C11.7.4	–	C12.6.1.9 <i>1 of 2</i>
C11.7.5	–	C12.6.1.11
–	–	C12.6.1.12
C11.7.6	–	C12.6.3
C11.7.7	–	C12.6.1.4
C11.7.7.1	–	C12.6.1.5
C11.7.7.2	–	C12.6.1.3
C11.7.8	–	C12.6.1.10
C11.7.9	–	C12.6.2

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PART C: COLLECTION FACILITY STANDARDS

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C11.7.9.1	–	C12.6.2.5
–	–	C12.6.2.2
C11.7.9.2	–	C12.6.2.3
–	–	C12.6.2.4
–	–	C12.6.2.6
C11.7.9.3	–	C12.6.2.1
C11.7.9.4	–	C12.6.1.6
	–	C12.6.1.7
–	–	C12.6.1.8

8th Edition <i>Apheresis</i>	8th Edition <i>Marrow</i>	9th Edition <i>All Collection</i>
C11.7.9.5	–	C12.6.2.7
C11.7.9.6	–	C12.6.2.8
C11.7.9.7	–	C12.6.1.9 <i>2 of 2</i>
C11.8	–	C12.7
C11.8.1	–	C12.7.2
C11.8.2	–	C12.7.1
C12	CM12	–
C12.1	CM12.1	C9.12

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PART D: PROCESSING FACILITY STANDARDS

8th Edition	9th Edition
D1	D1
D1.1	D1.1
D1.2	D1.2
D1.2.1	D1.2.1
D1.3	D1.3
D2	D2
D2.1	D2.1
D2.1.1	D2.1.1
D2.1.2	D2.1.2
D2.1.3	D2.1.3
D2.2	D2.2
D2.2.1	D2.11
–	D2.11.1
–	D2.11.2
–	D2.11.3
D2.3	D2.3
D2.4	D2.4
D2.4.1	D2.4.1
D2.4.2	D2.4.2
D2.4.3	D2.4.3
D2.5	D2.5
D2.6	D2.6
D2.7	D2.7
D2.8	D2.10
D2.9	D2.8
–	D2.9.1
D2.10	D2.9.2
	D2.9.3
–	D2.12
–	D2.12.1
D3	D3
D3.1	D3.1
D3.1.1	D3.1.1
D3.1.2	D3.1.2

8th Edition	9th Edition
D3.1.3	D3.1.3
D3.1.4	D3.1.4
D3.1.4.1	
D3.2	D3.2
D3.2.1	D3.2.1
D3.2.2	D3.2.2
D3.2.3	D3.2.3
D3.2.4	D3.2.4
D3.2.4.1	
D3.3	D3.3
D3.3.1	D3.3.1
D3.3.2	D3.3.2
D3.3.3	D3.3.3
D3.3.3.1	
D3.4	D3.4
D3.4.1	D3.4.1
D4	D4
D4.1	D4.1
D4.1.1	D4.1.1
D4.2	D4.2
D4.2.1	D4.2.1
D4.3	D4.3
D4.3.1	D4.3.1
D4.4	D4.4
D4.4.1	D4.4.1
D4.4.2	D4.4.2
D4.4.2.1	D4.4.2.1
D4.4.2.2	D4.4.2.2
D4.4.2.3	D4.4.2.3
D4.4.2.4	D4.4.2.4
D4.4.2.5	D4.4.2.5
D4.4.2.6	D4.4.2.6
D4.5	D4.5
D4.5.1	D4.5.1

8th Edition	9th Edition
D4.5.1.1	D4.5.1.1
D4.5.1.2	D4.5.1.2
D4.5.1.3	D4.5.1.3
D4.5.1.4	D4.5.1.4
D4.5.2	D4.5.2
D4.5.3	D4.5.3
D4.5.3.1	D4.5.3.1
D4.5.3.2	D4.5.3.2
D4.5.3.3	D4.5.3.3
D4.5.3.4	D4.5.3.4
D4.5.3.5	D4.5.3.5
D4.5.3.6	D4.5.3.6
D4.5.3.7	D4.5.3.7
D4.5.3.8	D4.5.3.8
D4.6	D4.6
D4.6.1	D4.6.1
D4.6.2	D4.6.2
D4.6.3	D4.6.3
D4.6.4	D4.6.4
D4.7	D4.7
D4.7.1	D4.7.1
D4.7.2	D4.7.2
D4.7.3	D4.7.3
D4.8	D4.8
D4.8.1	D4.8.1
–	D4.8.2
–	D4.8.2.1
–	D4.8.2.2
–	D4.8.2.3
–	D4.8.2.4
–	D4.8.2.5
–	D4.8.3
–	D4.8.3.1
–	D4.8.3.2

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PART D: PROCESSING FACILITY STANDARDS

