COMMON STANDARDS
Accreditation Manual

THIRD EDITION 3.0

FACT
FOUNDATION FOR THE ACCREDITATION OF CELLULAR THERAPY

COMMON STANDARDS
FOR CELLULAR THERAPIES
Accreditation Manual

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NOTICE

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

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

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INTRODUCTION

This Accreditation Manual is intended to accompany the *FACT Common Standards for Cellular Therapies, Third Edition, 2022* (the Standards). The purpose is to explain the intent and rationale for specific standards, to provide examples of alternative approaches considered to be 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 listed are not requirements and are not all-inclusive.

The major objective of the *FACT Common Standards for Cellular Therapies* is to promote quality medical and laboratory practice in a broad range of cellular therapies. The scope includes clinical services administering cellular therapies, collection services responsible for the collection of cellular therapy products or cell collections used as starting material in the manufacture of a final therapeutic product, and cellular product manufacturing or processing. These Standards represent basic principles of quality in cellular therapy that can be applied to any cell source or therapeutic application throughout product development and clinical trials. In early-stage product development and early phase clinical trials, these Standards provide the quality management infrastructure to facilitate patient and data accrual to advance the therapy. Ideally, disease, discipline, or product-specific standards will be added to these foundational standards in the future through collaboration with experts in those specialties where clinical teams and products are ready for additional standardization and voluntary accreditation.

FACT Standards have always required that there be in place a comprehensive quality management program that includes personnel training, written policies and standard operating procedures, validated processes, and robust occurrence management for adverse events, errors, accidents, and complaints. Complete and accurate records must be maintained, and clinical outcomes must be evaluated and reported.

This third edition of Common Standards reflects the maturation of cellular therapy with inclusion of more and diverse products such as genetically modified products, and broadening the comprehensive quality management requirements to include specific training in good manufacturing practices appropriate to the products being collected or processed, development and review of robust written agreements with entities providing services or products, comprehensive document control, and expanded auditing requirements. Requirements for outcome analysis and data management and reporting have also been expanded. Wherever possible, terminology and quality standards have been harmonized among the various sets of FACT Standards.

In this edition, emphasis is also placed on the criticality of labeling and chain of identity / chain of custody as product manufacturing frequently involves several cooperating entities to achieve collection of the cellular starting material, manufacture of the final product, transport of the cells and products among facilities, and clinical therapy administration. Because of its value in accurate

and unambiguous identification, encoding information, and labeling of medical products of human origin, full implementation of ISBT 128 coding and labeling is required where possible.

These *FACT Common Standards for Cellular Therapies* are not intended to suffice for hematopoietic cellular therapy programs, immune effector cell therapy services, or cord blood banks. More detailed and specific standards exist for these disciplines that include the relevant requirements from this document, and FACT accreditation in these disciplines is based on the specific standards. The current editions of these more specific standards are available at www.factglobal.org:

- *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration.*
- *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration.*
- *FACT Standards for Immune Effector Cells.*

This Accreditation Manual is not intended to establish new or stricter requirements than those in the Standards. If there appears to be a discrepancy between the Standards document and the Manual document, the Standards document will prevail. In the FACT 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. An applicant must revise its practice when that practice deviates from a "shall" standard. The term "should" indicates an activity that is highly 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.

This manual is organized in the alphanumeric order of the Standards. Each standard is quoted in its entirety, followed by the 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 of compliant processes. Inspectors are not restricted to the methods for verifying compliance described in this manual; rather, this information is intended to prepare applicants for making such evidence available to the inspector. Updates may be made to this manual periodically as needed to clarify the intent of the Standards. In the event that a printed copy of this manual differs from the version posted online at www.factglobal.org, the web version prevails.

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

expressly disclaims any responsibility for setting maximum standards and further expressly disclaims any responsibility, liability, or duty to member programs, directors, staff, or program donors or patients for any such liability arising out of injury or loss to any person by the failure of member programs, directors, or staff to adhere to the Standards or related guidance.

These Standards are effective March 30, 2023. All accredited programs and facilities are expected to be in compliance with these Standards by that date.

ACCREDITATION

The basis for FACT accreditation is documented compliance with the current edition of the applicable set of Standards as determined by evaluation of the written information provided by the applicant facility and an on-site inspection. All inspections are conducted by volunteers qualified by training and experience in cellular therapy who are affiliated with an accredited or applicant facility, have completed inspector training, and have a working knowledge of FACT Standards and of their application to various aspects of the cellular therapy program.

FACT accreditation under the Common Standards is intended for programs, collection services, and laboratories whose entire functions do not include any products, services, or therapies covered by the more specific Standards. Clinical programs, collections services, and processing facilities may apply together as a single program or independently as providers of specific services. Accredited clinical programs are expected to utilize products collected and processed by facilities that meet FACT Standards. Collection services are expected to use processing facilities that meet FACT Standards but may provide collection services for accredited and/or non-accredited clinical programs. Processing facilities may provide services for accredited and/or non-accredited collections services and clinical programs.

Eligibility for FACT accreditation under the Common Standards is determined by the FACT Board of Directors, which reviews each application for accreditation individually. As eligibility requirements become standardized, details will be listed on the FACT website at www.factglobal.org.

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TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

PART A

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PART A: TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

A1 TERMINOLOGY

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

The phrase, "policies and Standard Operating Procedures," is used for ease of reading. When used as 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, these Standards shall be followed.

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

A2.3 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 organization.

A3 ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

AABB	Association for the Advancement of Blood and Biotherapies
AAP	American Academy of Pediatrics
ABO	Major human blood group including erythrocyte antigens, A, B, O
AC	Accompany
ACGME	Accreditation Council for Graduate Medical Education
AF	Affix
Anti-	Antibody to the antigen designated
APBMT	Asia-Pacific Blood and Marrow Transplantation Group
APP	Advanced Practice Provider/Professional
ASHI	American Society for Histocompatibility and Immunogenetics
ASTCT	American Society for Transplantation and Cellular Therapy
AT	Attached
BLA	Biologics License Application
BMT	Bone Marrow Transplant
BSA	Body surface area
CAP	College of American Pathologists

CAPA	Corrective and Preventive Action
CAR	Chimeric antigen receptor
CAR-T	Chimeric antigen receptor T cells
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIBMTR	Center for International Blood and Marrow Transplant Research
CIDR	Cellular Immunotherapy Data Resource
CJD	Creutzfeldt-Jakob Disease
CLIA	Clinical Laboratory Improvement Amendments
CME	Continuing Medical Education
CMV	Cytomegalovirus
COA	Certificate of Analysis
CPD	Continuing Professional Development
CTCAE	Common Terminology Criteria for Adverse Events
CTCLAG	Cellular Therapy Coding and Labeling Advisory Group
CV	Curriculum vitae
DIN	Donation identification number
DLI	Donor lymphocyte infusion
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EBMT	European Society for Blood and Marrow Transplantation
EFI	European Federation for Immunogenetics
EMA	European Medicines Agency
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	U.S. Food and Drug Administration
GMP	Good Manufacturing Practice
GRID	Global Registry Identifier for Donors
GTP	Good Tissue Practice
GVHD	Graft versus host disease
GxP	Good practice
HCT	Hematopoietic Cellular Therapy
HCT/Ps	Human cells, tissues, and cellular and tissue-based products
HEPA	High Efficiency Particulate Air
HIPAA	Health Insurance Portability and Accountability Act
HLA	Human leukocyte antigen
HPC	Hematopoietic progenitor cell
HTLV	Human T-Lymphotropic Virus
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IEC	Immune Effector Cell
IND	Investigational New Drug
IRB	Institutional Review Board
ISCT	International Society for Cell and Gene Therapy
JACIE	Joint Accreditation Committee – ISCT and EBMT
MNC	Mononuclear cell
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSC	Mesenchymal stromal cell or mesenchymal stem cell
NIH	National Institutes of Health
NMDP	National Marrow Donor Program

QM	Quality Management
OSHA	Occupational Safety and Health Administration
RAC	Recombinant DNA Advisory Committee
RBC	Red blood cell
REC	Research Ethics Committee
REMS	Risk Evaluation and Mitigation Strategies
Rh	Rhesus systems of human red blood cell antigens; used in this document to refer to the Rh (D) antigen only, unless otherwise specified
RMP	Risk Management Plan
SARS	Severe acute respiratory syndrome
SCTOD	Stem Cell Therapeutic Outcomes Database
SEC	Single European Code
SOP	Standard Operating Procedure
U.S.	United States
WHO	World Health Organization
WMDA	World Marrow Donor Association

A4 DEFINITIONS

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

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

Advanced practice provider/professional (APP): Physician Assistant, Nurse Practitioner, or other licensed Advanced Practitioner authorized to provide primary patient care with physician oversight as defined by Applicable Law. 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 biologic relationship between genetically distinct individuals of the same species.

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, or administration and that is relevant to the location or activities of the organization.

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

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

Attending physician: The physician who is responsible for the delivery and oversight of care provided to cellular therapy recipients and who meets all qualifications defined in these Standards. For purposes of these Standards, this does not include physicians who do not provide cellular therapy services.

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, which is defined by a specific monoclonal antibody (anti-CD34) using the standardized cluster of differentiation (CD) terminology.

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

Cellular therapy product: Somatic cell-based product (e.g., HPC, mononuclear cells, cord blood cells, immune effector cells, genetically modified cells, and 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 cellular therapy, chimerism generally refers to the presence of allogeneic donor cells in the recipient.

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

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

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. An investigator's brochure or package insert may contain this information.

Clinical Program: An integrated medical team providing cellular therapy services and 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.

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

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

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

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

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 collected from placental and umbilical cord blood vessels after the umbilical cord has been clamped.

Corrective action: Action taken to eliminate the 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 transportation 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: 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 established course of action or accepted practice.

Planned deviation: Allowed to occur with documented prior approval as the best course of action when adherence to the established course or accepted practice is 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.

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: A therapy in which lymphocytes from the original cellular therapy product donor are given to a recipient who has received a hematopoietic progenitor cell 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 disease agents.

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 Eurocode International Blood Labeling Systems (IBLS).

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.

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 never been cryopreserved.

Genetically modified cell: A cell that has been modified by genetic transfer 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). Cellular therapy products that are more-than-minimally manipulated, are allogeneic and obtained from donors other than first- or second-degree relatives, or that are used for non-homologous purposes are examples of products controlled under GMP regulations. Similar requirements are delineated by the European Union as EU-GMP. Other countries such as the United Kingdom, Australia, Canada, and Singapore have equally well-developed systems of regulations.

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.

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: 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).

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

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

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

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

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

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 monitory 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 human blood, cell, tissue, and organ products 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 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 (ATMP) 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, or the screening and testing of a cell or tissue donor.

Marrow collection: Harvest of nucleated cells from the bone marrow cavity for 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 recipient: An individual receiving cellular therapy for the first time in the Clinical Program whether or not that individual was previously treated by that Clinical Program.

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 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 Food and Drug Administration, 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, 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 procedure used to prepare a patient for cellular therapy administration (e.g., chemotherapy, monoclonal antibody therapy, radiation therapy).

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

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

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

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

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

Processing: All aspects of manipulation, labeling, cryopreservation, and packaging of cellular therapy products regardless of source, including 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 a 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.

Product name: The ISBT 128 Cellular Therapy Class product database name and definition (format: type of cells, comma, source of cells) for products collected from marrow, peripheral blood, cord blood, or other tissue.

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

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

For the most current list of definitions, see www.isbt128.org/standard-terminology .

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

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

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

Quality Unit: Personnel with responsibility for and authority to approve or reject in-process materials, cellular therapy product containers, packaging material, labeling, and cellular therapy products.

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

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

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 have been met before a cellular therapy product may leave the control of the Collection or Processing Facility.

Responsible person: A person who is authorized to perform designated functions for which he or she is trained and qualified.

Risk management plan: A document that describes the current knowledge about the safety and efficacy of a cellular therapy product and the measures to be undertaken to identify, monitor, prevent, or minimize risk associated with the use of that product.

Risk Evaluation and Mitigation Strategy (REMS): A drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

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

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

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

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 Common Standards for Cellular Therapies*, which may be referred to herein as "these 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.

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 backward 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 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.

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CLINICAL PROGRAM STANDARDS

PART B

PART B: CLINICAL PROGRAM STANDARDS

B1: GENERAL

STANDARD:

B1.1 The Clinical Program shall consist of an integrated medical team with a Clinical Program Director and a defined location(s).

Explanation:

This standard is the definition of a Clinical Program, an entity that can be inspected and independently accredited. Different clinical sites that make up a single program must be within a defined location(s) 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 (EMR) 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 alone meets the criteria detailed in these 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. Different clinical sites ideally should be no more than one hour traveling distance in each direction, and they should exist within a single metropolitan area. Advancement in technology and travel may allow for more 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) 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 (QM) Program and meeting minutes demonstrating collaboration between sites on all aspects of the program at defined and regular intervals.

STANDARD:

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

Explanation:

The applicant for accreditation shall define the services and therapies included within the Clinical Program.

Examples(s):
Accreditation of the Clinical Program is all-inclusive of the cellular therapies administered.

STANDARD:

B1.1.2 *The Clinical Program shall demonstrate common staff training, protocols, Standard Operating Procedures, quality management systems, clinical outcome analysis, 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 with different directors or outside a defined network, joining together for the purpose of meeting criteria to qualify as a Clinical Program, do not fulfill the intent of these 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 these Standards. The FACT 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 individual must be named as the corresponding director for the accreditation activities and interaction with FACT.

Evidence:
The Clinical Program must demonstrate evidence that there is sufficient integration of activities to qualify as a single Clinical Program. 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 clinical protocols, whether local, regional, national, or international. This could include clinical treatment protocols, high-dose therapy and other preparative regimens, protocols for the management of fever, prophylactic antibiotics, antiviral and antifungal prophylaxis, and administration guidelines for medications or blood components.
- Common Standard Operating Procedures, forms, flow sheets, and patient databases would typically be found. This would include all procedures specifically required by these Standards.
- Regular interaction. Regular interaction means 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 for 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 that attendance is documented.

- A common database of all patients treated by the Clinical Program, including a single statistical support group and/or data management group.

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.
- Cancer networks.
- Any other robust organizational structure involving 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 treats patients in two clinical care areas with integrated nursing staff and physician coverage is considered one site.

STANDARD:

B1.2 The Clinical Program shall verify that cell collection procedures and processing facilities meet FACT Standards.

Explanation:
It is not the intent of this standard to require clinical facilities, collection activities, and processing facilities to be housed in one location. Various structures are acceptable for differing Clinical Programs. Provided that each component of the process independently meets these Standards as stated for the activities and functions it performs, the intent of this standard is met.

As Clinical Programs become involved with new approaches to standard-of-care cellular therapies or novel cellular therapies, they will likely see an increase in interactions with third parties who have Investigational Device Exemptions (IDEs), Investigational New Drug (IND) applications, or market approval from the United States (U.S.) Food and Drug Administration (FDA) or other equivalent regulatory pathways. While useful, such regulatory approval does not guarantee compliance with these Standards. Clinical Programs, and their collection activities and processing facilities that perform tasks related to the cellular therapy product, may only briefly or simply handle the product but they must meet these Standards while doing so.

Evidence:
If the site uses an external collection or processing facility, documentation of interactions and written agreements between the Clinical Program and that collection or processing facility must be available to the inspector.

Collection and processing facilities that are external to the Clinical Program must undergo the inspection and accreditation process to demonstrate compliance with these Standards. They may choose to be formally accredited or not; however, they still must follow the FACT process, submit evidence of compliance with Standards, undergo 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 collection activities and processing facilities meet these Standards.

Example(s):
There are several ways FACT accreditation may be sought, such as:

- A Collection Facility may be accredited independently, or in conjunction with a Clinical Program and a Processing Facility.
- 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.
- There may not be a separate facility where collections occur, rather the activities of collection are overseen by the Clinical Program or 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.

While it is required that cell collection activities meet these Standards, it is understood that the Clinical Program may not always know or be able to control where an unrelated donor product, procured through the National Marrow Donor Program (NMDP) or other 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.

When a cellular therapy product is manufactured by a third party, the Clinical Program may be responsible for securing collection of the source material or preparing the product for administration. If these responsibilities are designated to the Clinical Program in written agreements, the following examples would require compliance with Part C or Part D of these 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 starting material under the oversight of the Clinical Program.
- Temporary storage of the product in the Processing Facility and distribution to the clinical unit.

- Thawing and other needed manipulations of the product before administration to the recipient.

In the case of multi-center trials or centralized manufacturing, the Clinical Program may have limited control over the participating collection and processing facilities; however, it is still responsible for performing some qualification of those entities to verify that tasks are performed in a reputable manner with oversight by the appropriate regulatory agency (such as the FDA). This could be accomplished by documented verification of an approved IND application, post-market or licensure approval, or a questionnaire outlining established procedures of the third-party (see the FACT website for an example).

STANDARD:

B1.2.1 If clinical personnel or an intermediary facility receives cellular therapy products directly from a third-party provider, the following responsibilities shall be defined by a written agreement:

Explanation:

This standard applies to cellular therapy products that are manufactured by a third-party and received directly by the Clinical Program or routed through an intermediary facility (e.g., blood bank, tissue bank, or hospital pharmacy) rather than the usual affiliated Processing Facility. A written agreement between the third-party provider and the Clinical Program (and the intermediary facility, if applicable) must cover any receiving or storing of the cellular therapy product. Communication with manufacturers is critical to the safety, efficacy, and quality of the cellular therapy product, and the Clinical Program is responsible for handling products according to these Standards.

The level of participation of the Clinical Program in manufacturing cellular therapy products such as Immune Effector Cells (IECs) varies. Regardless of where the product is collected or manufactured, responsibilities must be clearly defined. If the program is utilizing licensed or research products, the program is responsible for verifying the manufacturer responsible for the entire manufacturing process (e.g., a commercial manufacturer) possesses an approved IND or Biologics License Application (BLA).

STANDARD:

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

Explanation:

Chain of custody documentation should include date, time, and responsible party for each step in distribution and receipt, storage, and release for administration. The 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 blood bank, tissue bank, or pharmacy) should have a designated space with suitable equipment for receiving and storing cellular therapy products. To prevent mix-ups, two professionals should confirm product identity. Before administration to a recipient, the product must be compared against the written physician order and patient identity.

Evidence:
Coordination among the program, the manufacturer, the blood bank, the tissue bank, or the pharmacy must be readily apparent to the inspector via written responsibilities and ongoing quality management documentation.

Example(s):
Programs may develop and utilize specific forms to accompany a cellular therapy product from collection to clinical administration that includes all chain of custody information for transport, shipping, manufacturing, and storage. Alternatively, manufacturers or transportation specialists may provide such documentation in other formats that could be assembled and maintained. The key elements of date, time, and responsible person must be included. A product's unique identifier is useful to link these documents.

STANDARD:

B1.2.1.2 Cellular therapy product storage and distribution.

B1.2.1.3 Verification of cellular therapy product identity.

B1.2.1.4 Review and verification of product specifications provided by the manufacturer, if applicable.

Explanation:
When the cellular therapy product is provided to a clinical site, there should be product specifications that would include cell count, cell viability, and sterility (microbiological culture and endotoxin testing). Examples of other specifications for cells that have a transduced vector would be efficiency of transduction and absence of free viral vector.

STANDARD:

B1.2.1.5 Readily available access to a summary of documents used to determine allogeneic donor eligibility.

B1.2.1.6 Documented evidence of allogeneic donor eligibility screening and testing in accordance with Applicable Law.

Evidence:
Coordination among the Clinical Program, the manufacturer, the blood bank, the tissue bank, or the pharmacy must be readily apparent to the inspector via written responsibilities, SOPs, forms, and ongoing quality management documentation.

STANDARD:

B1.2.2 If the Clinical Program is responsible for these activities, Parts C and D apply.

Explanation:
The standards specified in sections C and D of these Standards apply to the Clinical Program when the activities specified in B1.2.1 are performed by the Clinical Program.

STANDARD:

B1.3 The Clinical Program shall abide by Applicable Law.

Explanation:
FACT is a voluntary inspection and accreditation program founded by the American Society for Transplantation and Cellular Therapy (ASTCT) and the International Society for Cell and Gene Therapy (ISCT). Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with these 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 program may apply; for example, when a program receives cellular therapy products either to or from outside of its immediate jurisdiction.

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

Evidence:
Current certificates, permits, or licenses will demonstrate which areas of a facility have been authorized by other organizations or governmental authorities. 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 these Standards will require pre-inspection information identifying prevailing governmental authorities.

Example(s):
In the U.S., minimally manipulated cellular therapy products from first- or second-degree related donors are regulated under the 21 CFR (Code of Federal Regulations) 1271 Good Tissue Practices (GTP) regulations and section 361 of the Public Health Service Act. 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 (e.g., does not perform the same function in the recipient as in the donor) is regulated as a drug, device, or biologic product under section 351 of the Public Health Service Act and other applicable regulations in title 21 of the CFR, including Good Manufacturing Practices (GMPs).

STANDARD:

B1.3.1 *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 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 of the American Osteopathic Association, or Det Norske Veritas Healthcare, Inc. Alternatively, U.S. Clinical Programs may choose to be directly inspected by the Centers for Medicare & Medicaid Services. In addition, U.S. Clinical Programs must be licensed as required by Applicable Law.

Other examples of verified compliance with regulations include current FDA registration, acceptable FDA audit reports, state licensure, 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).

STANDARD:

B1.4 *The Clinical Program shall have a designated team that includes a Clinical Program Director, a Quality Manager, and a minimum of one (1) additional physician trained or experienced in cellular therapy. 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 cellular therapy patients. 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 patients. 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 cellular therapy 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 and develops a new Clinical Program, that new program must have been in place at least 12 months, and the team must have performed a minimum number of cellular therapy treatments 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 office within 90 days of the change and may require reinspection in accordance with FACT policies. The FACT 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, provided that 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 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):
If the collection or processing services were contracted to a new facility, reinspection would be required unless the new facility was already independently FACT accredited or had been inspected and determined to meet these Standards.

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

STANDARD:

B1.5 *The Clinical Program shall have administered cellular therapy products to a minimum of five (5) new recipients during the twelve (12) month period immediately preceding accreditation and shall administer to a minimum average of five (5) new recipients per year within the accreditation cycle.*

Explanation:
Clinical Programs treating patients with cellular therapy products in clinical trials using investigational products manufactured under IND may also be administering licensed products according to clinical indications. The stand-alone cellular therapy program must meet the required number of five new patients per 12-month period to be eligible for accreditation. To be eligible for initial accreditation for cellular therapies in conjunction with an HPC transplantation program, the Clinical Program must have treated at least one such patient. In addition, all other standards applicable to these cells must be met, including any risk evaluation and mitigation strategies (REMS) designated by the manufacturer.

Evidence:
Recipient logs with cellular therapy product type and regulatory status will be submitted as part of the application for accreditation. 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 recipient education.

Inspectors will select at least two recipients of commercial or investigational product to follow the chain of identity and 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):
REMS may be specifically defined by the manufacturer. These include detailed procedures for provider education, patient education and monitoring, adverse event management, patient discharge instructions, wallet cards that describe steps to take in the event of certain symptoms, and reporting of outcomes to manufacturers.

B2: CLINICAL UNIT

STANDARD:

B2.1 *A clinical unit of adequate space, design, and location shall be identified for the treatment of patients needing inpatient or outpatient care related to the cellular therapy.*

Explanation:
Clinical unit facilities vary among centers based on a number of factors, including the number and type (autologous or allogeneic) of cellular therapy patients treated, the patient case mix, the cell source, epidemiological factors influencing the prevalence of opportunistic infections, microbial resistance, increasing use of ambulatory facilities, and economic considerations.

Evidence:
Clinical Programs must submit a floor plan of the inpatient and outpatient facilities 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 inpatient unit during the on-site inspection. Because different patients have different infection control needs, the program must have policies and SOPs that define infection control requirements based upon differing patient conditions and room configurations. The type of air handling should be documentable from a facility management office. An SOP detailing alternatives in case there is a shortage of isolation rooms; steps for preventing and controlling specific health care-associated infections, such as methicillin-resistant *Staphylococcus aureus* (*MRSA), C. Difficile,* and community respiratory virus infections; and procedures for monitoring airborne infections will provide evidence of compliance.

Signs posted around the clinical unit and the behavior of the staff consistent with expectations for the type of infection control described in the policies and procedures demonstrate compliance with this standard. 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). 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 these Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT accreditation policies, which are available on the FACT website. The program is expected to submit a description and floor plans of the new facility, QM documents, and an expected relocation date. Most relocations will be assessed during regularly scheduled inspections or interim audits; however, if there are any concerns with the information submitted by the facility, a relocation inspection may be necessary.

Example(s):
HEPA filtration with positive pressure is recommended for patients with compromised immune systems who are at high-risk for infection but is not required for every unit. Single patient rooms should be located on a patient care unit where infection control policies can be implemented. Portable, industrial-grade HEPA filters may be available to accommodate vulnerable patients in case of a shortage of rooms.

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.

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

STANDARD:

B2.2 *There shall be designated inpatient and outpatient care areas that protect the patient from transmission of infectious agents and allow, as necessary, for appropriate patient isolation; confidential examination and evaluation; and preparation and administration of intravenous fluids, medications, blood products, and cellular therapy products.*

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 the facilities reasonably protect recipients 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 cellular therapy product treatment in an ambulatory setting and the admissions 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:
B2.3 The Clinical Program shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operation.

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:
B2.4 There shall be 24-hour access to care for assessment and treatment of potential cellular therapy complications.

B2.4.1 There shall be provisions for prompt evaluation and treatment by a physician who specializes in the therapeutic disease area available on a 24-hour basis.

Explanation:
An attending physician must be always available 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. In addition, physicians specializing in the therapeutic disease areas being treated with cellular therapy must also be available.

Evidence:
An on-call schedule 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. Such schedules should include therapeutic disease area specialists.

Example(s):
Numerous post-cellular therapy 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 to contact emergency medical services if needed for prompt care (e.g., 911 in the U.S.). Likewise, patients suffering from complications due to the therapeutic disease itself may require emergency treatment.

STANDARD:

B2.4.2 There shall be a pharmacy providing 24-hour availability of medications needed for the care of cellular therapy patients.

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 available on-site or on-call.

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 cytokine release syndrome but is not routinely available in 24-hour pharmacies. Clinical Programs must consult with their pharmacies to develop a plan for immediate access to emergency medications.

STANDARD:

B2.5 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 intensive care unit (ICU) or equivalent coverage 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 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 plan should address specific needs of recipients, such as the need for isolation protocols for immunocompromised patients, transfer to designated units related to clinical indications, and cellular therapy-specific discharge plans.

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 these 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 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 spread. For example, a busy trauma center may be inadequate to provide these safeguards.

STANDARD:

B2.5.1 *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 clinical unit. Facility guidelines may allow flexibility depending on patient characteristics. There should be quality parameters regarding the transfer, such as how quickly the patient 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 cellular therapy recipients and how these needs are met in the unit.

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 (common in recipients of CAR-T cellular therapy).

STANDARD:

B2.6 *There shall be attending physician oversight if general medical physicians or APPs provide care to cellular therapy patients. The scope of responsibility of general medical physicians or APPs shall be defined.*

Explanation:

There must always be an attending physician available to evaluate and treat cellular therapy patients, whether available on-site or on-call. This standard applies to hospitalists, general internists, physicians in other specialties, physician assistants, advanced nurse practitioners, or other advanced practice providers. It is acceptable for these general practitioners to provide patient care; however, the attending physician is 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. Providers providing coverage must have a clear understanding of when the attending physician must be notified and how to reach that physician.

Evidence:

There must be guidelines that describe inpatient, outpatient and afterhours care, including when and under what conditions general medicine physicians must contact the attending physician. 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:

B2.7 *Clinical Programs shall use human leukocyte antigen (HLA) testing laboratories that are capable of carrying out DNA-based intermediate and high resolution HLA typing and are appropriately accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), European Federation for Immunogenetics (EFI), College of American Pathologists (CAP), or other accrediting organizations providing histocompatibility services appropriate for the types of cellular therapy patients.*

Explanation:

Allogeneic cellular therapies may not require HLA matching between donor and recipient or may require only limited matching depending upon the nature of the cellular therapy product. The need for and level of HLA matching should be known before products are in clinical trials. If HLA matching is required, that testing must be performed by appropriately accredited laboratories.

ASHI accreditation consists of two parts: technologies and methods and area of accreditation. The HLA testing laboratory must be accredited for the appropriate technologies and methods. The area of accreditation depends on the relationship between the Clinical Program and the HLA testing laboratory, and the HLA expertise available at the Clinical Program.

In addition to ASHI, EFI, and CAP, other HLA typing laboratory accrediting organizations may be deemed appropriate based on standards that adequately address the cellular therapy and on accreditation processes that utilize qualified inspectors and a consistent review procedure. The FACT Guidelines for Histocompatibility Typing Standards and Accreditation Programs will be used to evaluate accrediting organizations that wish to be considered appropriate for cellular therapy. Accrediting organizations must demonstrate that they meet the guidelines. 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. The Clinical Program must describe the role the HLA testing laboratory fulfills in donor selection and demonstrate adequate HLA expertise in the program.

STANDARD:

B2.8 *Testing to monitor chimerism shall be performed in laboratories accredited for the techniques used.*

Explanation:
Chimerism is the coexistence of cells of more than one genotype in a single individual. The genotype of the cellular therapy product may differ from the recipient due to genetic modification or the cells may be allogeneic. Whether the infused cells are intended to permanently engraft or persist transiently, the need to detect the presence of cells after infusion should be known prior to the initiation of the therapy.

The genetic markers and laboratory methods used to test for and monitor chimerism are variable, depending on the type of cell being assessed and the antigens that provide informative genetic markers. In hematopoietic cell transplantation, presence of trilineage engraftment may be demonstrated using a variety of tests and target antigens or genetic sequences. Erythrocyte antigens, including ABO, Rhesus, MN, Kidd, Kell, and others have been used for analysis of engraftment. For assessment of myeloid and lymphoid engraftment, additional techniques such as cytogenetic analysis of metaphase chromosomes are useful, particularly when there is a gender disparity between donor and recipient. Molecular cytogenetic techniques involving in situ hybridization, polymerase chain reaction, and assessment of certain core DNA sequences including short tandem repeat sequences have demonstrated informative difference in virtually

all allogeneic donor/recipient pairs. Molecular techniques may vary in accuracy and sensitivity, and laboratories should state the level of sensitivity in test reports.

Many cellular therapies expected to be accredited under these Common Standards are not intended to coexist long term with the cells of the recipient. However, a short-term period of chimerism may be expected. For recipients of autologous CAR-T cells, the detection of the transduced CAR receptor may serve as an indication of chimerism. A rapid expansion of infused CAR-T cells may be associated with a positive clinical outcome.

The requirement of this standard is that whatever test is used monitor chimerism be performed in an appropriately licensed, accredited, or certified laboratory for that test. This ensures that the proper controls and validations were employed in the establishment of the testing methodology and that proficiency testing is routinely performed in that laboratory.

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 SOPs that guide clinical interpretations of chimerism monitoring test data.

Example(s):
ASHI, EFI, CAP, and other organizations provide external laboratory accreditation and proficiency testing. Laboratories are not required to be specifically accredited for chimerism testing but must be accredited for the techniques used to determine chimerism and must participate in an external proficiency testing program for the techniques.

STANDARD:

B2.9 *The Clinical Program shall be operated in a manner designed to minimize risks to the health and safety of all individuals.*

B2.10 *The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, radiological, electrical, or fire hazards.*

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; or chemical, biological, or radiological hazard), 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/or

biohazard waste disposal procedures that are unique to the program must be covered in the program's SOP Manual.

Safety training, including universal precautions for handling blood and body fluids, 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/or 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. This includes those exposed to cellular therapy products. The type of exposure that may be encountered will determine the appropriate suitable 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.

If genetically modified cellular therapy products are administered by the Clinical Program, the Institutional Biosafety Committee, 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 how cellular therapy products are handled and discarded and compare his/her observations with the written protocols. 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 the location of hard copies or how to access the information in the event of a computer failure or down time.

The Clinical Program may keep a condensed or summarized hard copy of the institutional safety manual 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 managing patients with a known communicable disease.

See also "Standard" precautions per the Centers for Disease Control (CDC) in the U.S.

STANDARD:

B2.11 *All waste generated by Clinical Program activities shall be disposed of in a manner that minimizes 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 potential toxins. Hazardous waste generated by the Clinical Program's activities includes a broad range of materials, including used supplies, sharps, chemicals, radioactive material, viral vectors, genetically modified cellular materials, 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 institutional Biosafety Committee, and potentially third-party manufacturers, will have specific procedures for waste disposal that must be followed. Investigator and staff training must include these procedures.

General waste that may contains confidential information, such as paper, CDs, or disks, should be stored in a secured container before disposal and ultimately shredded or destroyed.

Evidence:

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

Example(s):

Contaminated materials may be typically discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, or, in some locations, using a sanitary landfill. Sharps (e.g., needles, blades) should be considered highly hazardous health care waste and placed for disposal in puncture proof containers whether or not they are contaminated.

Chemicals such as cytostatic drugs used in purging procedures, shall be discarded in accordance with Applicable Law.

STANDARD:

B2.12 Personal protective equipment, including gloves and protective clothing, shall be used while handling biological specimens. Such protective equipment shall not be worn outside the work area.

Explanation:

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

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, shall have experience in cellular therapy, and shall have achieved specialist certification in at least one applicable therapeutic disease area. A physician trained prior to requirements for specialty training may serve as the Clinical Program Director if he/she has documented experience in the applicable therapeutic disease areas extending over ten (10) years.

Explanation:

The Clinical Program Director is the individual designated to fulfill the tasks and responsibilities outlined in B3.1 and its sub-standards. It is not necessary to create a position solely to comply with these Standards. An individual with other roles at an institution may serve as the director provided, he/she directs adequate attention to the program, actively participates, and fulfills the responsibilities.

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

The Clinical Program Director must have been specialist-certified in at least one area applicable to the diseases being treated with cellular therapies. Specialist certification may have been obtained from jurisdictions other than where the Clinical Program Director practices. Where physicians received training outside the EU or North America, the Accreditation Committee or Board of Directors will assess their documentation of training to determine appropriateness.

Maintenance of specialty and sub-specialty certification requires time, effort, and financial resources, and the value of maintaining certification has become controversial (NEJM 372(2):104-108; 2015). Maintenance of specialist certification is recommended; however, it is not required for the Clinical Program Director or for attending physicians. If a significant portion of a director's duties includes the direct care of cellular therapy patients, he/she will have the experience to maintain and continuously update the knowledge and skills required.

Evidence:
To fulfill this standard, the Clinical Program Director must provide a copy of his or her current medical license and specialist certification. Since documentation of the medical degree is required to obtain a medical license, the license will be considered documentation that the director is a physician.

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

STANDARD:

B3.1.2 *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 patients in the applicable therapeutic disease areas throughout the continuum of care.*

Explanation:
In addition to having achieved specialist certification, the Clinical Program Director must have two (2) years of experience providing direct patient care in 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 cellular therapy patients can be counted towards the required two 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, including an estimate of the actual number of weeks committed to this experience, an estimate of the number of patients the applicant has managed, and whether patient management included both inpatient and outpatient care.

STANDARD:

B3.1.3 The Clinical Program Director shall be responsible for administrative and clinical operations, including compliance with these Standards and Applicable Law.

B3.1.4 The Clinical Program Director shall be responsible for all elements of the design of the Clinical Program including quality management, the selection and care of recipients and donors, and cell collection and processing, whether internal or contracted services.

Explanation:

This standard is not intended to preclude the delegation of some of the duties associated with the operation of the Clinical Program to other qualified individuals. Because cell collection and processing services play a major role in recipient outcomes, the director must monitor whether these services meet these Standards and contractual requirements (see B4). The final responsibility for all delegated duties remains with the director.

"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 each FACT standard.

Example(s):

Individual physicians may accept patients or donors for entry into the Clinical Program according to institutional policies and procedures. It is the responsibility of the Clinical Program Director to ensure such policies exist and are followed.

STANDARD:

B3.1.5 The Clinical Program Director shall have oversight of the medical care provided by all members of the Clinical Program.

B3.1.5.1 The Clinical Program Director shall be responsible for defining physician responsibilities and verifying adequate training and education for all members of the Clinical Program.

B3.1.5.2 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 director is responsible for reviewing their knowledge and skills. Provisions should be made for verification of knowledge, skills, and competence of new staff within the first year of employment.

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 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).

Physicians not directly affiliated with the cellular therapy program may be credentialed through their own departments or hospital.

Evidence:
The inspector should review the organizational chart to determine what positions are included as part of the Clinical Program, and how appropriate training and competency are reviewed for each position (e.g., record review, direct teaching).

Verification of competence may be documented in various ways, such as through evidence of Continuing Medical Education (CME), Continuing Professional Development (CPD), annual faculty evaluations (in the case of academic programs), or minutes of meetings in which the medical care of donors and recipients was specifically addressed.

Example(s):
The annual verification of competency does not need to include all knowledge and skills required of members of the Clinical Program every year. A rotational schedule could be used that results in all knowledge and skills being verified within an accreditation cycle.

STANDARD:

B3.1.6 The Clinical Program Director shall participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy.

B3.1.6.1 Continuing education shall include, but is not limited to, activities related to the specific cellular therapy administered within the Clinical Program.

Explanation:
The field of cellular therapy continues to evolve rapidly. Clinical Program Directors must participate regularly in educational activities related to cellular therapy, including types of therapies routinely provided and other areas 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 his/her judgment to determine if 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.

To assess the appropriateness of the amount and type of continuing education in which the Clinical Program Director participated, 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, meeting, grand round).
- Topic of activity (e.g., hematology, cellular therapy).
- 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. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Example(s):
Examples of acceptable continuing education include topics specific to cellular therapy or diseases in which cellular therapy is a therapeutic option.

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.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or on-line 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 offers an Online Learning center that hosts recordings from Its many educational events. These can be accessed at https://learn.astct.org.

A downloadable Educational Activities form is available on the FACT website at

https://www.factglobal.org/education-and-resources/general/hematopoietic-cellular-therapy-library/. The use of this form is not required but can be used to document compliance with continuing education requirements.

STANDARD:

B3.2 ATTENDING PHYSICIANS

B3.2.1 Attending physicians shall be appropriately licensed to practice medicine in the jurisdiction of the Clinical Program and should be specialist certified or trained in the applicable therapeutic disease areas.

B3.2.1.1 There shall be at least one (1) attending physician who has achieved specialist certification in each applicable therapeutic disease area.

Explanation:

This standard is applicable for clinical attending physicians other than the Clinical Program Director and is parallel to the requirements for the director. The minimum requirement is for one attending physician to be specialist trained. 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 team must have at least two physicians).

Evidence:

A copy of the current medical license or non-U.S. equivalent of each attending physician is required to document licensure in the state, province, or country in which the Clinical Program is located. 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 is required.

Example(s):

Specialist certification in the U.S. means sub-specialty certification by the American Board of Medical Specialties, including physicians who are eligible to complete specialist Board examinations. Specialist 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 all of the formal training required by the particular Board and all other necessary requirements to be permitted to take the certification examination of that Board the next time it is offered.

STANDARD:

B3.2.2 *Attending physicians shall each have had a minimum of one year of supervised training in the management of patients in the applicable therapeutic disease area throughout the continuum of care.*

Explanation:

Attending physicians must have written confirmation of their training or experience and documentation of competency. Specialist certification is fulfillment of the training requirement. Other documentation could include a letter from the directors of the programs, departments, or institutions where this training or experience occurred, including an estimate of the number of patients the applicant has managed, whether patient management included both inpatient and outpatient care, 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 B3.3.1 - B3.3.3.

Competency in each of the areas must be documented for each attending physician by the Clinical Program Director. Clinical Programs do not have to assess competencies for all items listed in B3.3 each year; however, some competency assessment must be documented annually, and each area should be addressed at least once during each accreditation cycle.

Evidence:

Attending physicians will have documented specific training and competency evaluations submitted as part of the accreditation application. Documentation of competency may be a letter or checklist of competencies. Evaluation of competency may include a description of the number of times the physician has handled the particular situation, a self-assessment, preparation of SOPs, teaching sessions, discussion with the Clinical Program Director, or publication of a relevant article.

Evidence of competency may be reviewed by the inspector in advance and on-site by interview and observation.

Example(s):

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

STANDARD:

B3.2.3 *Clinical Programs treating pediatric recipients or donors shall have a team trained in the management of pediatric patients.*

B3.2.4 Clinical Programs treating adult recipients or donors shall have a team trained in the management of adult patients.

Explanation:
Teams treating children must include at least one attending physician who has experience and expertise in pediatrics, although specialist certification in pediatrics is not required. Pediatric expertise and experience are also required among the advanced practice providers and nursing, pharmacy, and social services staff.

STANDARD:

B3.2.5 Attending physicians shall participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy.

B3.2.5.1 Continuing education shall include, but is not limited to, activities related to the specific cellular therapy administered within the Clinical Program.

Explanation:
The field of cellular therapy continues to evolve rapidly. Clinical attending physicians must participate regularly in educational activities related to cellular therapy, including the types of therapies 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 attending physicians periodically, for example, as part of the annual performance review required in B4.

Examples of acceptable forms of continuing education are included 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 his/her judgment to determine whether 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.

To assess the appropriateness of the amount and type of continuing education in which the attending physician participated, 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, meeting, grand round).
- Topic of activity (e.g., hematology, cellular therapy).
- 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. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Example(s):
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.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or on-line tutorial.
- Review of article 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 offers an Online Learning center that hosts recordings from its many educational events. These can be accessed at https://learn.astct.org.