8th Edition	9th Edition
–	D4.8.3.3
–	D4.8.3.4
–	D4.8.3.5
–	D4.8.3.6
–	D4.8.3.7
D4.8.2	D4.8.4
D4.8.3	D4.8.5
D4.8.3.1	D4.8.5.1
D4.8.3.2	D4.8.5.2
–	D4.8.5.3
–	D4.8.6
–	D4.9
D4.9	D4.10
D4.9.1	D4.10.2
D4.9.2	D4.10.3
D4.9.3	D4.10.4
D4.9.4	D4.10.5
D4.9.5	D4.10.1
D4.9.6	D4.10.6
D4.9.7	D4.10.7
D4.10	D4.11
D4.10.1	D4.11.1
D4.10.2	D4.11.2
D4.10.2.1	D4.11.2.1
D4.10.2.2	D4.11.2.2
D4.10.2.3	D4.11.2.3
D4.10.3	D4.11.3
D4.10.3.1	D4.11.3.1
D4.10.3.2	D4.11.3.2
D4.10.3.3	D4.11.3.3
D4.10.4	D4.11.4
D4.10.4.1	D4.11.4.1 1 of 2

8th Edition	9th Edition
D4.10.4.2	D4.11.4.1 2 of 2
	D4.11.4.2
D4.10.5	D4.11.5
D4.10.5.1	D4.11.5.1
D4.10.5.2	D4.11.5.2
D4.11	D4.12
D4.12	D4.13
D4.13	D4.14
–	D4.14.1
D4.13.1	D4.14.1.1
D4.13.2	D4.14.2
D4.13.3	D4.14.3
D4.13.4	D4.14.4
D4.14	D4.15
D4.14.1	D4.15.1
D4.14.2	D4.15.2
D4.14.2.1	D4.15.2.1
D4.14.2.2	D4.15.2.2
D4.14.2.3	D4.15.2.3
D4.14.2.4	D4.15.2.4
D4.14.2.5	D4.15.2.5
D4.14.2.6	D4.15.2.6
D4.14.2.7	D4.15.2.7
D4.14.3	D4.15.3
D4.15	D4.16
D4.15.1	
D4.16	D4.17
D4.16.1	D4.17.1
D4.17	D4.18
D4.17.1	D4.18.1
D4.17.2	D4.18.2
D4.17.3	D4.18.3
D4.18	D4.19

8th Edition	9th Edition
D4.18.1	D4.19.1
D5	D5
D5.1	D5.1
D5.1.1	D5.1.1
D5.1.2	D5.1.2
D5.1.3	D5.1.3
D5.1.3.1	D5.1.3.1
D5.1.4	D5.1.4
D5.1.5	D5.1.5
D5.1.6	D5.1.6
D5.1.7	D5.1.7
D5.1.8	D5.1.8
D5.1.9	D5.1.9
D5.1.10	D5.1.10
D5.1.11	D5.1.11
D5.1.12	D5.1.12
D5.1.13	D5.1.13
D5.1.14	D5.1.14 1 of 2
D5.1.15	D5.1.15
D5.1.16	D5.1.16
D5.1.17	D2.9
D5.1.18	D5.1.17
D5.1.18.1	D5.1.18
D5.1.19	D5.1.19
–	D5.1.20
–	D5.1.21
D5.2	D5.2
D5.3	D5.3
D5.3.1	D5.3.1
D5.3.2	D5.3.2
D5.3.3	D5.3.3
D5.3.4	D5.3.4
D5.3.5	D5.3.5

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8th Edition	9th Edition
D5.3.6	D5.3.6
D5.3.7	D5.3.7
D5.3.8	D5.3.8
D5.3.9	D5.3.9
D5.4	D5.4
D5.5	D5.5
D5.6	D5.6
D5.7	D5.7
D6	D6
D6.1	D6.1
D6.2	D6.2
D6.3	D6.3
D6.3.1	D6.3.2
–	D6.3.2.1
D6.3.2	D6.3.3
D6.3.3	D6.3.4
D6.3.4	D6.3.5
D6.3.4.1	D6.3.5.1
–	D6.3.5.2
D6.3.4.2	D6.3.5.3
D6.3.4.3	
D6.3.5	D6.3.6
D6.3.6	D6.3.7
D6.3.7	D6.3.8
D6.4	D6.3.1
–	D6.4
D6.5	D6.4.1
D6.6	D6.4.1.1
D6.7	D6.4.2
D6.7.1	D6.4.2.1
–	D6.4.2.2
D6.7.2	D6.4.2.3
D6.8	D5.1.14 2 of 2