A downloadable Educational Activities form is available on the FACT website at https://www.factglobal.org/education-and-resources/general/hematopoietic-cellular-therapy-library/. The use of this form is not required but can be used to document compliance with continuing education requirements.

STANDARD:

B3.3 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

B3.3.1 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:
Clinical Program Directors and attending physicians must have written confirmation of their training. The minimum of one year of supervised training is a cumulative requirement; the standard does not require a year of continuous training.

Evidence:
Documentation could include a letter from the directors of the programs, departments, or institutions where this training occurred, including an estimate of the number of patients the physician has managed, whether patient management included both inpatient and outpatient care, and an estimate of the actual number of weeks committed to this training and/or experience. If appropriate, the letter could also document initial competency and/or knowledge (as required) in each of the subjects and procedural skills listed.

STANDARD:

B3.3.1.1 Indications for cellular therapy.

B3.3.1.2 Selection of suitable recipients and appropriate cellular therapy products.

B3.3.1.3 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.

STANDARD:

B3.3.1.4 Donor and recipient informed consent.

Explanation:
Given the experimental status of most cellular therapies accredited under these Standards, training in the process of informed consent is required. Most academic institutions have defined formats for informed consent.

STANDARD:

B3.3.1.5 Administration of cellular therapy products and anticipated complications.

Explanation:
The anticipated complications of cellular therapy product administration vary depending upon the product infused and the therapeutic indication. Indeed, at the early stage of development not all complications will be known. There should be data from preclinical studies and from the use of products similar to the one under investigation to serve as a guideline for anticipated complications.

STANDARD:

B3.3.1.6 Administration of preparative regimen.

Explanation:
The Clinical Program Director and attending physicians must be trained in preparative regimen selection and prescribing and understand the risks and benefits as they apply to an individual recipient. They are not required to administer the preparative regimen to the recipient. Not all cellular therapy protocols will require a formal preparative regimen.

STANDARD:

B3.3.1.7 Adverse events associated with cellular therapy.

Explanation:
It is difficult to anticipate adverse events caused by novel cellular therapies, but Clinical Programs must endeavor to learn about theoretical risks and experiences of others. It may be useful to attend investigator meetings hosted by pharmaceutical companies, conduct in-house training based on information provided at conferences and in medical literature, or review cases with an experienced physician.

Example:
For attending physicians at Clinical Programs administering immune effector cellular therapy products such as CAR-T cells, familiarity with management of cytokine release syndrome and neurologic toxicities is required.

STANDARD:

B3.3.1.8 Management of complications related to the administration of cellular therapy products.

B3.3.1.9 Evaluation of post-treatment cellular therapy outcomes.

B3.3.1.10 Evaluation of late effects of cellular therapy.

Explanation:
Late effects can be caused by the cellular therapy or by disease being treated. Different cellular therapies may have different considerations.

STANDARD:

B3.3.1.11 Documentation and reporting for patients on investigational protocols.

B3.3.1.12 Reporting responsibilities for adverse events according to Applicable Law.

Explanation:
Training should include the requirements for reporting adverse events within the institution (e.g., Institutional Review Board or Institutional Safety Board), to sponsors for patients receiving products under IND or, IDE, and to FDA or other regulatory authorities.

STANDARD:

B3.3.2 If applicable to the cellular therapy product, specific training required for physicians in Clinical Programs requesting accreditation for allogeneic cellular therapy shall include:

Explanation:
This group of standards applies to the use of allogeneic cellular therapy products with the anticipation that the dual issues of rejection of the infused product and Graft Versus Host Disease (GVHD) caused by the product may occur. However, these risks are potentially unique to the cellular therapy product itself. For Clinical Programs using cellular products from allogeneic donors that might be rejected or cause GVHD, training in the listed elements is required.

Evidence:
Clinical Program Directors and attending physicians will have documented specific training and competency for these elements submitted as part of the accreditation application. Documentation of competency can be in the form of a letter or a checklist and may include a description of the number of times the physician has handled the particular situation, a self-assessment, preparation of SOPs, teaching sessions, presentations, publications, or discussion with the Clinical Program Director.

Evidence of competency may be reviewed by the inspector in advance and by interview and observation on-site.

Example(s):
Clinical Programs may divide the required competencies into thirds (or fourths), and each year of the accreditation cycle perform competency evaluations on a portion. This would allow some

competency assessment each year and assessment for all standards within each accreditation cycle.

STANDARD:

B3.3.2.1 Identification, evaluation, and selection of cell source, including use of donor registries.

B3.3.2.2 Donor eligibility determination.

B3.3.2.3 Methodology and implications of HLA typing.

B3.3.2.4 Methodology and implications of testing for chimerism.

B3.3.2.5 Management of patients receiving ABO incompatible cellular therapy products.

Explanation:
A concern over the use of ABO incompatible cellular therapy products is based on the red blood cell or plasma content of the administered product. Many cellular therapy products currently available are red cell and plasma free or reduced to such low levels that infusion reactions are unlikely. If that is not the case, which might be true for stem cell derived red blood cells or for patients receiving whole blood or whole bone marrow, then such training is required.

STANDARD:

B3.3.3 The attending physicians shall be knowledgeable in the following procedures for cellular therapy products:

B3.3.3.1 Collection.

B3.3.3.2 Processing.

B3.3.3.3 Cryopreservation.

B3.3.3.4 Shipping and transportation.

B3.3.3.5 Storage.

Explanation:
Cell collection and cellular therapy product processing and cryopreservation are procedures that must be familiar to every attending physician; however, it is not necessary for every attending

physician to be specifically trained or competent to perform these procedures. Physician should know the basic principles of product collection, the indications for and limitations of some common cell processing procedures, reasons to cryopreserve or not to cryopreserve a product, and some consequences of cryopreservation.

Clinical attending physicians must be knowledgeable in cellular therapy product preparation for administration to ensure they are competent to provide appropriate orders 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.

Example(s):
The Clinical Program Director may document each physician's knowledge in these areas utilizing a letter, evidence of CME, a copy of a publication authored by the physician, or other documents.

STANDARD:

B3.4 PHYSICIANS-IN-TRAINING

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

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:
In the US, the Accreditation Council for Graduate Medical Education (ACGME) is a private, nonprofit organization that accredits residency programs in 140 specialties and subspecialties. Its mission is to improve health care by assessing and advancing the quality of resident physicians' education through accreditation. Accredited training programs are inspected every two to five years, and accreditation is based upon substantial compliance with common and specialty-specific standards. Documentation that the physician-in-training is a resident or fellow in an -AGME-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 ACGME-accredited training program, it is sufficient for the program to submit one certification of accreditation to cover all trainees. For programs that are accredited by a state or other agency, that documentation will be required. Individuals with less formal training arrangements may be required to submit individual credentials. FACT may audit a training program if needed.

STANDARD:

B3.4.2 *Physicians-in-training shall receive specific training and develop competence in patient management, and cellular therapy-related skills included within, but not limited to those listed in B3.3.1 and B3.3.2.*

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) will determine the level of cellular therapy-related knowledge and competence a physician in training is expected to achieve.

Evidence:

Physicians in training should be routinely evaluated as part of their training. Milestones of progress should be documented.

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 treatment, risks and benefits of cellular therapy, and alternative therapies.")
- Type of patient contact (e.g., pre-cellular therapy consultation, inpatient management, post-cellular therapy outpatient management).
- Type of cellular therapy (e.g., autologous, allogeneic, matched related, unrelated, mismatched donors).
- Source of cells for cellular therapy (e.g., peripheral blood, marrow, cord blood, T cells, MSC, NK cells).
- Participation in cellular therapy grand rounds, journal clubs, morbidity and mortality conferences, and orientation lectures.

ASTCT offers an Online Learning center that hosts recordings its many educational events. These can be accessed at https://learn.astct.org/.
The Tandem Meetings – Transplantation and Cellular Therapy Meetings of ASTCT and CIBMTR offer specific education for Nurse Practitioners, Physician Assistants, Fellows and Junior Faculty.

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 licenses.*

Evidence:
If APPs are a part of the cellular therapy team, evidence of current licensure to practice in the jurisdiction of the Clinical Program will be submitted with the accreditation application. A written description of 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 patient management, and cellular therapy-related skills included within, but not limited to, those listed in B3.3.1 and B3.3.2.

Evidence:
Competency in each of the areas described in B3.3.1 and B3.3.2, 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 B3.2.3.

Documentation of training and competency may be provided to FACT in a variety of formats, including a copy of reports or listings submitted to professional organizations to obtain related credentials. Competency for each critical function performed by APPs must be assessed annually, at a minimum, as described in Standard B4.4.2.4.

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

The Tandem Meetings – Transplantation and Cellular Therapy Meetings of ASTCT and CIBMTR offer the BMT Clinical Education Conference for Nurse Practitioners, Physician Assistants, Fellows and Junior Faculty.

STANDARD:

B3.5.3 APPs shall participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy.

B3.5.3.1 Continuing education shall include, but is not limited to, activities related to the specific cellular therapy administered within the Clinical Program.

Explanation:
The field of cellular therapy continues to evolve rapidly. APPs must participate regularly in educational activities related to cellular therapy. The purpose is for key personnel to keep up with current advancements in the field. The Clinical Program Director should evaluate the continuing education obtained by APPs.

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 his/her 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.

To assess the appropriateness of the amount and type of continuing education in which the APP participated, the following information must be submitted for each of the completed continuing education activities within each accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, meeting, grand round).
- Topic of activity (e.g., hematology, cellular therapy).
- 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. Content must reflect regular education in cellular therapy or diseases in which cellular therapy is a therapeutic option.

Example(s):
Evidence of compliance may include either formal or informal study. Educational activities do not necessarily require large financial resources. Clinical Programs may choose to establish their 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 acceptable forms of education are included in this Accreditation Manual and may include topics specific to cellular therapy and/or diseases in which cellular therapy is a therapeutic option. These include:

- The annual meetings of several 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 on-line tutorial.
- Review of an article 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. These can be accessed at https://learn.astct.org/.

A downloadable Educational Activities form is available on the FACT website at https://www.factglobal.org/education-and-resources/general/hematopoietic-cellular-therapy-library/. The use of this form is not required but can be used to document compliance with continuing education requirements.

STANDARD:

B3.6 NURSES

B3.6.1 The Clinical Program shall have nurses formally trained and experienced in the management of patients in the therapeutic disease areas.

Explanation:

Nurses who occasionally treat cellular therapy patients, such as nurses in an intensive care unit, may not have the degree of training and experience in management of the various therapeutic disease areas that may be treated with cellular therapy, but they must have sufficient expertise to safely care for the patients. How these issues are addressed when the recipient must be treated on a unit other than the primary cell therapy unit must be defined.

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 or donors shall have nurses formally trained and experienced in the management of pediatric patients.

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

B3.6.2.1 Administration of preparative medications.

B3.6.2.2 Administration of cellular therapy products.

B3.6.2.3 Care interventions to manage cellular therapy related complications.

B3.6.2.4 Recognition of cellular therapy related complications and emergencies requiring rapid notification of the clinical team.

Explanation:
Specific training is required for each nurse who is involved in the care of cellular therapy patients. Training may be a part of the formal job orientation, or may be provided in increments over a specified period of employment. Nurse competencies should be evaluated and documented according to a defined process. Nursing personnel must be able to recognize when rapid notification of another Clinical Program team member is required. The program is responsible for identifying what situations would constitute a need for rapid notification.

Example(s):
Cytokine release syndrome has been observed in recipients of certain cellular therapy products of T cell origin and requires rapid care and attention. Nurse training on cytokine release syndrome should include institutional policies on accessing and administering pertinent medications (such as tocilizumab).

STANDARD:

B3.6.3 There shall be an adequate number of nurses experienced in the care of patients in the applicable therapeutic disease areas.

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 adequate numbers 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)," a report from *The Online Journal of Issues in Nursing* on U.S. nursing structure, process, and outcome indicators, is a growing effort to assess nursing numbers and quality. It is located at: https://www.researchgate.net/publication/26571296_The_National_Database_of_Nursing_Quality_Indicators_NDNQIR.

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 An overview of the process of cellular therapy.

B3.7.2.2 Pharmacological management of expected complications, if applicable.

Explanation:
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 without input from the Clinical Program 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) should be shown to the inspector.

STANDARD:
B3.8 CONSULTING SPECIALISTS

B3.8.1 The Clinical Program shall define and have access to certified or trained consulting specialists or specialist groups from key disciplines who are capable of assisting in the management of recipients or donors requiring medical care.

B3.8.2 A Clinical Program treating pediatric recipients or donors shall define and have access to consultants qualified to manage pediatric patients.

Explanation:
A given cellular therapy program accredited under these Standards may use the same cellular therapy product for different indications, or different products for the same or different indications. It is expected that specialist will be available for the different products specific for the diseases that are being treated. The complications of the cellular therapy itself may be unique to the product regardless of the disease being treated. It is critical that the Clinical Program have access to disease experts to assist with medical care. The intent is that specialist would be available to cover recipients of all ages being treated.

Evidence:
The inspector should look for documentation that specialists from the appropriate disciplines are available to the Clinical Program as needed. Such evidence could be an agreement, a letter of commitment, an appointment to the program, or other documentation. There should also be evidence that the identified consultants have the proper credentials for the discipline they represent.

Example(s):
A cellular therapy program providing MSC for cardiac repair should have a formal agreement with one or more cardiologists before providing cardiac specific treatment therapies.

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, Applicable Law, or the performance of the Clinical Program.

Explanation:
The Clinical Program must identify at least one person with the responsibility for quality management (QM). This individual can be the Program Director or a qualified designee. Delegation to a qualified designee must be documented in the QM Plan, in related SOPs, a job description, or other document. The title held by this individual is not mandated by these Standards and may differ among facilities. This is acceptable provided that the duties include those described in these 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.

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, or he/she could be a member of the clinical team who has these additional responsibilities.

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 at http://asq.org.

The Clinical Program Quality Manager must have an active role in preparing, reviewing, approving, or implementing QM policies and SOPs and must confirm that the SOPs comply with FACT Standards and all 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.

Evidence:
A Quality Manager's curriculum vitae (CV), a job description, organizational chart, audit reports, or proficiency test reports (if applicable) are all examples of documentation that may demonstrate compliance.

Example(s):
A Quality Manager may have an operational role in the Clinical Program provided that he/she does not audit his/her own work. In this scenario, it is acceptable for the individual's job description to state "other duties as assigned," rather than specifically state quality management supervisory responsibilities provided that there is documentation of who is assigned the supervisory role.

The FACT *Quality Handbook: A Guide to Implementing Quality Management in Cellular Therapy Organizations* is an excellent resource, available at: https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/.

STANDARD:

B3.9.2 *The Clinical Program Quality Manager shall participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy, cell collection, or quality management.*

Explanation:
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 the scope of knowledge and keep up with current advancements in the fields. While continuing education in cellular therapy 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; and process improvement. A total of 10 hours in combination of these topics is required.

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 his/her judgment to determine if 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.

To assess the appropriateness of the amount and type of continuing education in which the Clinical Program Quality Manager participated, the following information must be submitted for each of the completed continuing education activities within each accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, meeting, grand round).
- Topic of activity (e.g., hematology, cellular therapy)
- Date of activity.
- Approximate number of hours of activity.

STANDARD:

B3.10 SUPPORT SERVICES STAFF

B3.10.1 The Clinical Program shall have one or more designated staff with appropriate training and education to assist in recipient evaluation, cellular therapy product administration, and follow-up care.

B3.10.1.1 Designated staff shall include data management staff.

Explanation:
These Standards require that other staff, as listed above, are available to support the Clinical Program. These staff members do not need to be completely dedicated to the cellular therapy program, but a sufficient number of employees (or full-time equivalents) must be available to meet the recipient's needs throughout the continuum of the cellular therapy process. Support services staff must be available to both inpatient and outpatient facilities. Staff must have sufficient training to allow them to meet specific needs of cellular therapy patients.

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 and CIBMTR.

Evidence:
Adequacy of data management personnel could be assessed based on accuracy and timeliness of registry reporting.

B4: QUALITY MANAGEMENT

STANDARD:

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

B4.1.1 The Clinical Program Director shall have authority over and responsibility for ensuring that the overall Quality Management Program is effectively established, documented, 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, Collection Facility, and Processing Facility must define what key performance data they are going to analyze. Minimally this should include data necessary to complete the quality management activities required in these Standards.

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 Quality Management 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.

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 does not have to be fully described in the QM Plan but must be referenced within the plan and linked to the appropriate document where the details are described.

The QM Plan does not necessarily need to be stand-alone, serving only the Clinical Program. If a plan is shared, it must include all elements required by these 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 Quality Management Plan.

Explanation:
The Clinical Program 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 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 he/she 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) may have a distinct individual responsible for QM, so long as there is a mechanism for sharing information to all participating entities.

STANDARD:

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

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

Explanation:
The overall 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. In some cellular therapy programs, there is no collection facility; rather, the Clinical Program or Processing Facility oversees collection activities.

Remote Directors or Medical Directors are those with professional responsibilities in more than one metropolitan geographic area, or those whose residence is outside of the metropolitan geographic area of the accredited facility. 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 any director; however, there may be

more challenges in completion and documentation of these responsibilities. The following are requirements for remote Clinical Program 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 these Standards.
- A director is responsible for leading the program 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 quality management 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 these Standards. Documentation of director involvement in these responsibilities must be available on-site for review.

At times, a program organization chart will clearly show reporting structure but not necessarily quality management responsibilities. To properly provide a description of how key positions interact to implement quality management activities, a second chart may be needed. This is especially important if laboratory, collection, and clinical programs have a different reporting structure. To comply with these Standards, separate quality management structures must report to a single entity that includes all aspects of the cellular therapy program.

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 is as described in the chart and QM Plan (e.g., meetings, participants, schedules, reporting, and documentation). This should include how separate reporting structures report to a program wide quality management program.

Documentary evidence of a remote director's specific involvement in leadership and oversight of the Clinical Program, 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.

- Investigation report review.
- Qualification/validation studies: plan and final report review and approval.
- Planned deviation pre-approval.
- Cellular therapy product release authorization.

Example(s):
If a Clinical Program contracts its collection or processing service to an outside entity, the organizational chart must include the contracted service and summarize the reporting structure in the QM Plan.

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

STANDARD:

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

Explanation:
In the event of collection-related complications, the Clinical Program must have guidelines for communication with both collection personnel and donor registries. For additional requirements on communication related to issues with donor health that pertains to the safety of the collection procedure, see section B6.3.

STANDARD:

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

B4.4.1 *A current job description for all staff.*

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. These must include all individuals responsible for critical elements of the Clinical Program. Documentation of training for all key personnel must include all procedural skills routinely practiced. These requirements are detailed in B3.

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 as described in B3.

The inspector should review the records of one or more personnel to confirm that all required elements are 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 his/her 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-B4.4.2.5.

STANDARD:

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

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 (RN) or 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). Such documentation 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 formal or informal presentations, self-learning by reading suggested materials on the topic, or reviewing previously presented audio/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 competency. The inspector should review policies or SOPs describing the elements of staff training and continued competency assessment as described in B4.4 and the records of one or more employees to determine whether all of the required elements are documented.

Example(s):
Annual competency assessment may be performed in conjunction with performance reviews during which a staff member's collective competencies and behaviors are evaluated to determine if the individual is meeting expectations and to identify areas of needed improvement.

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

STANDARD:

B4.4.2.5 Continuing education.

Explanation:
Staff should adhere to local and governmental continuing education requirements.

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

STANDARD:

B4.5 The Quality Management 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 these 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.

STANDARD:

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

B4.5.1.1 Policies, protocols, and Standard Operating Procedures.

B4.5.1.2 Worksheets.

B4.5.1.3 Forms.

B4.5.1.4 Labels.

Explanation:
The QM Program must maintain identification of the types of documents considered critical. A critical document refers to a document that is directly related to and could impact patient care or cellular therapy product integrity. For example, all SOPs required by these Standards must be considered to be critical documents and must be controlled. Clinical Programs may call documents 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.

In this context, policies and SOPs means that a single document, either a policy or SOP, could suffice. Documents serve multiple purposes for the QM Program and can consist of different document types such as policies, SOPs, worksheets, or forms. Documents provide the structure needed for quality assurance through policies and SOPs, provide quality control using such forms as preprinted orders and worksheets, and substantiate QM activities with audit reports, outcomes analyses, and training records. The QM Program must identify which documents are critical and describe how they are controlled.

Clinical Programs may not be responsible for label creation, but they do use labels to verify the appropriate cellular therapy product and patient. Program personnel need to be aware that the appropriate version of labels must be used. This does not include labels for other types of products (e.g., diagnostic samples) for which other requirements might apply.

Evidence:
The inspector should review a listing of which documents fall under the document control system.

STANDARD:

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

Explanation:
The Clinical Program should be consistent in the format or design of controlled documents.

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 program must 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 an alphanumeric identifier and a title to each document and document version regulated within the system.

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, alphanumerical). Worksheets and forms must also be controlled documents and contain a title and unique identifier.

Evidence:
The inspector must verify that controlled documents are consistently 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 the effective date.

Explanation
The effective date is when the previous version of a document has been recalled or archived, and the new version that is available has been implemented.

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 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:
Regular record review should alert Clinical Programs to areas needing improvement, particularly specific elements that are repeatedly missing or contain errors. This allows forms, worksheets, or SOPs to be revised and improved. The process should specify who reviews the records and the time interval for review.

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.

Example(s):
If controlled documents are associated with an SOP, the document review may occur in conjunction with the SOP review. If this is done, a separate review process for each controlled document is not required. Controlled documents could also be reviewed independently provided that they are reviewed and updated at a minimum every two years and when relevant to changes in procedures.

STANDARD:

B4.5.3.6 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 changes 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 these Standards and Applicable Law, risk and impact assessment on existing processes and controlled documents, approval of change and revision of documents, communication and/or training on the change as applicable, and implementation of the change. Change 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 he/she has reviewed the SOP and 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 Archival of controlled documents, the inclusive dates of use, and their historical sequence for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

Explanation:
Documentation is especially important for the investigation of occurrences since these investigations are frequently retrospective in nature. If outcomes change over time, one needs to be able to go back to previous versions of controlled documents to determine if an operational change is the cause.

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, and title).

Example(s):
The archival system may contain items such as date removed, version number, reasons for removal, and identification of the individual who performed removal.

STANDARD:

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

Explanation:
Hard copies of controlled documents may exist, and when documents are updated, there needs to be a secure process in place to ensure that any hard copies are not used beyond their expiry date.

Example(s):
Clinical Programs may have documents, such as forms, worksheets, or patient brochures that are printed and distributed. There should be a system in place to recall/remove these obsolete documents to prevent unintended use. A clear statement could be printed on hard copies that they may not be the current version, which can only be reviewed by going to the source library.

STANDARD:

B4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for 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, or donor or recipient follow-up). This standard does not apply to entities within the Clinical Program's own facility or institution.

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. However, it is recommended that a Clinical Program have a contingency plan in the event that the Collection or Processing Facility is unable to provide services as intended (e.g., significant personnel change or 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; written agreements with donor registries; external laboratories performing testing of donors, recipients, or cellular therapy products; and external facilities used for the storage of cryopreserved cellular therapy products).

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 health and safety of the donor or recipient.*

Explanation:
It is the Clinical Program's responsibility to determine which entities providing critical contracted services are external or internal.

Documented agreements must clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements must be dated, reviewed, revised, and approved by both parties and legal counsel, if necessary, on a regular basis as defined by the program, and at least every two years. Agreements must also describe the maintenance or transfer of records and cellular therapy products following termination of the agreement.

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 signature), but which are relevant to the clinical care of the recipient or donor or impact the cellular therapy product.

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 maintain required accreditations and to comply with these Standards and Applicable Law.

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

Explanation:

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

The standard does not require Clinical Programs to monitor third-party manufacturing entities' 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 entities are responsible for complying with Applicable Law, and requires that responsibilities for specific tasks between the program and manufacturer are defined.

Example(s):

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

- Whether 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 failures such as purity (positive sterilities, mycoplasma endotoxin), cell dose, characterization, or vector copy number (VCN).
- Potential scheduling / production issues that impact availability.

Additionally, if contracting out critical services that may impact care, language can be added to address communication pathways and notification timeframes. For example, if contracting apheresis services, the following are questions related to how relevant information will be communicated if the donor has a reaction or adverse event:

- How is updated donor suitability information communicated?
- Does the center notify you of breaches in aseptic collection?
- How might post-donation information be communicated (e.g., donor contacts the collection center two days after donation that they have an infection or identifies a risk that impacts donor eligibility)?
- What changes in operational availability or regulatory status will be communicated?

Similar information should be found in agreements for other critical services which may include 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 at least every two years, similar to SOPs, although greater or lesser time intervals may be appropriate under some conditions. 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 ask to review agreements and the documentation of regular review as required.

Example(s):

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

STANDARD:

B4.7 The Quality Management 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 products can be demonstrated to produce a desired or intended function.

Product efficacy based on patient outcome may be more difficult to document for cellular therapy products other than HPCs, and that assessment will differ for each product type. Minimally, the QM Plan must address the need for the development of a validated potency assay as regulated products enter the later stages of clinical trials. Validation of product potency assays has become a significant issue as more therapies enter phase III trials, and, although FDA is aware of the difficulties for certain product types (e.g., MSCs), the need for a test of product potency is still required. The development of potency assay methods should begin early in product development.

Evidence:
The inspector should confirm documentation of all activities from definition of expected outcome to process improvement and potency assay development, 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, minutes of meetings, and Clinical Program review of the data (including personnel in attendance and where data are presented).

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 still be assessed. Data should include products from both commercial and clinical trial sources, when applicable.

It is expected that programs applying for accreditation under these Common Standards will be using novel cellular therapies manufactured internally in addition to participating trials from outside manufacturers. The program must still perform some outcome analysis on all products 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.

Evidence:
These Standards require written agreements that clearly designate responsibilities of the Clinical Program and third parties (e.g., commercial manufacturers). Financial agreements are outside the scope of these Standards and may be redacted from documentation.

Example(s):
Different committees may review outcome analyses for cellular therapy products under research (e.g., investigational new drugs) or commercially available products (e.g., those licensed by the applicable governmental authority). Examples of such committees include Quality Management 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 for each type of cellular therapy product and recipient type shall be evaluated.

Explanation:

Outcome analysis should include each individual cellular therapy 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 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 be performed on aggregate data 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.

Clinical Programs are required to collect data included in CIBMTR forms as appropriate (see B9.1) and should use these data when analyzing outcomes. The program is encouraged to define internal benchmarks and compare these benchmarks 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 in a regular fashion should be prospectively identified in the QM Plan and should address all key elements of the program.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported with each occurrence while others may be prospectively 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 cellular therapy product source (e.g., marrow, peripheral blood, or cord blood) or immune effector cell therapies and by relationship of donor to recipient (i.e., allogeneic donor [related, unrelated] or autologous donor). Disease-specific analysis is also recommended. Some Clinical Programs may find the numbers of recipients limit the number of groups that can be independently assessed.

STANDARD:

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

B4.7.3.1 An endpoint of clinical function as approved by the Clinical Program Director.

Explanation:

If a recipient is being formally managed and followed by a separate service (e.g., cellular therapy administered to a cardiac patient and followed on a cardiac unit), the Clinical Program and the requesting unit should define who is responsible for determining the endpoint of clinical function and assessing outcomes accordingly. If a recipient is transferred to the requesting unit after administration of the cellular therapy product, the program's ability to monitor outcomes is dependent on data received by the requesting unit. The opposite might also be the case in that the cardiac patient may be monitored on the program's clinical unit, but with outcome monitoring by a cardiac specialist working with the program.

Example(s):

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

- Time to white cell and platelet recovery.
- Incidence of cytokine release syndrome and neurotoxicity.
- Karnofsky performance status.
- Target disease response.
- Disease-free survival.

STANDARD:

B4.7.3.2 Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration or in accordance with Applicable Law.

Explanation:

Performance measures may include survival, specific complication rates, adherence to selected policies or SOPs, and other clinical outcomes in addition to overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration. Morbidity may include rehospitalization, 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.

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, or distribution of the cellular therapy product.*

Explanation:

Because patient outcome data are 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 are dependent on these data to adequately assess their practices. Data should be shared quarterly at a minimum.

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 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.

STANDARD:

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

Explanation:

Audits represent one of the principal activities of the QM Program. An audit is a documented, independent inspection and retrospective review of an establishment's activities to determine if they are performed according to written SOPs. Compliance is verified by examination of objective evidence. Audits are conducted to determine that the QM Program is operating effectively and to identify trends and recurring problems in all aspects of facility operation. Processes to be audited should include those where lack of compliance would potentially result in an adverse event.

The head of the QM Program should identify areas to be audited and audit frequency. 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 activities; frequency will depend on the importance of these activities, and to some extent on the audit results. Where there are published studies, these should be used to help assess audit results.

A schedule of prospective audits is expected. Required audits for the Clinical Program are listed in B4.8.3. Other audits may be 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 and the Collection Facility Director and Processing Facility Director as appropriate.

Further information is available in the FACT *Quality Handbook* (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

Evidence:
The Clinical Program should facilitate the on-site inspection with a concise presentation of recent audits, supported by policies and SOPs, and including documentation of corrective and preventive action and follow-up. Examples of how results are trended and presented to relevant directors and staff are also helpful. The inspector should review the schedule of planned audits, audit results, and with whom audit report data has been shared, 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):
Examples of audits in the Clinical Program include:

- Adherence to policies and SOPs (e.g., recipient/donor selection).
- Timely distribution of complete medical information to facilitate appropriate medical care.
- Turn-around time for laboratory results.

Audit reports are an important tool to provide inspectors evidence of adherence to standards and effectiveness of implemented corrective and preventative action plans (CAPA); to provide management guidance on future actions and decisions; and to document the evaluation process and decisions made in response to issues detected. An acceptable audit report contains the following elements:

- Audit title.
- 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.
- Name and title of staff assigned to complete the audit.
- Audit period (date range).
- Audit purpose.
- Audit scope.
- Audit plan.
- Date audit started and completed.

- Audit findings and recommendations: if errors were found but not included in the final analysis, an explanation must be provided.
- Summary (includes assessment/evaluation of results): identifying the underlying cause (root cause) of the errors guides a program to develop an appropriate CAPA, which should be included in the audit report to demonstrate that an appropriate corrective action plan was implemented.
- Timeline for follow-up: a CAPA is required when errors are found. Should an organization determine that a CAPA is not required, this should be documented along with why it arrived at that conclusion. When a CAPA is implemented, follow-up audits should be performed to assess the effectiveness of the corrective actions and demonstrate improvement in the area where the original deficiency occurred.
- Signatures and Comments.
    - Auditor signature and date.
    - Quality Manager signature, date, and comments.
    - Clinical Program Director signature, date, and comments.
- Documented staff review (initials) and date of review.
- Quality meeting results presentation date, if required.

Initially, the audit report is completed by the auditor and reviewed and approved by the appropriate personnel (e.g., Quality Manager or Clinical Program 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 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:

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

Explanation:

The individual(s) performing an audit does not need to be external to the Clinical Program, but he/she should not have performed the actions being audited.

The auditor must be knowledgeable in the process and competent in auditing techniques. Sufficient knowledge must include auditing and the subject manner. 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 *The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow up on the effectiveness of these actions in a timely manner.*

Evidence:
The 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 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:

B4.8.3 *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 includes at least the required annual audits listed below. 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 can be replaced on the schedule by a new audit topic.

Example(s):
An example of another recommended audit is a gap analysis when a new version of these Standards has been published.

STANDARD:

B4.8.3.1 Accuracy of clinical data.

B4.8.3.2 Documentation of proper donor eligibility and suitability determination.

Explanation:
This audit should determine that eligibility was appropriately determined according to SOPs and Applicable Law and that the eligibility was documented before the collection procedure started.

STANDARD:

B4.8.3.3 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 Clinical Program's defined responsibilities.

Evidence:
The Clinical Program does need to know that all aspects of the management have been performed. They should have a final copy of the full workup by all sections to show to the inspectors.

STANDARD:

B4.8.3.4 Infectious disease resulting from cellular therapy product collection or administration.

B4.8.3.5 Documentation that external facilities performing critical services met the requirements of the written agreements.

Explanation:
The audit of external facilities performing critical contracted services is essential 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. 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. There may be other

alternatives, but the contracting facility must establish that their contracted services are meeting requirements.

STANDARD:

B4.8.3.6 Chain of identity and chain of custody of cellular therapy products.

Explanation:
The chain of identity refers to the association of the cellular therapy product unique identifiers from procurement throughout the full product life cycle, including post treatment monitoring of the recipient. The chain of custody illustrates the guardianship of the product from origin to final disposition. The Clinical Program must ensure that it is able to track the chains through to their end.

Example:
Cellular therapy products cover a wide spectrum of situations which require different approaches. In the case of third-party donors and manufacturing, written agreements should be in place with service providers which outline the process, auditing, and responsibility of chain of identity and chain of custody.

STANDARD:

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

Explanation:
If the Clinical Program administers cellular therapy products for commercial manufacturers, it will most likely be asked to participate in audits of its procedures. The requests may be varied. It is responsibility of the program to ensure that such audits are handled in a consistent fashion.

STANDARD:

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

B4.9.1 Criteria for the administration of cellular therapy products with positive microbial culture results.

B4.9.2 Notification of the recipient, recipient's physician, collection staff, processing staff, any other facility in receipt of the cellular therapy product, and, if relevant, the donor and the sponsor.

B4.9.3 Recipient follow-up.

B4.9.4 Follow-up of the donor, if relevant.

B4.9.5 Documentation and investigation of cause.

B4.9.6 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 listed above. This requirement may be satisfied with a single policy or SOP or there may be separate documents. For each topic, SOPs should detail what action is to be taken, who is responsible to take the action (e.g., the Clinical Program, collection personnel, or the Processing Facility), and the expected timeframe of the actions. Different approaches to management may be acceptable if these approaches are consistently followed and meet regulatory requirements.

Policies and SOPs should cover investigation of the cause of the positive microbial culture and the reporting to regulatory authorities if applicable. Responsibilities for some of these activities may be in the Processing or Collection Facility (if not part of the Clinical Program); however, the documents should include this overview. A positive microbial result may only become known after the cellular therapy product has been administered. It is important to note that the extent of the investigation may vary depending on the type of organism or source of the graft.

If a positive microbial result is detected prior to administration, the Clinical Program must have criteria for use of a cellular therapy product. This policy should include when another collection should be considered, and, if the product is administered, guidelines for recipient management, such as prophylactic antibiotics, increased monitoring, or other precautions, and regulatory reporting.

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 B4.9 and the regulatory requirements of the FDA must be met.

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 if this is allowed by any protocols. 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, outcome analysis of the function of the infused product, 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 over-arching document for the management of cellular therapy products with positive cultures is recommended to clarify responsibilities.

An example of donor follow-up is a situation in which the investigation found that the donor was infected at the time of collection. This is most common in the case of an autologous donor, particularly when a central venous catheter may have become colonized. However, it is advisable 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 generally responsible for donor follow-up; however, a donor center or collection center may have a role in follow-up of the unrelated donor.

Criteria for administration of a positive cellular therapy product could include when no other collection is possible and/or no other donor is available. Administration of the product is also dependent upon the effect of the contamination on the cells. A contamination during manufacture could render the cells non-viable. However, there may be instances of a positive microbial culture from a sample taken at collection that is found to be negative after the processing procedure.

In the U.S., reporting regulations are detailed in 21 CFR 1271. A cellular therapy product with a positive microbial result must be reported to FDA only if the product is administered, whether the result was known prior to administration or only after administration. Marrow-derived products used to restore hematopoiesis found to have positive microbial culture results are not reported to FDA. However, if the contaminated marrow is the source of a cellular therapy product that is extensively manipulated and is infused, it must be reported to FDA.

STANDARD:

B4.10 *The Quality Management 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:
A goal of a QM Program is to continuously improve processes. Monitoring occurrences and trends facilitates recognition of improvement opportunities. There must be policies, processes, and procedures to detect, evaluate, take immediate action, document, and report occurrences 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 Part A (Definitions). Management of each of these types of occurrences is slightly different; however, the same steps (detection, evaluation/investigation, documentation, determination of corrective and preventive action, and reporting) apply to all types.

Evidence:
The inspector should expect to find a documented process for 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, and reported, as appropriate, to the Collection Facility, the Processing Facility, appropriate governmental agencies and other third parties involved in the manufacture of the cellular therapy product.

STANDARD:

B4.10.1 Detection.

Explanation:
Immediate actions must be taken and documented to mitigate further risk to cellular therapy products staff, patient, or donor safety.

STANDARD:

B4.10.2 Investigation.

B4.10.2.1 A thorough and timely investigation shall be conducted by the Clinical Program in collaboration with all entities involved in the collection, manufacture, testing, or administration of the cellular therapy product, as appropriate.

B4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective and preventive actions as warranted.

B4.10.2.3 Occurrences shall be tracked and trended.

Explanation:
Investigation of the cause(s) of any deviation is critical to determine what corrective and preventive action will most likely be effective. The focus of the investigation should be to learn and improve, not to cast blame or be punitive. Often "systems" play a role in causation. Serious events require more in-depth investigation to find the root cause. Clinical Programs should be encouraged to stratify deviations 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 systems, policies, or procedures that will correct the issue and prevent recurrence of the deviation.

Investigation must be performed and documented in a timely fashion so as to mitigate further risk to the cellular therapy product and to patient safety. Investigation may also identify clinical outcomes that are not necessarily related to products.

Example(s):
Use of an ineligible donor may be an occurrence. The investigation of should focus on the documentation required for urgent medical need, including recipient notification, physician approval, and proper product labeling. Ineligible allogeneic donors for cellular therapy products that require a high degree of HLA matching are usually chosen based on HLA match. The small risk of CDJ when the best matched donor lives in Europe is generally acceptable.

STANDARD:

B4.10.3 Documentation.

B4.10.3.1 Documentation shall include a description of the occurrence, date and time of the occurrence, the involved individuals and cellular therapy product(s), when and to whom the occurrence was reported, and the immediate actions taken.

B4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Clinical Program Director and Quality Manager.

B4.10.3.3 Cumulative files of occurrences shall be maintained and shall include written investigation reports containing conclusions, follow-up, corrective and preventive actions, 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/time, and actions are captured.

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

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 decrease the risk of transmission of a communicable disease. Corrective action or process improvement must be implemented to prevent re-occurrence 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.

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:

B4.10.4 Reporting.

B4.10.4.1 When it is determined that a cellular therapy product has resulted in an adverse event or reaction, the event and results of the investigation shall be reported to the donor's and recipient's physician(s), as applicable, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by Applicable Law.

B4.10.4.2 Occurrences shall be reported as required to other facilities performing cellular therapy product functions on the affected cellular therapy product.

B4.10.4.3 Occurrences shall be reported as required to the appropriate regulatory and accrediting agencies, registries, grant agencies, and Institutional Review Boards or Ethics Committees.

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 include unexpected reactions to the product 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 cellular therapy 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, and Investigational Review Boards [IRBs] or Ethics Committees).

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. 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.

Examples:
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. FDA guidance for such plans in the U.S. can be found in *Guidance for Industry: E2E Pharmacovigilance Planning* (2005) available at https://www.fda.gov/media/71238/download and *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005) available at https://www.fda.gov/media/71546/download.

STANDARD:

B4.10.5 Corrective and preventive action.

B4.10.5.1 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.

B4.10.5.2 Follow-up audits of the effectiveness of corrective and preventive actions shall be performed in a timeframe as indicated in the investigative report.

Explanation:
All events may not require corrective and preventive action (CAPA). 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 when events warrant CAPA plans along with their plan to audit the effectiveness of the changes.

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

- Identification of the involved individuals and/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 corrective action.
- 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 *The Quality Management 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, Single European Code (SEC) or equivalent if used, content of the cellular therapy product, identification of the donor including medical record numbers or unrelated donor registry identifiers, Global Registry Identifier for Donors (GRID), allogeneic donor eligibility status, and the unique registry identifiers of the intended recipient 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 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 these 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 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, provided that 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 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:

B4.12 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event the Clinical Program's 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, these 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 preparative regimen 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 back up 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 or 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 if 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 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, and/or alternative preparative regimens.

STANDARD:

B4.13 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services relevant to the cellular therapy product.*

Explanation:
Quality can be maintained only if there is control over critical 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 had 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.

Example(s):
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 and recipient care or cellular therapy product integrity.
- Updated software versions have the potential to materially affect performance of equipment.

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 that require qualification.

For further definitions and examples of qualification, see the FACT *Quality Handbook* (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

STANDARD:

B4.13.1 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 are compliant with Applicable Law and that there is a system in place that is consistent with these Standards, such that they can demonstrate process control. Suppliers of infectious disease testing must also be qualified.

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):
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 and 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. An example might be the qualification of a new administration pump or marrow collection set. This qualification may be delegated to other institutional departments.

Facility qualification is based on the level of services being provided, such as air-handling and air-filtration, or drug security.

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, 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 suppliers' past performance history.

STANDARD:

B4.13.2 Qualification shall be required following any significant changes to these items.

B4.13.3 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Clinical Program Director.

B4.14 The Quality Management 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 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 verification demonstrates that the products of a process meet the required conditions.