8th Edition	9th Edition
D6.9	D6.3.9
D6.10	D6.5
D6.11	–
D6.11.1	–
D6.11.2	–
D6.11.3	–
D7	D7
D7.1	D7.1
D7.1.1	D7.1.1
D7.1.2	D7.1.2
–	D7.1.3
D7.2	D7.2
D7.2.1	D7.2.1
D7.2.1.1	D7.2.1.1
D7.2.1.2	D7.2.1.2
D7.2.2	D7.2.2
D7.2.3	D7.2.3
D7.2.4	D7.2.4
D7.2.5	D7.2.5
D7.2.5.1	D7.2.5.1
D7.2.6	D7.2.6
D7.2.6.1	D7.2.6.3
D7.2.6.2	D7.2.6.2
D7.2.7	D7.2.7
D7.2.8	D7.2.6.1
D7.2.9	D7.2.8
D7.2.10	D7.2.9
D7.2.11	D7.2.10
D7.2.12	D7.2.12
D7.2.13	D7.2.11
D7.3	D7.3
D7.3.1	D7.3.1
D7.3.1.1	D7.3.1.1
D7.3.1.2	D7.3.1.2

8th Edition	9th Edition
D7.3.1.3	D7.3.1.3
D7.3.1.4	D7.3.1.4
D7.3.1.5	D7.3.1.5
D7.3.1.6	D7.3.1.6
–	D7.3.2
–	D7.3.2.1
D7.4	D7.4
D7.4.1	D7.4.1
D7.4.2	D7.4.2
D7.4.3	D7.4.3
–	D7.4.4
D7.4.4	D7.4.5
D7.4.4.1	–
D7.4.5	D7.4.6
D7.4.6	D7.4.7
D7.4.7	D7.4.8
–	D7.4.10
D7.4.8	D7.4.9
D8	D8
D8.1	D8.1
D8.1.1	D8.1.1
D8.1.2	D8.1.2
D8.1.2.1	D8.1.2.1
D8.1.2.2	D8.1.2.2
D8.1.3	D8.1.3
–	D8.1.3.1
–	D8.1.3.2
–	D8.1.3.3
–	D8.1.3.4
–	D8.1.3.5
–	D8.1.4
D8.1.3.1	D8.1.4.1
D8.1.3.2	D8.1.4.2
D8.1.3.3	D8.1.4.3

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8th Edition	9th Edition
D8.1.4	D8.1.5
D8.1.4.1	D8.1.5.1
D8.1.4.2	D8.1.5.2
D8.1.4.3	D8.1.5.3
D8.1.4.4	D8.1.5.4
D8.1.4.5	D8.1.5.5
D8.1.5	D8.1.6
D8.1.6	D8.1.7
D8.1.7	D8.1.8
D8.1.8	D8.1.9
D8.2	D8.2
D8.3	D8.3
D8.3.1	D8.3.1
D8.3.2	D8.3.2
D8.3.3	D8.3.3
D8.4	D8.4
D8.4.1	D8.4.1
D8.4.2	D8.4.2
D8.4.3	D8.4.3
D8.4.4	D8.4.4
D8.4.5	D8.4.5
D8.4.5.1	D8.4.5.1
D8.4.5.2	D8.4.5.2
D8.5	D8.5
D8.6	D8.6
D8.7	D8.7
D8.7.1	D8.7.1
D8.7.2	D8.7.2
D8.8	D8.8
D8.8.1	D8.8.1
D8.8.2	D8.8.2
D8.9	D8.9
D8.9.1	D8.9.1
D8.9.2	D8.9.2

8th Edition	9th Edition
D8.10	D8.10
D8.11	D8.11
D8.12	D8.12
D8.12.1	D8.12.1
D8.12.2	D8.12.2
D8.13	D8.13
D8.13.1	D8.13.1
D8.13.2	D8.13.2
D8.14	D8.14
D8.15	D8.15
D9	D9
D9.1	D9.1
D9.2	D9.2
D9.2.1	D9.2.1
–	D9.2.1.1
D9.2.2	D9.2.2
D9.2.3	D9.2.3
D9.2.3.1	D9.2.3.1
D9.3	D9.3
D9.3.1	D9.3.1
D9.3.2	D9.3.2
D9.3.3	D9.3.3
D9.3.4	D9.3.4
D9.4	D9.4
D9.4.1	D9.4.1
D9.4.2	D9.4.2
D9.4.3	D9.4.3
D9.4.3.1	D9.4.3.1
D9.4.3.2	D9.4.3.2
D9.4.3.3	D9.4.3.3
D9.5	D9.5
D9.5.1	D9.5.1
D9.5.2	D9.5.2
D9.6	D9.6