Example(s):
For further definitions and examples of validation, see the FACT *Quality Handbook* (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

STANDARD:

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

Explanation:
The starting cell source for a cellular therapy product can be highly variable, ranging from whole blood, mobilized or un-mobilized apheresis products, skin biopsies, bone marrow aspirates, and body fat, among others. In the Clinical Program, the following procedures should be validated if performed:

- Cellular therapy product collection procedures. Validation of the collection procedures should include all the variables used in the collection of each product, such as donor variables (e.g., white blood cell (WBC) count, CD34 cell count or T cell counts at initiation of collection, blood volume, or weight) and procedural variables (e.g., 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 to serve as the starting material for the cellular therapy product.
- Labeling of cellular therapy products after collection.
- Storage of cellular therapy products prior to distribution to the processing facility.
- 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 Standard B4.14.1 would apply. For example, there are new products that require dosing at the bedside.

It is not the intent of these Standards to include hospital-based computer systems and clinical medical records. For further guidance see Standard B10.

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.

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 Clinical Program Director and Quality Manager.

STANDARD:

B4.14.2 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 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.

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:

B4.14.2.1 An approved plan, including conditions to be assessed.

B4.14.2.2 Acceptance criteria.

B4.14.2.3 Data collection.

B4.14.2.4 Evaluation of data.

B4.14.2.5 Summary of results.

B4.14.2.6 References, if applicable.

B4.14.2.7 Review and approval of the plan, report, and conclusion by the Clinical Program Director and 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 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 maternity leave). In this situation, the Quality Manager designee must be qualified to complete the review and approval process.

STANDARD:

B4.14.3 Significant changes to critical procedures shall be validated or verified as appropriate.

B4.15 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the evaluation of risk in changes to a process to assess the effect of the change elsewhere in the operation.

B4.15.1 Evaluation of risk shall be completed for changes in critical procedures.

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, patient care, or the cellular therapy product integrity, sterility, viability, or recovery.
Evaluation of risk may be documented in a validation plan or exist as a separate document and may include:

- Identification of a risk.
- Context.
- Evaluation.
- Impact.
- Management Plan, including mitigation strategies.

Evidence:
The inspector should ask to see the SOP for evaluation of risk for changes to a practice, process, SOP, or environment and an example of how it has been applied.

Example(s):
An example might be a change in using another reagent or supply item of suitable grade.

Identification of a risk can be made by providing a description of a potential or known risk. Establishing the context or scope means that all risks are identified and that the possible ramifications or impact in all areas are analyzed thoroughly. The next step is identification and evaluation of source or effect of the potential risks. 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.

Risk must be next be assessed for the potential of criticality or likelihood of occurrence and the 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 the magnitude of risk under different scenarios.

After the risk assessment has been established, 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. It is comprised of the effective controls for mitigation of risk. This can often be established in a simple one-page document for change with low impact and risk.

Below is an example of a risk assessment matrix that combines the concept of likelihood and severity.

Risk Matrix

		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)
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:

B4.16 The Clinical Program Director shall review the quality management activities with representatives in key positions in all areas of the cellular therapy program, at a minimum, quarterly.

B4.16.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

B4.16.2 Performance data and review findings shall be reported to key positions and staff.

Explanation:

The frequency of Quality Meetings is determined by the Program. Quarterly meetings are the minimum requirement. The minutes and attendance of regularly scheduled QM meetings are effective ways to document QM activities and to communicate quality assessments to key individuals within the cellular therapy program.

Quality Management Meetings are held 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. 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.

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:

B4.16.3 The Clinical Program Director shall not approve their own work.

Explanation:
Any person responsible for overseeing the QM activities should not be directly responsible for review of work solely performed by that person. It is important that the final review be non-biased, and that there has been sufficient time away from the work for the review to be objective. In small Clinical Programs where there may be only one person responsible for most of the clinical activity, the Clinical Program Director, Apheresis Collection Facility Medical Director, or a person from the Processing Facility may be designated for review of these activities. It may also be acceptable for an individual to review his/her own work at a time and place removed from the actual performance of the task.

STANDARD:

B4.17 *The Clinical Program Director shall annually review the effectiveness of the overall Quality Management Program.*

Explanation:
The ultimate responsibility for performance and monitoring of the QM Program, including internal or contracted components, is that of the Clinical Program Director. This includes a documented review of key performance data across clinical, collection, and processing services.

The overall effectiveness of the QM Program must be reviewed on an annual basis and should be reported to staff. 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 Facility and Processing Facility, and identify opportunities for improvement. There should be documentation of measurement results, analysis, quality 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, new services, patient volumes, 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 update).
- Quality measures (including clinical, collection, and processing):
  - Clinical outcomes.
  - Audits.
  - Validations.
  - Risk assessments.
  - Service level agreements.

- Process improvements.
- Biological product and other deviations and nonconformances.
- 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 Quality Management data among all participating entities.

STANDARD:

B4.17.1 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.

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 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 recipient 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, provided that each item is addressed within one (e.g., policy, SOPs, or clinical guideline). 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 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 two 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 (suitable 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.

STANDARD:

B5.1.1 *Recipient evaluation, selection, and treatment across the continuum of care related to cellular therapy.*

B5.1.2 *Donor and recipient confidentiality.*

B5.1.3 Donor informed consent for cellular therapy product collection and manufacturing, storage, distribution, and disposition.

B5.1.4 Donor search and selection, including screening, testing, eligibility determination, and management.

B5.1.5 Preparation of the recipient prior to cellular therapy product administration.

B5.1.6 Administration of preparative regimens.

B5.1.7 Administration of blood products.

B5.1.8 Administration of cellular therapy products, including products under exceptional release.

B5.1.9 Management of ABO incompatible products, if applicable.

B5.1.10 Detection and management of complications that include toxicities related to preparative medications or cellular therapy product administration.

Explanation:
The complications and toxicities for a given cellular therapy product may differ significantly from other products. It is important that there be SOPs specific for the products used by the Clinical Program that include recommended responses and treatments.

STANDARD:

B5.1.11 Duration and conditions of cellular therapy product storage and indications for disposal.

Example(s):
A Clinical Program could have a policy corresponding to a Processing Facility's policy on cellular therapy product disposal that considers the length of product stability, the number of collections that are performed, quality assurance, and the costs of storing these products.

STANDARD:

B5.1.12 Hygiene and use of personal protective equipment and attire.

B5.1.13 Disposal of medical and biohazard waste.

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

B5.1.14 Cellular therapy emergency and disaster plan, including the Clinical Program response.

B5.1.15 Response to emerging disease agents, including recipient care, donor evaluation and management, and personnel safety.

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, 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 back up 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 these 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, RSV or (para) influenza; or pandemics, leading to an emergency closure or modifications to practices of the clinical unit. The article *Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program* (Wingard et all, 2006) provides a framework for disaster plans that can be customized for individual Clinical Programs (available at https://higherlogicdownload.s3.amazonaws.com/ASBMT/43a1f41f-55cb-4c97-9e78-c03e867db505/UploadedImages/EmergencyPreparednessGuideli.pdf).

The FDA offers information on its webpage titled, "The Impact of Severe Weather Conditions on Biological Products," at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/impact-severe-weather-conditions-biological-products.

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 its controlled documents. Also, institutions may build standardized forms and ordering systems within electronic health records, but it is still the programs' 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 a quality, a policy, and a database manual 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:
This standard defines the minimum elements required in each SOP. SOPs are controlled documents and must also comply with the requirements in B4.

STANDARD:

B5.3.1 *A clearly written description of the objectives.*

B5.3.2 *A description of equipment, reagents, 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 Standard Operating Procedures or policies required to perform the procedure.*

B5.3.6 *Age-specific issues where relevant.*

Explanation:
Process adjustments are required for pediatric and geriatric recipients and donors to address issues of co-morbidity, age, venous access, and body size. 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 also have appropriate SOPs that address issues of informed consent. A program that includes geriatric patients should perform geriatric assessments.

Example(s):
Examples of age-specific issues include total parenteral nutrition and blood product volume guidelines, delirium management, geriatric evaluation, and medication management. Psychological, educational, family, and social needs of adolescent and young adult patients should also be addressed where applicable. 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. For additional information visit https://www.cancer.gov/news-events/cancer-currents-blog/2018/geriatric-assessment-cancer-care-mohile.

STANDARD:

B5.3.7 *A reference section listing appropriate and current literature.*

B5.3.8 *Documented approval of each procedure by the Clinical Program Director or designated physician prior to implementation and every two (2) years thereafter.*

B5.3.9 *Documented approval of each modification to a Standard Operating Procedure 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 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.

Copies of worksheets, reports, labels, and forms, where applicable, must be identified in or be attached to each SOP as paper copies or via electronic links. The Clinical Program may use the format of its choice, provided that all listed elements are present. The purpose of this standard is to assure 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.

Approving several SOPs at once with a single signature and date is not sufficient, as it does not demonstrate that individual SOPs were reviewed and approved.

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, forms, or other supporting documents can be referenced rather than included in the actual SOP provided that the forms are under document control and can be easily accessed by personnel and presented to the inspector on request. These 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 www.clsi.org for more information). Some Clinical Programs may utilize a format consistent with ISO 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 processes being performed shall be readily available to the facility staff.*

Explanation:
The written copy or electronic version (with provisions for hard copies as necessary) of the Clinical Program's policies and SOPs relevant to the work schedule and duties must be immediately available to all relevant staff in their working environment. Programs may choose to only have the procedures necessary to perform specified processes at a workstation. However, all procedures

that an employee must comply with related to that process must be readily available to him/her for reference when needed.

Evidence:
Staff should be able to readily identify the written copy or electronic version of the SOPs for the inspector in all performance areas of the Clinical Program., including all locations of patient care (BMT 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 Standard Operating Procedure.

Explanation:
Before a staff member is allowed to perform new and revised policies or SOPs, he/she must have reviewed or received training on the new document. Clinical Programs are not required to train all staff members before implementing a new policy or SOP rather, they must document an individual's review or training before that person uses the revised policy or SOP.

Example(s):
It is recommended that there be a specific signoff sheet for every policy and SOP and associated revisions to document that each staff member required to review a policy or procedural revision has done so prior to performing the tasks 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.

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. Review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

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 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 within a peer-review process (i.e., more than one individual), but approval from the Clinical Program Director is required at a minimum. Approval of a planned deviation must include an assessment of risk. Processes set up for review of variances are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately. Retrospective review must be performed in compliance with processes designed for deviations.

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

Explanation:

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, nearly all the requirements in B6 apply, including standards to safeguard appropriate confidentiality, confirm histocompatibility matching (if required), and protect the recipient from the risks of transmissible disease.

For autologous-only Clinical Programs, many, but not all, of the requirements in this section apply. The term "donor" is used by these Standards even in the autologous setting because considerations for informed consent and suitability (i.e., safety) of the individual include issues above and beyond the individual's status as a cellular therapy patient.

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 aspects of donor identification, evaluation, selection, and management, including identification of the personnel responsible for each aspect (when in the control of the program).

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. The Clinical Program must identify the institutional criteria for allogeneic and autologous donor medical suitability and selection.

Written criteria for allogeneic donors 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. The Clinical Program should be aware of the number of times an unrelated donor has donated, as it may factor into whether that donor should be selected or not.

Clinical Programs performing allogeneic therapies should endeavor to receive only voluntary and unpaid donations of cells. Donors may receive compensation limited to reimbursement for the expenses and inconveniences (e.g., lost wages, travel) related to the donation. This is based on national and international standards for donation.

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. For example, an older donor in a pediatric program may be a donor that is 20 years old; an adult program would use an older age. The United Nations has attempted an international definition of old age, which is 60+ years old.

STANDARD:

B6.2 Allogeneic and Autologous Donor Information and Consent to Donate

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

Explanation:
The informed consent substance and process is 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 told, in terms they can reasonably be expected to understand and in their native language via an approved interpreter when indicated, the reasons for the proposed therapy or procedure, alternative therapies or procedures, the risks associated with the treatment or procedure, and potential benefits. In addition, the donor should be given the opportunity to ask questions and to have those questions answered to their satisfaction.

The discussion that ensues is the 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 confirm that donors have a) understood the information provided, b) had an opportunity to ask questions and had 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:
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):
This process may take place over several visits. A preprinted consent form detailing the above 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.

It is recommended that the consent process be documented in the clinic chart by the consenting physician. In addition, it is recommended that a signed copy of the informed consent for cellular therapy product donation, even outside of a research protocol, be provided to the donor.

STANDARD:

B6.2.1.1 The risks and benefits of the procedure.

B6.2.1.2 Intent of the collection for treatment or research.

B6.2.1.3 Tests and procedures performed on the donor 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 Alternative collection methods.

B6.2.1.6 Protection of medical information and confidentiality.

B6.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.

B6.2.2.1 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. 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.

STANDARD:

B6.2.3 The donor shall have an opportunity to ask questions.

B6.2.4 The donor shall have the right to refuse to donate or withdraw consent.

B6.2.4.1 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 had already been given. This standard is not meant to be coercive, but to require full disclosure of the effects of a donor's decision 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 the planned cellular therapy. If the potential donor declines prior to donor workup, versus refusing after selection or on the day before the product is administered, then the degree of risk incurred to the recipient will be very different.

STANDARD:

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

B6.2.5.1 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, 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 clinical team but has knowledge of the collection procedures.

STANDARD:

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

B6.2.7 In the case of a donor who is a minor, informed consent shall be obtained from the donor's legally authorized representative in accordance with Applicable 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 factors in a minor, allogeneic donor. It is appropriate to discuss the donation procedure with the pediatric donor in terms he/she 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. Clinical Programs must be compliant with institutional policy and Applicable Law 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.

In the event that the legally authorized representative is the potential recipient, an alternative donor advocate should be appointed. There may be other Applicable Law.

Evidence:

Inspectors may 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 is appropriate to discuss the donation procedure with the pediatric donor in terms he/she 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. 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:

B6.2.8 *The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician or the recipient.*

Explanation:
The purpose of this standard is to protect donor confidentiality regarding his or her 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 his/her cells/ Donors do have the option to specifically limit disclosure of certain information upfront.

The consent procedure for the recipient should inform him/her of the right to review his/her own testing results and those relevant testing and screening results of the selected donor only. The recipient does not have the right to review health information, including the HLA typing of siblings or other potential donors, who are not selected.

Example(s):
It is acceptable to obtain informed consent and authorization to release this information after donor screening and testing provided that it is obtained prior to sharing the results.

STANDARD:

B6.2.9 *The donor shall be informed of the policy for cellular therapy product discard, 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 fate of a donated cellular therapy product that is not or 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. Some registries that facilitate unrelated donations may have requirements for what information is provided to the donor regarding cellular therapy product discard. In most cases, leftover cells after death can be discarded.

STANDARD:

B6.2.10 Documentation of consent shall be made available to collection staff prior to the collection procedure.

B6.3 Allogeneic and Autologous Donor Suitability for Cellular Therapy Product Collection

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:
The criteria and evaluation SOPs must account for the entire collection process from initial evaluation, mobilization where applicable, to collection, and post-collection care.

Example(s):
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.

To avoid overlooking important information, especially in larger Clinical Programs, the program could have a separate document that highlights major concerns that is distributed to the individuals performing cellular therapy product collection.

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 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 his/her role in the collection process. Appropriate care of the donor requires that clinically significant abnormalities be communicated to him/her 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 unsuitable 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 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:
An independent physician or health care professional must be utilized for evaluating donor suitability to minimize potential bias of the recipient's health care professional(s). This individual must not be the primary health care professional of the recipient and should have knowledge of the risks of the donation procedures.

Medical literature supports the idea that having the allogeneic donor evaluated by a 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 (see "Family Donor Care Management: Principles and recommendations," [Walraven et al, 2010]. 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 health care professional evaluates the donor for suitability.

Example(s):
Another attending physician of the Clinical Program could evaluate a potential donor; 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 he/she possesses 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 tested as required by Applicable Law.

Explanation:
Testing or screening of autologous donors in connection with cellular therapy product collection is not required by these Standards. However, consistent with B1, testing required by Applicable Law is required.

Clinical Programs may choose not to test autologous donors for infectious diseases or disease agents, or they may choose to test autologous donors with diagnostic tests. Positive screening tests for autologous donors must have the appropriate warning statements on the label. It is important for the program to notify the Processing Facility so that the final product can be labeled in accordance with these Standards and Applicable Law.

STANDARD:

B6.3.2 The risks of donation shall be evaluated and documented.

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

B6.3.3.1 For collection with mobilization, a pregnancy test shall be performed within seven (7) days prior to the initiation of the mobilization 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 collection or before the initiation of the mobilization agent (if used) or administration of anesthesia and before the recipient starts the conditioning regimen, if conditioning is required. Child-bearing potential includes include all female donors from puberty through menopause, unless there is definite medical indication that pregnancy is impossible (e.g., a past hysterectomy).

The purpose of the required timeframe is to prevent donor mobilization and recipient conditioning 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 cryopreserved for administration later, the donor does not have to be retested for pregnancy. However, if a recipient is on a prolonged (e.g.,)21-day conditioning regimen, a pregnancy test must be performed within seven days prior to beginning that regimen.

Evidence:
Donor records will provide information on results and timing of pregnancy tests.

Example(s):
A pregnancy test is required; serologic assays or urinalysis may be used.

STANDARD:

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

Example(s):
Examples of relevant accreditation organizations in the US include CLIA, CAP, ASHI, and AABB.

STANDARD:

B6.3.5 *The Clinical Program shall inform collection staff and the Processing Facility of donor test results or if any testing was not performed.*

B6.3.6 *There shall be a written order from a physician specifying, at a minimum, an anticipated date and goals of collection and processing.*

B6.3.7 *Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for their selection by the administering physician.*

Explanation:
These standards are meant to require the Clinical Program Director to review all donor data prior to collection, and to document 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 may communicate needed information by a documented note in the collection chart record. Such records may include the electronic medical record.

STANDARD:

B6.3.7.1 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the collection 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 staff.

Evidence:
The inspector can review the method in use to convey to the collection staff the health status of the donor and ask to review the SOP regarding donor follow-up.

STANDARD:

B6.3.8 There shall be a policy or Standard Operating Procedure for the management of collection-associated adverse events and follow-up of donors that includes routine management.

Explanation:
In the event of collection-related complications, the Clinical Program must have guidelines for communication with both the Collection Facility and the registry.

STANDARD:

B6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

B6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated, as those terms are defined by Applicable Law.

Explanation:
A donor advocate is an individual distinct from the cellular therapy recipient's primary treating physician whose primary obligation is to help the donor understand the risks and benefits of donation and promotes the interests, well-being, and safety of the donor. According to Donor

Registries for Bone Marrow Transplantation: Technology Assessment (National Institutes of Health [NIH] Office of Medical Applications of Research, 1985), 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 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/recipient. Specific examples that illustrate this circumstance 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 to do so by the family or healthcare team.

Example(s):
Examples of donor advocates include chaplains, patient advocates, social workers. "Family Donor Care Management: Principles and Recommendations," (Walraven et al, 2010) provides recommendations for donor advocacy in the related donor setting. The ASTCT is also a source of information.

When Applicable Law defines donor advocate and specific requirements, those must be followed.

STANDARD:

B6.4.2 Allogeneic donor infectious disease testing shall be performed using donor screening tests that are licensed, approved, or cleared by the governmental authority.

B6.4.2.1 Hemodilution in the donor prior to collection of blood samples for infectious disease testing and acceptance criteria shall be assessed and documented.

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 US, tests specifically licensed for donor screening must be used according to manufacturer's instructions.

Hemodilution is a decreased concentration of cells and solids in the blood resulting from gain of fluid. This is most likely to occur if a donor has received a large volume of fluids, blood, or plasma in the period before blood samples for testing occurs. This could occur if a cadaveric donor is used. The danger is that detection of relevant communicable disease agents might be missed if the test sample is too diluted. A test of blood volume analysis may help to identify hemodilution.

Evidence:

A review of the medical chart of a cadaveric donor must occur to document the volume of fluids the donor received in the hours prior to blood sample acquisition. If hemodilution is suspected, donors should be tested singly and not in pools to increase test sensitivity.

Example(s):

The U.S. FDA guidance document, titled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" describes algorithms for determining if plasma dilution is sufficient enough to affect test results. This guidance is available at https://www.fda.gov/media/73072/download.

For example, the guidance states that for donors over 12 years of age, an infusion of more than 2000 milliliters of crystalloids within one hour immediately preceding the collection of samples is believed to be sufficient to affect the results of communicable disease agent testing. Based on this information, a Clinical Program should specify in SOPs that samples should not be drawn if the donor has received two or more liters of intravenous fluids in the previous hour.

STANDARD:

B6.4.3 *For allogeneic products containing red blood cells sufficient to cause a transfusion reaction, donors and 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:

It is unusual that cellular therapy products other than whole blood or bone marrow will contain sufficient red blood cells to cause a transfusion reaction, but in the event that the risk is present, it is critical to ensure both the donor and recipient ABO group and Rh type have been determined accurately. For this reason, these 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., independent donor identification, different needle sticks, and different phlebotomists if possible). 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 staff. The cellular therapy program determines who collects the samples and who performs the testing. 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 unrelated donor cord blood products are selected for cellular therapy, two independent donor ABO tests can only be performed when additional cord blood samples are available for testing. However, the recipient should still have two independently determined results for ABO and Rh.

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 verification testing or cellular therapy product collection.

STANDARD:

B6.4.4 *When relevant, a red blood cell antibody screen shall be performed on allogeneic recipients.*

Explanation:

RBC antibody screening is important for recipients who receive cellular therapy products containing red blood cells. 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 the patient lacks. 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. If they do, the specificity may not be directed against an antigen that the recipient possesses or the antibody may not be in high enough concentration to cause a reaction if administered with the product. Routine antibody screening of normal allogeneic donors is not recommended.

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:

B6.4.5 *Allogeneic donors shall be evaluated for risk factors that might result in disease transmission from the cellular therapy product by medical history, physical examination, examination of relevant medical records, and laboratory testing.*

Explanation:
Cellular therapy products can transmit disease agents even after being extensively manipulated. Such agents may be difficult to detect in the product itself so are best detected using blood samples from the product donor. Indeed, 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 screened and tested for these infectious agents by the Clinical Program 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 he/she is 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. This information is provided to the Collection Facility prior to collection.

STANDARD:

B6.4.6 When appropriate for the cellular therapy product, the medical history for allogeneic donors shall include at least the following:

B6.4.6.1 Vaccination history.

B6.4.6.2 Travel history.

B6.4.6.3 Blood transfusion history.

B6.4.6.4 Questions to identify persons at increased risk for transmission of relevant communicable disease agents as defined by the applicable governmental authority.

B6.4.6.5 Questions to identify persons at increased risk of transmitting hematologic, immunologic, or genetic conditions.

B6.4.6.6 Questions to identify a past history of malignant disease.

B6.4.6.7 The allogeneic donor shall confirm that all the information provided is true to the best of their knowledge.

Explanation:

These 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 (typically within 7 days of donation). 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-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. For 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 in dealing with donors who had received smallpox vaccination. Donors must be screened for travel to the area that would put them at risk for malaria, human transmissible spongiform encephalopathy, or severe acute respiratory syndrome (SARS) during periods of world-wide prevalence.
If cadaveric donors are used as a source for the cellular therapy product, the medical and social history must be obtained from the donor's next of kin or another knowledgeable person.

Evidence:
Donor medical examination notes and questionnaire records can be reviewed to determine if all 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 National Marrow Donor Program's "Donor Health History Screening Questionnaire." Another option is the hematopoietic progenitor cell (HPC), Apheresis and HPC, Marrow Donor History Questionnaire (DHQ) materials were developed by the AABB Interorganizational Uniform Donor History - HPC Task Force to provide establishments with a standardized tool to screen allogeneic HPC donors for communicable disease risk factors in accordance with requirements of the FDA, AABB, FACT, and the NMDP. This is available on the FACT website at https://factglobl.org. Information about areas of the world where CJD is a risk factor is also available here.

Specific diseases for which screening is required by the FDA can be found in 21 CFR 1271.75 and at https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable.

The FDA published guidance, "Donor Screening Recommendations to Reduce the Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products;

Guidance for Industry," to provide recommendations for screening donors of HCT/Ps for risk of transmitting the Zika virus. FDA considers the virus a relevant communicable disease or disease agent (RCDAD) as defined in 21 CFR 1271.3(r)(2). Therefore, review of relevant medical records must indicate that a potential donor of HCT/Ps is free from risk factors for, or clinical evidence of, Zika virus infection for the purpose of determining donor eligibility. Newer guidance may be issued, and other countries may have additional guidelines. This document can be found at: https://www.fda.gov/media/96528/download?utm_campaign=What%27sNew2018-05-02&utm_medium=email&utm_source=Eloqua.

STANDARD:

B6.4.7 *Allogeneic donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests as 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.

Testing must occur in accordance with written SOPs and using appropriate donor-screening tests licensed, approved, or cleared by applicable governmental 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.

Evidence:

Medical records and lab results will provide evidence of testing performed and when.

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 through published guidance additional relevant communicable diseases. See FDA Guidance Document ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products [HCT/Ps]", 2007) at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/eligibility-determination-donors-human-cells-tissues-and-cellular-and-tissue-based-products

for additional information. 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 as to affect the potential donor population.
- There could be fatal or life-threatening consequences as a result of transmission.
- Effective screening mechanisms and/or an approved screening test for donor specimens has been developed.

Other communicable disease tests should be added to the donor evaluation as they become available and recommended.

STANDARD:

B6.4.7.1 Human immunodeficiency virus, type 1.

B6.4.7.2 Human immunodeficiency virus, type 2.

B6.4.7.3 Hepatitis B virus.

B6.4.7.4 Hepatitis C virus.

B6.4.7.5 Treponema pallidum (syphilis).

B6.4.8 If required by Applicable Law, allogeneic donors shall also be tested for evidence of clinically relevant infection by the following disease agents:

B6.4.8.1 Human T- Lymphotropic Virus I.

B6.4.8.2 Human T- Lymphotropic Virus II.

B6.4.8.3 West Nile Virus.

B6.4.8.4 Trypanosoma cruzi (Chagas Disease).

Explanation:

In the US, allogeneic HCT/P donors must be tested for HTLV-I and HTLV-II and, on a seasonal basis, for West Nile Virus. Test 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:

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

STANDARD:

B6.4.9.1 For viable, lymphocyte rich cells, including mononuclear cells and other cellular therapy products, blood samples from allogeneic donors shall be obtained within seven (7) days prior to or after collection in the U.S.

B6.4.10 Allogeneic donors shall be tested for cytomegalovirus unless previously documented to be positive.

Explanation:

Cytomegalovirus (CMV) is not a relevant communicable agent or disease. However, allogeneic donors must be tested for evidence of infection with CMV, and 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 provided that 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 warning 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:

B6.4.11 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, CDC/EU/WHO reports) was conducted to determine the need for additional donor testing.

STANDARD:

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

B6.4.12.1 DNA high resolution molecular typing shall be used for HLA typing, if indicated.

Explanation:
This standard applies to all allogeneic donor sources, including cord blood, provided that HLA matching has been shown to be important for the cellular therapy administered. The resolution of HLA matching and the specific loci that should be matched are also variables that need to be assessed.

High resolution is defined as the first and second fields, as defined by WHO nomenclature, and which encode the same protein sequence within the antigen binding site.

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 is often misinterpreted as an antigen level typing.

Standards continue to evolve, and the program must ensure they are utilizing the most up to date version.

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.

STANDARD:

B6.4.12.2 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.

Explanation:
Verification typing is not required for all potential donors, but it is required for the final selected donor for those cellular therapy products that should be HLA matched. Results must be available and confirmed prior to administration of the preparative regimen (if a preparative regimen is utilized) so that any discrepancies may be resolved in advance. Verification typing should be performed according to ASHI or EFI standards. The same resolution is not required for the initial and verification typing.

Verification typing is not required to be performed by the Clinical Program and may be completed through a different facility.

Example(s):
High resolution typing is required; however, the verification typing can be performed at low resolution. There must be concordance between the two results.

STANDARD:

B6.4.12.3 When relevant to the cellular therapy product, there shall be a policy for anti-HLA antibody testing for mismatched donors and recipients.

Explanation:
This standard refers to the testing of the 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 such testing is required and who will be tested for specific antibodies.

Example(s):
Guidance in regard to what details should be included in this policy can be found in the ASHI or EFI Standards. Examples include timeframe of testing, crossmatch testing, etc.

STANDARD:

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

B6.4.14 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., FDA requires that an accompanying statement of authenticity be present for records translated into English.

STANDARD:

B6.4.15 The use of an ineligible allogeneic donor, or an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of urgent medical need that includes the rationale for the selection and documentation of the informed consent of the donor and the recipient.

Explanation:
If a chosen allogeneic donor is ineligible according to Applicable Law or does 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 responsible attending physician of urgent medical need for the cellular therapy product for use of an ineligible donor.

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 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.

FDA regulations and these 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 eligibility determination and urgent medical need documentation does not apply to an autologous donor.

Evidence:
The rationale and informed consent for a specific ineligible donor should be available to the inspector for verifying the appropriate urgent medical need documentation and labeling.

Example(s):
According to U.S. FDA Final Guidance ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products [HCT/Ps]", August 2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This guidance document is available at: https://www.fda.gov/media/73072/download.

STANDARD:

B6.4.16 *Allogeneic donor eligibility and suitability shall be communicated in writing to the collection personnel and Processing Facilities.*

B6.4.17 *There shall be a policy covering the creation and retention of allogeneic donor records.*

B6.4.17.1 *Allogeneic donor records shall include donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.*

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, sex, and medical and behavioral history (the information collected must be sufficient to allow application of exclusion criteria, where required).
  - Consent/authorization form(s), where applicable.
  - 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 and/or governmental regulatory requirements.

Example(s):
It is recommended that a separate medical record be maintained for donors.

STANDARD:

B6.5 Allogeneic Cellular Therapy Products Manufactured for Multiple Recipients.

B6.5.1 At the time of selection for administration, the Clinical Program shall request all technical data from the cellular therapy product manufacturing facility regarding the product after processing prior to cryopreservation, including at a minimum:

B6.5.1.1 Total count of relevant cell.

B6.5.1.2 Viability and/or potency, if applicable.

B6.5.1.3 Microbial cultures from the cellular therapy product after processing prior to cryopreservation.

B6.5.1.4 ABO group and Rh type, if applicable.

B6.5.1.5 All HLA Class I and II typing results, if applicable.

B6.5.1.6 Communicable disease testing results performed on the donor.

B6.5.1.7 Final donor eligibility determination and risks of communicable or genetic diseases disclosed by the donor, medical, and genetic screening or clinical chart review, and the results of any investigation or further testing performed.

B6.5.1.8 The method of processing.

B6.5.1.9 Any variances in collection, processing, testing, cryopreservation, storage, or transport or shipping procedures that may influence the integrity or quality of the cellular therapy product.

B6.5.1.10 Physical characteristics of the cellular therapy product, including at a minimum the number and type of bags or compartments used for storage.

Explanation:
When the Processing Facility is part of the Clinical Program, this information should be readily available. For products obtained from outside the program it is best to request by written agreement that relevant information is provided. If the manufacturer is unable or unwilling due to proprietary or confidentiality reasons to provide the information specified in standards B6.5.1.1 through B6.5.1.10, the reason(s) should be explained.

Evidence:
The inspector should review the information provided to the Clinician Program with products received from a third-party manufacturer. An IB, package insert, certificate of conformance, or certificate of analysis can be requested. If information is missing, the reason should be specified in the records.

B7: RECIPIENT CARE

STANDARD:

B7.1 Recipient informed consent for the cellular therapy shall be obtained and documented by a licensed healthcare professional knowledgeable of the proposed therapy.

B7.1.1 The Clinical Program shall provide information regarding the risks and benefits of the proposed cellular therapy.

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

Explanation
Recipients of cellular therapy products must receive comprehensive information prior to initiating any preparative treatment, recommended either 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 alternative treatment options and their anticipated outcome, use of immunosuppression, the legal rights of the recipient and the protection of the recipient's 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 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 confirm that cell therapy recipients have a) understood the information provided, b) had an opportunity to ask questions and had 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:
B7.2 The attending physician shall confirm the availability and suitability of a donor or cellular therapy product prior to preparing the recipient for cellular therapy.

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 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 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. Refer also to B1.2 if cellular therapy products provided by third parties will be utilized.

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, if appropriate, times.

B7.4 There shall be policies or Standard Operating Procedures addressing safe administration of the preparative regimen, if applicable.

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 these regimens. Staff administering the preparative regimen shall be appropriately credentialed as required by Applicable Law and as defined by institutional policies.

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):

Administration of chemotherapy when required for the preparative regimen 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.

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 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, ideal body weight, or other calculation (e.g., adjusted body weight) on the treatment orders. Verification of Body Surface Area, 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 equivalents 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 are preprinted 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 inspection team may review orders of patients currently receiving chemotherapy. There should be evidence that the orders were reviewed and approved by an attending physician.

As in other industries, a final checklist is required to confirm each step in preparing for and administering therapy is performed prior to cellular therapy product administration. The ordering physician shall provide electronic or written signature verifying critical functions have been performed, (e.g., HLA typing, consent, eligibility) and any other issues have been considered, are correct, and documented.

STANDARD:

B7.5 *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 must 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., donor lymphocytes, IECs, mesenchymal stromal cells), cell counts, etc. should be taken into consideration. Programs should work with their Processing Facilities to verify appropriate processing and preparation of the product 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. Clinical Programs are responsible for communicating with the Processing Facility regarding any delayed administration.

Non-cryopreserved (often referred to as "fresh") cellular therapy products must be administered within the time specified by Clinical Program policies. When using frozen stem cell products, individual bags should be thawed and infused before thawing subsequent bags to reduce the duration of room temperature storage or thawed products.

In addition, all other standards applicable to these cells must be met, including any risk evaluation and mitigation strategies in the U.S. (REMS) or Risk Management Plans in the EU or Canada (RMP) designated by the manufacturer.

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 a product administration is scheduled on the day of inspection, the inspector should be notified so that he/she may observe at least portions of the procedure. If not, a mock procedure should be performed for inspector observation.

Example(s):
Cryopreserved products may include administration of significant amounts of DMSO. Bone marrow infusions may include administration of significantly more ABO-mismatched RBCs than apheresis-derived products. Specific administration guidelines should exist to address such issues.

Clinical Program must communicate with the Processing Facility to ensure appropriate scheduling and timing of product administration. One way to manage communication is to use a summary sheet or other written documentation of the start and end date of the preparative regimen and the date and time, if needed, of the planned cellular therapy product administration. If plans change, updated information should be provided to the Processing Facility prior to the day of planned product administration.

Monitoring of vital signs is 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 during and at least one hour after cellular therapy product administration. Some cellular therapies are known to elicit early adverse reactions such as cytokine release syndrome following CAR-T cell infusions.

REMS or RMPs may be specifically defined by the manufacturer for licensed products. These include detailed procedures for provider education, patient education and monitoring, adverse event management, patient discharge instructions (including wallet cards that describe steps to take in the event of certain symptoms), and reporting of outcomes to manufacturers.

STANDARD:

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

B7.5.2 *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.*

B7.5.3 *There shall be documentation in the recipient's medical record of the unique identifier of the administered cellular therapy product, initiation and completion times of administration, and any adverse events related to administration.*

B7.5.4 *A circular of information or investigator's brochure 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. The current version can be found on the FACT website. For novel cellular therapy products, the institution should create its own circular of information. 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 circular of information is and what information is included in it. An IB or package insert may contain this information.

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:

B7.6 There shall be policies or Standard Operating Procedures addressing appropriate follow-up after administration of cellular therapy products.

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 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 (see also Standard B5.1).

STANDARD:

B7.7 There shall be policies or Standard Operating Procedures in place for the planned discharge and provision of follow-up care.

Explanation:

The plans for discharge after administration of cellular therapy products will vary based on the product given. A period of observation to monitor potential adverse reactions is required after which ongoing inpatient care may be 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-treatment care. This might include additional laboratory testing, such as C-reactive protein, lactate dehydrogenase, ferritin, and fibrinogen levels to monitor complications. This may not involve direct provision of care but must work operationally within the Quality Management 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-cellular therapy 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 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.

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., emergency department, clinical unit).

STANDARD:

B7.8 There shall be policies or Standard Operating Procedures in place for provision of appropriate long-term follow-up care to recipients.

Explanation:
Long-term follow-up care is a critical component of the comprehensive care that the Clinical Program is responsible for providing to recipients of cellular therapy. 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.

SOPs should include procedures for monitoring the effects of the cellular therapy on the patient's primary disease as well as late effects.

B8: CLINICAL RESEARCH

STANDARD:

B8.1 Clinical Programs shall have formal review of investigational treatment protocols and patient consent forms by a process that is approved under institutional policies and Applicable Law.

B8.1.1 Clinical Programs utilizing investigational treatment protocols shall have in place a pharmacy equipped for research activities, including a process for tracking, inventory, and secured storage of investigational drugs.

B8.1.2 There shall be a process to manage investigational cellular therapy products.

B8.2 Clinical research protocols shall be performed 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 Institutional Review Board (IRB), Ethics Committee, or equivalent.

B8.2.1.2 If applicable, documentation of approval by the Institutional Biosafety Committee (IBC) or equivalent.

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 requirements is to confirm that the Clinical Program is obtaining appropriate review of clinical research protocols. These Standards apply to clinical research performed under INDs held by the Clinical Program, its institution, industry sponsors, or any other entity for whom the program is conducting the research.

The cellular therapy 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 and/or the FDA in the U.S. Genetically modified IEC products, such as CAR products, may also be under the oversight of the Recombinant DNA Advisory Committee (RAC), which applies to investigators supported by the NIH in the U.S.

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 Clinical Program must comply with Applicable Law.

Evidence:
The inspector may ask about the process for review of protocols, ask which IRB or Research Ethics Committee (REC) is used by the Clinical Program, and examine the regulatory binder for a specific study. A signed consent form in one of the patient charts can be used to cross check approval dates with IRB regulatory agency documents. If the center carries out any studies under IND or IDE application or non-U.S. equivalent, the regulatory binder for such studies needs to 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. One aspect requiring management is clinical research monitoring by institutional monitors, independent monitors contracted by industry, national cooperative group monitors, lead research center monitors, etc.

There are a variety of ways to manage cellular therapy products. Management in a cellular therapy Processing Facility is influenced by staff experience, storage facilities, and validated procedures. 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 aspects should be appropriately described in policies and SOPs.

STANDARD:

B8.3 For clinical research, informed consent shall be obtained from each research subject or legally authorized representative, in language he or she can understand, and under circumstances that minimize the possibility of coercion or undue influence.

B8.3.1 The research subjects or legally authorized representatives shall be given the opportunity to ask questions and to have their questions answered to their satisfaction, and to withdraw from the research without prejudice.

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

Explanation:

This standard addresses the appropriate elements of informed consent for subjects treated on clinical research protocols.

Language the subject can understand shall be conveyed via the process of informed consent following Applicable Law and institutional policies. This may include the grade-level or laymen's terms, cultural considerations, assent, language translation, and interpretation.

Detailed information about the scope of the clinical research, such as if the research is conducted at single or multiple sites, may influence the subject's decision to participate. In the U.S., sources such as clinicaltrials.gov are required by the informed consent process.

Evidence:
The informed consent documentation in some of the charts being reviewed can be used to confirm that it is compliant with applicable regulatory requirements.

Example(s):
A Clinical Program may use an IRB that provides template consents that cover all elements 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 have 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:
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.

Management plans for identified potential conflicts of interest must exist in accordance with Applicable Law and institutional policies and SOPs. Conflict of interest policies and SOPs must 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 participating subjects, depending on governmental and institutional mandates. In the U.S., CFR Part 54 applies.

STANDARD:

B9.1 The Clinical Program shall collect and maintain complete and accurate data necessary to complete the Cellular Immunotherapy Data Resource (CIDR) forms, Cellular Therapy Med-A forms, or other appropriate forms of the EBMT

B9.1.1 Clinical Programs shall submit the data specified in B9.1 to a national or international database if required by Applicable Law.

B9.1.2 Clinical Programs should collect the data specified in B9.1 for all patients for at least one (1) year following administration of the cellular therapy product.

Explanation:

FACT acknowledges the importance of complete and accurate data for self-assessment in individual Clinical Programs, for research and outcome reporting, and for compliance with FACT Standards. FACT strongly recommends the publication of cellular therapy data and strongly encourages the submission of data to the CIBMTR or EBMT as appropriate. Standard B9.1 does not require that program data be submitted to these registries; however, it does recommend that data collected in their forms be maintained by the program.

Clinical Programs applying for FACT accreditation of their novel cellular therapy programs should use the appropriate CIBMTR forms for these therapies. CIBMTR frequently revises its forms to remain current in the rapidly evolving field of cellular therapy. Programs should use the forms that are appropriate for the novel cellular therapy products they administer. Some of these therapies have very specific forms and some are included on general cellular therapy forms.

Over the years, both FACT inspectors and CIBMTR auditors have continued to observe some Clinical Programs and personnel who struggle with data accuracy and completeness. The two organizations collaborate to help FACT-accredited programs improve through intensified support between inspections, increased emphasis on implementation of corrective action plans, and follow up to document continuous improvement. Programs submitting data to CIBMTR may be included in this collaboration to promote effective data management.

Evidence:

If the Clinical Program does not submit data to these registries, it must provide reasonable explanations for not submitting the data.

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):
In July 2016, CIBMTR released three new forms for use with novel cellular therapies. These include:

- Pre-Cellular Therapy Essential Data (Pre-CTED), Form 4000: Pre-infusion data,
- Cellular Therapy Infusion, Form 4006: Infusion and product manufacturing data, and
- Post-Cellular Therapy Essential Data (Post-CTED), Form 4100: Post-infusion follow up data.

STANDARD:

B9.2 The Clinical Program shall define staff responsible for collecting and reporting data.

B9.2.1 Defined data management staff should participate in continuing education annually.

Example(s):
Continuing education for data management staff may include CIBMTR educational activities and training found at https://www.cibmtr.org/DataManagement/Pages/index.aspx.