8th Edition	9th Edition
D9.6.1	D9.6.1
D9.6.2	D9.6.2
D9.6.3	D9.6.3
D9.6.4	D9.6.4
D9.6.5	D9.6.5
D9.6.6	D9.7
D9.6.6.1	D9.7.1
D9.6.7	D9.6.6
D9.7	D9.8
D9.8	D9.9
D9.8.1	D9.9.1
D9.8.2	D9.9.2
D9.8.3	D9.9.3
D9.8.4	D9.9.4
D10	D10
D10.1	D10.1
D10.2	D10.2
D10.3	D10.6
–	D10.6.1
–	D10.7
D10.4	D10.3
D10.5	D10.5
D10.5.1	D10.5.1
D10.5.2	D10.5.2
D10.5.2.1	D10.5.2.1
D10.5.2.2	D10.5.2.2
D10.5.3	D10.5.3
D10.5.4	D10.5.4
D10.5.5	D10.5.5
D10.5.6	D10.5.6
D10.6	D10.4
D10.6.1	D10.4.1
D10.7	D10.9
D10.8	D10.8

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8th Edition	9th Edition
D10.9	D10.10
–	D10.11
–	D10.12
D10.10	D10.13
D11	D11
D11.1	D11.1
D11.1.1	D11.1.1
D11.1.2	D11.1.2
D11.1.2.1	D11.1.2.1
D11.1.2.2	D11.1.2.2
D11.1.2.3	D11.1.2.3
D11.1.3	D11.1.3
D11.1.3.1	D11.1.3.1
D11.1.3.2	D11.1.3.2
D11.1.4	D11.1.4
D11.1.5	–
D11.1.6	D11.1.6.2
D11.1.7	D11.1.5
D11.1.7.1	D11.1.5.1
D11.1.8	D11.1.6
D11.1.8.1	D11.1.6.1
D11.2	D11.2
D11.2.1	D11.2.1
D11.2.1.1	D11.2.1.1
D11.2.2	D11.2.2
D11.2.2.1	D11.2.2.1
D11.2.2.2	D11.2.2.2
D11.2.2.3	D11.2.2.3
D11.2.3	D11.2.3
D11.2.3.1	D11.2.3.1
D11.2.4	D11.2.4
D11.2.4.1	D11.2.4.1
D11.2.4.2	D11.2.4.2
D11.2.4.3	D11.2.4.3

8th Edition	9th Edition
D11.3	D11.3
D11.3.1	D11.3.1
D11.3.1.1	D11.3.1.1
D11.3.1.2	D11.3.1.2
D11.3.1.3	D11.3.1.3
D11.3.1.4	D11.3.1.4
D11.3.1.5	D11.3.1.5
D11.3.1.6	D11.3.1.6
D11.3.1.7	D11.3.1.7
D11.3.1.8	D11.3.1.8
D11.3.1.9	D11.3.1.9
D11.3.1.10	D11.3.1.10
D11.3.1.11	D11.3.1.11
D12	D12
D12.1	D12.1
D12.1.1	D12.1.1
D12.1.2	D12.1.2
D12.1.3	D12.1.3
D12.1.3.1	D12.1.3.1
D12.1.4	D12.1.4
D12.1.5	D12.1.5
D12.2	D12.2
D12.2.1	–
D12.2.2	D12.2.1
D12.3	D12.3
D13	D13
D13.1	D13.1
D13.1.1	D13.1.1
D13.1.2	D13.1.2
D13.1.3	D13.1.3
D13.1.4	D13.1.5
D13.1.5	D13.1.6
D13.1.6	D13.1.4
D13.1.7	D13.1.7

8th Edition	9th Edition
D13.2	D13.2
D13.3	D13.4
D13.3.1	D13.4.1
D13.3.2	D13.4.1.1
D13.3.3	D13.4.1.2
D13.3.4	D13.4.1.9 1 of 2
D13.3.5	D13.4.1.11
D13.3.6	D13.4.3
D13.3.7	D13.4.1.4
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D13.3.7.2	D13.4.1.3
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**FACT-JACIE Hematopoietic Cellular Therapy Standards Crosswalk
Edition 8 to Edition 9**

PART D: PROCESSING FACILITY STANDARDS

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Setting
the *global standard*
for high quality patient care
in cellular therapies.

About FACT

Founded in 1995, FACT establishes standards for high quality medical and laboratory practice in cellular therapies. FACT is a non-profit corporation co-founded by the International Society for Cell and Gene Therapy (ISCT) and the American Society for Transplantation and Cellular Therapy (ASTCT) for the purposes of voluntary inspection and accreditation in the field of cellular therapy.

About JACIE

Established in 1998 as a committee of the EBMT and the ISCT, JACIE develops and maintains global standards for the provision of quality clinical, collection and laboratory practice in cellular therapy. Based on these standards, JACIE offers certification to transplant and cellular therapy programmes in order to encourage health institutions and facilities to establish and maintain quality management systems impacting all aspects of their activities and to engage in continuous improvement.