B10: RECORDS

STANDARD:

B10.1 Clinical Program records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years by the Clinical Program, or longer in accordance with Applicable Law.

Explanation:
Each Clinical Program has the flexibility to develop individualized systems of maintaining and organizing records provided that the objectives of these Standards are achieved. The methods for filing and transfer of records to archival storage should be specified. Records may be maintained in more than one location, provided that the records management system is designed to allow prompt identification, location, and retrieval of all records. However, it is recommended that recent records should be kept on-site, and archived records should be readily accessible within a reasonable time frame relevant to the current operations of the facility. Records may be maintained as original paper records, electronic files, photocopies, microfiche, or microfilm. Suitable equipment must be available for reading and/or photocopying records maintained on microfiche or microfilm.

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 should the program cease operation.

Quality management records include all of the items referred to in B4 (Quality Management) including the results of audits; errors, accidents, and adverse reaction reports; complaints; and outcome analysis.

Personnel training and competency records include all of the items referred to in B3 (Personnel), including licenses and board certifications for all attending and consulting physicians, licenses for all 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 identification of responsible individuals including job titles and areas of oversight and resolution of facility problems. 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 and disposal; and the outcome of any building or clinical unit inspections for safety or compliance with governmental or other agencies.

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):
Examples of good documentation practices can be found via the U.S. Pharmacopeia or clinical research offices.

STANDARD:

B10.1.1 Employee records shall be maintained by the Clinical Program in a confidential manner and for as long as required by Applicable Law.

B10.1.2 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 Clinical Program records is for the documentation of cleaning and sanitation. These records must be retained for at least 3 years after creation and should include cleaning schedules, methods, and identification of personnel responsible for cleaning and documentation of their initial training and retraining.

Evidence:
If documentation of cleaning and sanitation is performed directly by the institutional environmental services department, the Clinical Program should have knowledge of this documentation and the ability to show that it is complete.

STANDARD:

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

B10.2 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, whichever is latest.

Explanation:
Recipient and donor records (either electronic or hard copy) include allogeneic donor eligibility determination, including results and interpretation of testing and screening. These records must be maintained with a secure system that ensures confidentiality and is compliant with Applicable Law on confidentiality and data protection. The inspector should be alert to breaches in policy or security that potentially compromise patient confidentiality.

Recipient 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.

Data to be provided to other facilities involved in the collection or processing of the cellular therapy product include 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 and/or Processing Facilities.

STANDARD:

B10.3 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. Research records should also comply with GxPs.

Example(s):

In the case of genetically modified cellular therapy products, 15-year follow-up is required by the U.S. FDA and EMA. Consequently, records must be maintained for the duration of follow-up. In the U.S., HIPAA regulations on confidentiality and data protection apply.

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 under the control of the Clinical Program that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

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." As Clinical Programs 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 applies:

- 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).

It is not the intent of these Standards to include hospital-based electronic 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 program is required to meet these Standards.

Each Clinical Program 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 Clinical Program's list of critical electronic record systems to confirm it includes all electronic record systems used by the facility and under control of the Clinical Program that meet the criteria in this standard. Additionally, a list of critical electronic record types should be provided pre-inspection.

The inspector should determine the scope of electronic records used by the Clinical Program 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.
- 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 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, for guidance to assess the validation procedures (https://www.fda.gov/media/75414/download), as well as the applicable requirements of HIPAA.

STANDARD:

B10.4.2 For all critical electronic record systems, there shall be policies, Standard Operating Procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

B10.4.3 There shall be a means by which access to electronic records is limited to authorized individuals.

B10.4.4 The critical electronic record system shall maintain unique identifiers.

B10.4.5 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

B10.4.6 For each critical electronic record system, there shall be an alternative system for all electronic records to allow for continuous operation in the event that a critical electronic record system is not available. The alternative system shall be validated, and Clinical Program staff shall be trained in its use.

B10.4.7 For all critical electronic record systems, there shall be written Standard Operating Procedures for record entry, verification, and revision.

B10.4.7.1 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 does 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:

B10.4.7.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

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 log-in credentials.

STANDARD:

B10.4.8 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

B10.4.9 For all critical electronic record systems, there shall be validated procedures 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 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:

- 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]), or 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 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 back-ups that include storage of back-up data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the back-up copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include all of 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 to assure 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 must 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 back-ups of records maintained electronically is in place.

STANDARD:

B10.4.9.1 Training and continued competency of personnel in systems use.

Explanation:
Personnel must be trained to appropriately use all critical electronic record systems (including record entry, verification, and revision) and back-up 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.

STANDARD:

B10.4.9.2 Monitoring of data integrity.

B10.4.9.3 Back-up of the electronic records system on a regular schedule.

B10.4.9.4 System assignment of unique identifiers.

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.

B10.5.2 The Clinical Program shall furnish outcome data, related to the safety, purity, or potency of the cellular therapy product involved, to other facilities involved in the collection or processing of the cellular therapy product.

Explanation:
This standard applies to both in-house and contracted collection, processing, or administration Facilities. Generally, relevant records will be maintained by the facility that performs the work.

Maintenance of records must be specified in the SOPs, and it must be clear who the responsible party is 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 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 program to clearly outline what the other facilities' requirements are to help achieve quality cellular therapy.

Donor and recipient confidentiality must be maintained by using identifiers when this is required by unrelated donor registries. The location of each facility must be known to the relevant personnel at each facility but should not be known to the recipient or donor. Facilities that participate in programs such as NMDP will have well-defined procedures for divided responsibility. In the case of the NMDP, the appropriate Limited Data Set Use Agreement should be in use. Applicable Law regarding data confidentiality must be followed.

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 agreement or 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):
Donor eligibility is an 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 facility can verify that an eligibility determination was made. It should be obvious in the record who performed each of these responsibilities.

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COLLECTION STANDARDS

PART C

PART C: COLLECTION STANDARDS

C1: GENERAL

STANDARD:

C1.1 These Standards apply to all collection, storage, and distribution services performed on cellular therapy products.

Explanation:

Part C of these Standards apply to all activities on a cellular therapy product, which include storage and distribution in addition to the collection. Once a product has been collected, it is being stored until it is distributed by collection staff. 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.

Cellular therapy product starting material may come from other tissues sources such as marrow, peripheral blood, fat, solid or liquid tumors, and small whole blood donations, among others. In some cases, the Clinical Program may oversee the collection operations and will be responsible for complying with the standards in this section.

Note that for ease of description, when referencing a "Collection Facility" in these Standards, that term also includes collection services that are overseen by the Clinical Program.

STANDARD:

C1.2 Collected cellular therapy products shall be distributed to facilities that meet FACT Standards with respect to their role in cellular therapy.

Explanation:

Products collected under these Standards must use cell processing facilities that meet the requirements of these Standards in order to be eligible for accreditation. The Processing Facility is not required to be formally acknowledged as FACT accredited; however, even if not pursuing accreditation, the facility must comply with these Standards.

When a cellular therapy product is centrally manufactured by a third-party, the Clinical Program or Collection Facility may be responsible for securing collection of the cells or preparing the product for administration. If these responsibilities are designated to the Clinical Program or Collection Facility in written agreements, the following examples would require compliance with Part C or Part D of these Standards as applicable:

- Evaluation of the autologous or allogeneic donor for suitability (medical fitness) to undergo the collection procedure.
- Evaluation of the allogeneic donor for donor eligibility (free of risks of transmission of infectious diseases).

- Collection of the cells.
- Temporary storage of the product in the Processing Facility and distribution to the clinical unit.
- Thawing and other needed manipulations of the product before administration to the recipient.

Evidence:
Processing Facilities must be inspected to ascertain that they meet these Standards in regard to their interactions with the Collection Facility. If a Processing Facility is already FACT accredited to provide services to multiple facilities, this may satisfy the inspection requirement. If a facility is not FACT accredited to provide these services, it must provide evidence of compliance with these Standards, including compliance with Applicable Law. Evidence includes pre-inspection documentation and on-site inspection.

STANDARD:
C1.3 Collection of cellular therapy products shall comply with Applicable Law.

Explanation:
FACT is a voluntary inspection and accreditation program sponsored by the ASTCT and ISCT. Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with these Standards does not guarantee compliance with Applicable Law. Applicable Law must also be followed. It is the responsibility of the individual Collection Facility or 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; for example, when a facility is sending or receiving cellular therapy products from outside of its immediate jurisdiction.

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

Evidence:
Current certificates, registrations, permits, or licenses will demonstrate which areas of a facility have been authorized by other organizations or governmental authorities.

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 these 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 1271 GTP regulations and section 361 of the Public Health Service Act, with the exception of products collected from marrow. 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 (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. Most programs accredited under the FACT Common Standards fall in this category. 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.

STANDARD:

C1.3.1 *Collections shall be performed in a facility licensed, registered, or accredited as required by the appropriate governmental authority for the activities performed.*

Explanation:
Facilities must be appropriately licensed, registered, and/or accredited as required by Applicable Law, including registration or certification with the government or 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 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 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 recovery, screening, testing, packaging, processing, storage, labeling, or distribution of cellular therapy products in the U.S. is required to register with the FDA annually (21 CFR 207, 807, and 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 207 and 807). More information regarding the requirements and process for FDA registration can be found at http://www.fda.gov/cber/tissue/tisreg.htm. 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 facility include the screening of donors for infectious disease risk to determine eligibility, temporary storage of products, and the apheresis collection procedure.

Examples of verified compliance with Applicable Law include acceptable FDA audits, state licensure, CLIA certification, OSHA inspections, or accreditation by the AABB, ASHI/EFI, CAP, or any other applicable accreditation body.

STANDARD:

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

Explanation:

Facilities that are active in the collection of licensed blood products or therapeutic procedures may have significant apheresis experience from these activities; however, the facility and personnel must document specific experience in the cellular therapy product collection for which they are seeking accreditation.

Evidence:

Current employee files and curriculum vitae should document evidence of length of employment and experience with cellular therapy product collections.

STANDARD:

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

Explanation:

This standard refers specifically to the number of collection procedures for cellular therapy products, not the number of patients from whom cells were collected. Both allogeneic and autologous donors may be included. New facilities that want to gain the required experience needed for initial accreditation may conduct validation runs and use normal volunteers for collection of cellular therapy products that are never administered. These would count toward the goal of 5 cellular therapy products; however, those types of collections (normal volunteers for products that are never administered) are not accepted for renewal accreditation.

This standard allows application for accreditation prior to meeting the minimum volume. In this scenario, there must be adequate Quality Management (QM) data to demonstrate compliance with these Standards, and the facility's team must be experienced (see C3 Personnel). Accreditation will not be awarded until the minimum number is met. The facility must decide if it is in a position to accept the risk of not meeting the minimum number (and not becoming accredited) within the accreditation timeline.

Evidence:
A review of current Collection Facility statistical reports can be used to ascertain whether the facility has complied with the required minimum number of cellular therapy product collection procedures.

Example(s):
FACT will use the average number of collections per year over the accreditation cycle to determine if collection activity meets the minimum number. For example, if a FACT-accredited facility performs 3 collection procedures in the first year, 7 in the second, and then 5 in the third, the program will have performed an average of 5 procedures per year during the accreditation cycle and will have met the standard.

C2: COLLECTION ENVIRONMENT

STANDARD:

C2.1 *There shall be secured and controlled access to designated areas appropriate for collection of cellular therapy products and for storage of cellular therapy products, equipment, supplies, and reagents.*

Explanation:
Storage areas for cellular therapy products must be designated and controlled 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 without risk of contamination or cross-contamination. Upon receipt of supplies, kits, and reagents, inspection for suitability must be docuD2.1mented. For items requiring storage at a specified temperature range, the temperature of the storage area must be monitored and documented.

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 include a mechanism to identify the location or disposition of a specific lot of a supply or reagent in the event of a manufacturing recall.

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 facility during the on-site inspection, including all

locations where cellular therapy products are collected, stored, or distributed. The areas should be designed to facilitate proper workflow and cleanliness. Observation of the organization, design, location, and amount of space available can determine if it is adequate for the number and types of collections performed, and if the collection environment is adequate to minimize the risk of product contamination.

If there are no collection procedures occurring on the day of the on-site inspection, the inspector should ask that a mock collection for each type of product being collected 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 other procedures performed using the same instruments and 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.

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, compromise product integrity, or pose a risk of contamination or cross-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.

When an accredited Collection Facility (or the location where collections are performed) is to be relocated, qualification and validation must be performed to confirm the new space meets these Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT Accreditation Policies, available on the FACT website. The Collection Facility is expected to submit a description and floor plans of the new facility, QM documents, and an expected relocation date. Most relocations will be assessed during regularly scheduled inspections or interim audits; however, if there are any concerns with the information submitted by the facility, a relocation inspection may be necessary.

Example(s):
Adequate storage can be accomplished by storing 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 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 or research material must be clearly separated from clinical material and appropriately labeled.
A first in, first out system is most frequently used in the Processing Facility, with paper-based or electronic tracking. program.

STANDARD:

C2.1.1 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:
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 patient and an isolation room to prevent cross contamination, especially when the facility is also performing other therapeutic procedures.

Evidence:
Although there is no standard for the amount of space necessary to provide a safe environment for collection, the inspector should evaluate this issue based on his/her own experience. It is also helpful to see results of surveys submitted by donors and recipients. The inspector should investigate what other activities are performed on the equipment and in the space.

STANDARD:

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

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:
Where applicable, 21 CFR 211.42(b) in the U.S. requires that facilities have adequate space and measures for product segregation and for the orderly placement of equipment and materials to prevent mix-ups and/or contamination between different components, including cellular therapy products. Separate or defined areas, or other control systems, must be in place for the operations as necessary to prevent contamination or mix-ups.

STANDARD:

C2.1.3 There shall be suitable space for confidential donor examination and evaluation.

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

Explanation:
The layout and design of the Collection Facility must minimize the risk of error and permit effective cleaning and maintenance 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.

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 parameters of the facility in which collection is performed 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 Parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.

Explanation:
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 as well as conditions that would diminish equipment or personnel performance, such as extreme humidity. Some but not all, equipment has defined operating limits that should not be exceeded.

Environmental monitors for measures of air quality, such as particle counts and/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, documentation of the reasoning behind this decision must be provided prior to inspection. It is the inspector's responsibility to determine while on site if identified facility parameters affecting cellular therapy product viability, integrity, contamination, or cross-contamination 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 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 and cellular therapy product safety. Adverse temperatures and humidity levels may result in aborted collections and suboptimal personnel performance. Temperatures below freezing may damage products, and studies show a poorer survival of stem cells correlated with higher temperatures. 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 verify acceptable humidity and temperature ranges with equipment manufacturers to set limits. If those limits are outside of usual conditions of the facility, it may choose not to control those parameters. The facility may also reference facility management policies, such as the use of an air conditioning unit (which controls humidity and temperature) that is maintained by the institution. On-site inspections have revealed instances when humidity did impact the safety of the cellular therapy product. For example, in one particularly humid climate, a Processing Facility's liquid nitrogen freezer lids defrosted enough to cause frost build-up and prevent the lids from closing completely.

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 facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.

Explanation:
Collection Facility cleaning and sanitation must be performed on a regular basis 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 methods used must be specified by an SOP (see C5.1). While the bench-top 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 also fall under this standard. The facility, together with the cleaning services vendor, must establish SOPs for this activity.

For some specialized collection procedures, equipment or instruments that contact the cellular therapy product may require cleaning and sterilization between uses. When this is the case, the cleaning and sterilization methods used must be verified to remove infectious agents.
Beds and chairs or other surfaces that patients contact must be cleaned between patients. If an institutional policy is followed for the cleaning and sanitation of beds, chairs and surfaces, 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, chairs, and surfaces between patients has been completed.

Evidence:
Collection Facility cleaning must be documented, and the records maintained for the period of time specified in institutional policies or Applicable Law.

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 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 collections performed, proportionate to the volume of work done, and should be conveniently located.

There should be policies and SOPs that address interruption in collection due to equipment failure that address the handling and labeling of cellular therapy products. There should also be policies and SOPs that prevent subsequent delay in collections, such as the requirement for 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 back-up plan in the event of equipment failure.

STANDARD:
C2.7 There shall be access to an intensive care unit or emergency services.

Explanation:
These Standards aim to protect recipient and donor safety in rare emergency situations. There must be documentation that there is ready access to an ICU or equivalent coverage in an immediate fashion for recipients and donors when appropriate. This requires the ability to provide multisystem support including assisted respiration.

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):
Examples of appropriate training and emergency equipment include an electrocardiograph, crash cart, code team (in the hospital), or ACLS- and/or CPR-trained individuals (in freestanding Collection Facilities). If the only emergency response available to the facility is a community-based emergency service (such as 911), the inspector should be able to verify that such an option is feasible and provides for a safe collection. Ideally, there should be documentation that there was at least one test of the emergency response system, particularly when community-based services are used.

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

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 hospitalists, general internists, physician assistants, nurse practitioners, or other advanced practice providers. It is acceptable to allow these general practitioners to provide patient care during specified hours; however, the attending physician is 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 or by physicians in specialties specific for the cellular therapies performed. Providers providing coverage must have a clear understanding of when the attending physician must be notified and how to reach that physician.

Evidence:
There must be guidelines that describe inpatient, outpatient, and afterhours care, including when and under what conditions general medicine physicians must contact the attending physician. 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:
C2.9 The facility in which collection is performed shall be operated in a manner designed to minimize risks to the health and safety of employees, donors, visitors, caregivers, and volunteers.

C2.10 There shall be 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 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. Safety, infection control, or biohazard waste disposal procedures that are unique to the facility must be covered in the facility's SOP 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.

Evidence:
Ideally, the inspector should observe an apheresis 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 how cellular therapy products are handled and discarded (e.g., incinerator, waste field) and compare his/her observations with the written protocols. The inspector should examine selected employee files for training in biological, chemical, radiation, electrical, and fire safety (when appropriate). Compliance with Applicable Law should be addressed by the 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.

A condensed or summarized hard copy of the institutional safety manual must 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 recipients or donors with a known communicable disease.

STANDARD:

C2.11 All waste generated by collection 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 handlers, and the community to injuries, infections, and potential toxins. Hazardous waste generated by the Collection Facility's activities includes a broad range of materials, including used supplies, sharps, chemicals, radioactive material, 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. General waste that contains confidential information including paper or compact discs should be stored in a secured container before disposal and ultimately shredded or destroyed.

Evidence:

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

Example(s):

Contaminated materials may be typically 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 health care waste and placed for disposal in puncture proof containers. Chemicals such as cytostatic drugs shall be discarded in accordance with Applicable Law.

STANDARD:

C2.12 Personal protective equipment, including gloves and protective clothing, shall be used while handling biological specimens. Such protective equipment shall not be worn outside the work area.

Explanation:

Collection Facilities must follow their institutional policy regarding appropriate personal protective equipment (e.g., gowns, goggles, plastic apron, 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, personal protective equipment must be removed before leaving the workspace.

STANDARD:

C2.13 When a collection kit is prepared and sent to collection staff, there shall be adequate instructions and materials to collect, label, store, pack, and transport or ship the cellular therapy product and associated samples to the Processing Facility.

C2.13.1 The collection kit shall be transported or shipped under conditions validated to maintain the designated temperature range from the time it leaves the shipping facility until it is received by the collection staff.

Explanation:

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 provider of the kit 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 for the use and storage of the collection kit, and the documentation that the kit was correctly used and stored.

Example:

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.
- During return to the Processing Facility.

C3: PERSONNEL

STANDARD:

C3.1 MEDICAL DIRECTOR OF COLLECTION SERVICES

C3.1.1 There shall be a Medical Director who is a licensed physician with postgraduate training in the methods required for cellular therapy product collection or the therapeutic disease areas.

Explanation:
The Collection Services Medical Director must 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 cell collection, cellular therapy, and/or the therapeutic disease area for which the cellular therapy is performed.

Evidence:
To fulfill this standard, the Medical Director must provide a photocopy of his/her current state, provincial, or national license. Since documentation of the medical degree is required to obtain a medical license, the license will be sufficient documentation that the Medical Director is a physician. This documentation is submitted with the application and should be available to the inspector prior to the on-site inspection.

STANDARD:

C3.1.2 The Medical Director shall be responsible for the following elements:

C3.1.2.1 All technical procedures.

C3.1.2.2 Performance of the collection procedures.

C3.1.2.3 Supervision of staff.

C3.1.2.4 Administrative operations.

C3.1.2.5 The medical care of donors undergoing cell collections.

C3.1.2.6 Pre-collection evaluation of donors at the time of donation.

C3.1.2.7 Care of any complications resulting from the collection procedure.

C3.1.2.8 Compliance with the Quality Management Program, these Standards, and Applicable Law.

Explanation:
The Medical Director of Collection Services is responsible for all administrative and technical aspects of the Collection Facility similar to the Collection Facility Director under the FACT-JACIE Standards for HCT in addition to the responsibilities of the Medical Director under those standards. The specific responsibilities are shown in the standards above. However, some of these responsibilities can be designated.

The Medical Director of Collection Services may have other responsibilities, but he/she or a designee should be available at all times when the Collection Facility could be operational. The director responsibilities should be specifically documented.

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 and the QM Plan, including identification of designee(s) and their responsibilities.

Example(s):
Documentation of evidence may include the Medical Director of Collection Services signature for reviewing SOPs and the QM Plan.

STANDARD:

C3.1.3 *The Medical Director shall have at least one (1) year experience in performing or supervising cellular therapy product collection procedures.*

Explanation:
The term "supervised" in this standard differs from the supervision of technologists during training, or directly observing collection procedures. The term refers to the Medical Director of Collection Services 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.

STANDARD:

C3.1.4 *The Medical Director shall participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy product collection or the applicable therapeutic disease areas.*

Explanation:
The Medical Director of Collection Services must participate regularly in educational activities related to cellular therapy 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 his/her judgment to determine if the Medical Director of Collection Services 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 included 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 in which the Medical Director of Collection Services participated, the following information must be submitted for each of the completed continuing education activities within the previous accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, meeting, grand round).
- Topic of activity (e.g., hematology, cellular therapy).
- 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. Content must reflect regular education in cellular therapy and diseases in which cellular therapy is a therapeutic option.

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/CPD lectures.
- Presentation of a paper at a scientific meeting.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or on-line 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. These can be accessed at https://learn.astct.org/.

A downloadable Educational Activities form is available on the FACT website at https://www.factglobal.org/education-and-resources/general/hematopoietic-cellular-therapy-library/.

The use of this form is not required but can be used to document compliance with continuing education requirements.

STANDARD:

C3.2 QUALITY MANAGER

C3.2.1 There shall be a Quality Manager for collection activities to establish and maintain systems to review, modify, and approve all policies and Standard Operating Procedures intended to monitor compliance with these Standards, Applicable Law, or the performance of the collection activities.

Explanation:

The title held by this individual may differ among facilities and is not relevant provided that the duties include those described in these Standards. The Quality Manager for collections 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 provided that the Medical Director of Collection Services 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 and/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 compliant with these 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.

Example(s):

Formal training may include documented practical work experience in a facility, fellowship, or a certification program.

STANDARD:

C3.2.2 The Quality Manager of collection activities should have a reporting structure independent of cellular therapy product collections.

Explanation:

The Medical Director of Collection Services 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 is responsible for the QM Plan and its proper implementation.

Evidence:
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):
These Standards do not prohibit the Quality Manager from participating in collection activities, as many facilities or institutions may not be large enough to support free-standing QM staff. However, the Quality Manager should not review or approve technical procedures for which he/she is solely responsible. In such cases, that review should be delegated to another staff member or to the Medical Director of Collection Services. The Quality Manager can review SOPs where they have contributed to the activity following a reasonable time to reduce the potential for bias. What constitutes a reasonable time lapse may vary based on the type of activity being reviewed. Audits most often will be performed weeks or months after the activity that is being audited was performed. The reasonable time for specific activities to be reviewed should be defined by the facility's policies and SOPs.

The Medical Director of Collection Services can also assume the Quality Manager role provided that the role does not pose a conflict on proper implementation of a QM Plan for the Collection Facility. Such a situation may occur more often in a small facility where technical responsibilities do not allow time for the activities of QM supervision.

STANDARD:

C3.2.3 *The Quality Manager shall participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy, cell collection, or quality management.*

Explanation:
The Quality Manager must participate regularly in educational activities related to cellular therapy product collection and QM 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 included 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 (10) hours in combination of these topics is required. Each topic does not need to be covered in ten (10) hours individually. The inspector should assess the documented number and

content of the continuing education activities and use his/her judgment to determine if a QM Manager meets this Standard.

To assess the appropriateness of the amount and type of continuing education in which the Quality Management Manager participated, the following information must be submitted for each of the completed continuing education activities within the previous accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, meeting, grand round).
- Topic of activity (e.g., hematology, cellular therapy).
- 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. Content must reflect regular education in cellular therapy and diseases in which cellular therapy is a therapeutic option.

Example(s):
Evidence of compliance may include either formal or informal study. Educational activities do not necessarily require large financial resources. The 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 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 on-line tutorial.
- Review of an article 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 offers an Online Learning center that hosts recordings from its many educational events. These can be accessed at https://learn.astct.org/.

A downloadable Educational Activities form is available on the FACT website at https://www.factglobal.org/education-and-resources/general/hematopoietic-cellular-therapy-library/. The use of this form is not required but can be used to document compliance with continuing education requirements.

STANDARD:

C3.3 STAFF

C3.3.1 The number of trained 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 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 these Standards. There should be sufficient staff present to manage in the event of any donor emergency without neglecting ongoing collections. A designated back-up, 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 Medical Director of Collection Services 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 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 dated personnel records demonstrating competency and experience. The inspector should not request or be given confidential information such as staff medical records (e.g., vaccinations and health records).

Example(s):
Insufficient staffing may be indicated by excessive overtime, rapid turnover of personnel, incomplete record keeping, or an increase in adverse events.

Competency testing may include observation of performance of a procedure by a supervisor or coworker, oral or written examination of expected areas of performance, and/or participation in proficiency testing programs.

STANDARD:

C3.3.2 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 and/or documented experience with this special population of donors. Other procedures involving pediatric patients performed by the Collection Facility might serve as experience.

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 competency in dealing with pediatric patients as well as experience. The inspector might look for specific training applying to pediatrics.

C4: QUALITY MANAGEMENT

STANDARD:

C4.1 There shall be a Quality Management Program that incorporates key performance data.

C4.1.1 The Medical Director shall have authority over and responsibility for ensuring that the Quality Management 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 Collection Facility must define what key performance data it will analyze. Minimally this should include data necessary to complete the QM activities required in these Standards.

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, or have a stand-alone QM Program.

STANDARD:
C4.2 Collection activities shall be performed in compliance with a written Quality Management 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 does not have to be fully described in the QM Plan but must be referenced within the plan and linked to the appropriate document 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 these Standards and clarify the nature and extent of participation by other areas and/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 needs to be addressed (e.g., donor assessment).

STANDARD:
C4.2.1 The Medical Director shall be responsible for the Quality Management Plan as it pertains to collection activities.

Explanation:
The Medical Director of Collection Services 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 Medical Director of Collection Service's and designee's (if applicable) 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 he/she could be a member of the 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, provided that there is a mechanism for sharing information to all participating entities.

STANDARD:

C4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions, functions, and reporting relationships required for collection.

C4.3.1 The Quality Management 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 for the Collection Facility and the QM Program. In addition, these charts must illustrate relationships to the Clinical Program 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. In some cellular therapy programs, there is no separate Collection Facility; rather, the Clinical Program oversees collection activities. This should be clearly indicated.

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.

Remote Directors or Medical Directors are those with professional responsibilities in more than one metropolitan geographic area, or those whose residence is outside of the metropolitan geographic area of the accredited facility. When a director works remotely, the Collection Facility must clearly outline how the responsibilities of the position are performed. Responsibilities for

remote directors do not differ from the responsibilities of any 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 quality management 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 these Standards. Documentation of director involvement in these responsibilities must be available on-site for review.

At times, a program organization chart will clearly show reporting structure but not necessarily quality management responsibilities. To properly provide a description of how key positions interact to implement quality management activities, a second chart may be needed. This is especially important if laboratory, collection, and clinical programs have a different reporting structure. To comply with these Standards, separate quality management structures must report to a single entity that includes all aspects of the cellular therapy program.

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 is as described in the chart and QM Plan (e.g., meetings, participants, schedule, reporting, and documentation). This should include how separate reporting structures report to a program wide quality management program.

Documentary evidence of a remote director's specific involvement in leadership and oversight of the Collection 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.
- Investigation report review.

- Qualification/validation studies: plan and final report review and approval.
- Planned deviation pre-approval.
- Cellular therapy product release authorization.

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

STANDARD:

C4.3.2 *There shall be written guidelines for communication between the collection or registry personnel and the Clinical Program for the management of collection-related complications.*

Explanation:
In the event of collection-related complications, the Collection Facility must have guidelines for communication with both collection personnel and donor registries. For additional requirements on communication related to issues with donor health that pertains to the safety of the collection procedure, see section B6.3.

STANDARD:

C4.4 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position required for cellular therapy product collection. Personnel requirements shall include at a minimum:*

Explanation:
The QM Plan, as approved by the Medical Director of Collection Services, identifies the key personnel for whom documentation of training, competency, and continuing education is expected. These must include all individuals responsible for critical elements of the collection activities. Documentation of training for all key personnel 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 as described in C4.4.

The inspector should review the records of one or more employees to determine if 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 his/her 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.

STANDARD:

C4.4.1 A current job description for all staff.

C4.4.2 A system to document the following for all staff:

C4.4.2.1 Initial qualifications.

Explanation:
Initial qualifications generally include minimal educational requirements, formal training that is either required or preferred, and licensing or certification.

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, benefits, and institutional policies.

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, and in accordance with Applicable Law.

Explanation:
Initial training documentation must include all specific procedures that an individual staff member will perform (as defined in the job description). Such documentation 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 formal or informal presentations, self-learning by reading suggested materials on the topic, or reviewing previously presented audio/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 Part A for the definition of "critical").

Evidence:
The inspector will review policies or SOPs describing the elements of competency assessment as described in C4.4 and the records of one or more employees to determine whether all of the required elements are documented. The inspector should review records of employees' initial and annual competency.

Example(s):
Annual competency assessment may be performed in conjunction with performance reviews during which a staff member's collective competencies and behaviors are evaluated to determine if the individual is meeting expectations and to identify areas of needed improvement.

Competency may be assessed by direct observation, the use of written tests, successful completion of proficiency surveys, review of collection procedure endpoints, or other ways as determined by the Collection Facility.

STANDARD:

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

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.

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; 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 annually be some training based on a GxP topic.

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 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 MSCs, 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 1271.
- Current Good Manufacturing Practice (GMP or cGMP) on a sliding scale.
- Good Documentation Practice (GDP) and data integrity practices.

STANDARD:

C4.4.2.6 Continuing education.

Explanation:
Staff should adhere to local and governmental continuing education requirements. Collection staff should be offered the opportunity of appropriate education if there is no national requirement.

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

STANDARD:

C4.5 The Quality Management 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 these 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.

In this context, "policies and SOPs" means that a single document, either a policy or SOP, could suffice. Documents serve multiple purposes for the QM Program and can consist of different document types, such as policies, SOPs, worksheets, or forms. Documents provide the structure needed for quality assurance through policies and SOPs, demonstrate quality control using forms and worksheets, and substantiate QM activities, such as audit reports, occurrence trends, outcome analyses, or training records. 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 shall comply with the document control system requirements. Controlled documents shall include at a minimum:

C4.5.1.1 Policies and Standard Operating Procedures.

C4.5.1.2 Worksheets.

C4.5.1.3 Forms.

C4.5.1.4 Labels.

Explanation:
The QM Program must maintain identification of the types of documents considered critical. For example, all SOPs required by these Standards are considered to be critical documents and must be controlled. Collection Facilities may call documents different names and may identify additional types of documents as critical within the scope of the document control system.

Evidence:
The inspector should review a listing of which documents fall under the document control system.

STANDARD:

C4.5.2 There shall be policies or Standard Operating Procedures for development, approval, implementation, distribution, review, revision, and archival of all critical 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 these 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 critical documents.

Explanation:
The Collection Facility should be consistent in the format or design of controlled documents.

Documents authored by the Collection Facility must 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:

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

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, alphanumerical). Worksheets and forms must also be controlled documents and contain a title and unique identifier.

Evidence:
The inspector must verify that controlled documents are consistently 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 the effective date.

Explanation:
The effective date is when the previous version of a document has been recalled or archived, and the new version that is available has been implemented.

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 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:

Regular record review should alert the Collection Facility to areas needing improvement, particularly specific elements that are repeatedly missing or contain errors. This allows forms, worksheets, or SOPs to be revised and improved. The process should specify who reviews the records and the time interval for review.

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.

Example(s):

If controlled documents are associated with an SOP, the document review may occur in conjunction with the SOP review. If this is done, a separate review process for each controlled document is not required. Controlled documents could also be reviewed independently provided that they are reviewed and updated at a minimum every two years and when relevant to changes in procedures.

STANDARD:

C4.5.3.6 A system for document change control that includes a description of the change, the signature of the approving individual(s), approval date(s), communication or training on the changes 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 these Standards and Applicable Law, risk and impact assessment on existing process and controlled documents, approval of change and revision of documents, communication and/or training on the change as applicable, and implementation of the change. Change 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 he/she has reviewed the SOP and 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 Archival of controlled documents, the inclusive dates of use, and their historical sequence for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

Explanation:
Documentation is especially important for the investigation of occurrences since these investigations are frequently retrospective in nature. If outcomes change over time, one needs to be able to go back to previous versions of controlled documents to determine if an operational change is the cause.

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, and title).

Example(s):
The archival system may contain items such as date removed, version number, reason for removal, and identification of the person who performed removal.

STANDARD:

C4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

Explanation:
Hard copies of controlled documents may exist, and when documents are updated, there needs to be a secure process in place to ensure that any hard copies are not used beyond their expiry date.

Example(s):
Collection Facilities may have forms or worksheets that are printed and distributed. There should be a system in place to recall/remove these obsolete documents to prevent unintended use. A clear statement could be printed on hard copies that they may not be the current version, which can only be reviewed by going to the source library.

STANDARD:

C4.6 *The Quality Management 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 (e.g., donor or recipient work up prior to cellular therapy; collection, processing, testing, storage or administration of cellular therapy products; or donor or recipient follow-up). Agreements are also required when critical services are provided by the Collection Facility to external parties. This standard does not apply to entities within the Collection Facility's own facility or institution.

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

Example(s):
It is recommended that a Collection Facility have a contingency plan in the event that it is unable to provide services as intended (e.g., significant personnel change or 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).

It is required that Collection Facilities must only use Processing Facilities that meet these Standards. An accredited Collection Facility may; however, collect cellular therapy products for one or more programs that are not FACT 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 health and safety of the donor or recipient.

Explanation:
It is the Collection Facility's responsibility to determine which entities providing critical contracted services are external or internal.

Documented agreements must clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements must be dated, reviewed, revised, and approved by both parties and legal counsel, if necessary, on a regular basis as defined by the program, and at least every two years. Agreements must also describe the maintenance or transfer of records and cellular therapy products following termination of the agreement.

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 signature), but which are relevant to the clinical care of the recipient or donor or impact the cellular therapy product.

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 Medical Director of Collection Services.

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 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 collections or other critical services are performed for external parties.

Example(s):
When formulating written agreements either for clinical trial cellular therapy products or licensed products, the Collection Facility can add language to require that it be notified of information such as:

- Whether 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 scheduling / production issues that impact scheduling.

Additionally, if providing critical 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:

- How is updated donor eligibility information communicated?
- Is the facility required to provide notification of breaches in aseptic collection?
- How should post-donation information be communicated (e.g., donor contacts the facility two days after donation that they have an infection or identifies a risk that impacts donor eligibility)?
- What changes in operational availability or regulatory status must be communicated?

STANDARD:

C4.6.4 *Agreements shall be dated and reviewed on a regular basis, at a minimum every two (2) years.*

Explanation:
This standard does not require that agreements be renewed every two years, only that they have been reviewed to ensure that the needed requirements are met. This review should also confirm that the signatories to the agreement are the appropriate individuals.

Evidence:
The inspector should ask to review agreements and the documentation of regular review as required.

Example(s):
A master list of written agreements and a checklist could assist with appropriate review and ensure that important elements are included, and a designee in the Collection Facility is notified when changes are made.

STANDARD:

C4.7 *The Quality Management 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 products can be demonstrated to produce a desired or intended function. It is understood that products may not produce the desired or intended result for every patient, but if the outcome or efficacy are never what was expected, there is clearly a problem.

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, minutes of meetings, and Collection Facility review of the data including the personnel in attendance and where data are presented.

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 type of product by the Collection Facility in conjunction with the clinical team, and this process defined in 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 failed persistence of the cells.

Cellular therapy product efficacy based on outcome may be more difficult to document for products other than HPCs, and that outcome will differ for each product type. Where product efficacy cannot be established, it is expected that product safety 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 for each type of cellular therapy product or recipient type shall be evaluated.

Explanation:

Outcome analysis should not only be performed on individual cellular therapy products, but on aggregate data 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. In cases where a given cellular therapy product is used for different therapeutic indications or recipient types, the role of the recipient type must be considered. 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 quality management 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, and recipient type (age, disease characteristics, relationship to the donor) in its analysis.

STANDARD:

C4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:

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 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.

STANDARD:

C4.7.3.1 An endpoint of clinical function as approved by the Clinical Program Director.

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

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 thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy. Morbidity may include rehospitalization, 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.

STANDARD:

C4.7.4 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, or distribution of the cellular therapy product.

Explanation:
Because patient outcome data are 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 are dependent on these data to adequately assess their practices. Data should be shared quarterly at a minimum.

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 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.

STANDARD:

C4.8 The Quality Management Plan shall include, or summarize and reference, policies, Standard Operating Procedures for, and a schedule of, audits of the collection activities to verify compliance with the Quality Management Program, operational policies and Standard Operating Procedures, these Standards, and Applicable Law.

Explanation:
Audits represent one of the principal activities of the QM Program. An audit is a documented, independent inspection and retrospective review of an establishment's activities to determine if

they are performed according to written SOP or policy. Compliance is verified by examination of objective evidence. Audits are conducted to determine that the QM Program is operating effectively and to identify trends and recurring problems in all aspects of facility operation. Processes to be audited should include those where lack of compliance would potentially result in an adverse event, errors have been identified, or follow-up audits are required. The head of the QM Program should identify areas to be audited and audit frequency.

The audit process should occur throughout the year 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 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.

A schedule of prospective audits is expected. There may be other audits required in response to specific occurrences.

Evidence:
The Collection Facility should facilitate the on-site inspection with a concise presentation of recent audits, supported by policies and SOPs, and including documentation of corrective and preventive action 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):
Examples of audits in the Collection Facility include:

- Adherence to policies and SOPs (e.g., correct labeling procedures).
- Presence in the facility of written medical orders prior to collection of cellular therapy products.
- Equipment maintenance performed according to schedule.
- Identification of collection equipment used for each collection.
- Collection efficiency, if relevant.
- Availability of complete records of allogeneic donor eligibility for each collection.
- Complete documentation that reagents and supplies were used prior to expiration.
- Cleaning and sanitation performed according to SOP and documented.
- Effectiveness checks or assessments on corrective action plans.

Audit reports are an important tool to provide inspectors evidence regarding adherence to standards and effectiveness of implemented CAPA; management guidance on future actions and

decisions; and document the evaluation process and decisions made in response to issues detected. An acceptable audit report contains the following elements:

- Audit title.
- 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.
- Name and title of staff assigned to complete the audit.
- Audit period (date range).
- Audit purpose.
- Audit scope.
- Audit plan.
- Date audit started and completed.
- Audit findings and recommendations: if errors were found but not included in the final analysis, an explanation must be provided.
- Summary (includes assessment/evaluation of results): identifying the underlying cause (root cause) of the errors guides a program to develop an appropriate CAPA, which should be included in the audit report to demonstrate that appropriate action was implemented.
- Timeline for follow-up: a CAPA is required when errors are found. Should an organization determine that a CAPA is not required, this should be documented along with why it arrived at that conclusion. When a CAPA is implemented, follow-up audits should be performed to assess the effectiveness of the corrective actions and demonstrate improvement in the area where the original deficiency occurred.
- Signatures and Comments.
    - Auditor signature and date.
    - Quality Manager signature, date, and comments.
    - Medical Director of Collection Services signature, date, and comments.
    - 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 or Medical Director of Collection Services). 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 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.

Further information is available in the FACT *Quality Handbook* (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

STANDARD:

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

Explanation:

The individual(s) performing an audit does not need to be external to the Collection Facility, but he/she should not have performed the actions being audited.

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

STANDARD:

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

Evidence:

The 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, cellular therapy 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:

C4.8.3 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 includes at least the required audits shown in the standards below, annually. Other processes should be chosen for audits at the discretion of each individual facility or identified by risk assessment. Audits that continuously fail to identify

potential problems or opportunities for improvement can be replaced on the schedule by a new audit topic.

Example(s):
An example of another recommended audit is a gap analysis when a new version of these Standards has been published.

STANDARD:

C4.8.3.1 Documentation of proper donor eligibility and suitability determination.

Explanation:
This audit should determine that eligibility was appropriately determined according to SOPs and Applicable Law and that the eligibility was documented before the collection procedure started.

STANDARD:

C4.8.3.2 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.

Evidence:
The Collection Facility does need to know that all aspects of the management have been performed. They should have a final copy of the full workup by all sections to show to the inspectors.

STANDARD:

C4.8.3.3 Infectious disease resulting from cellular therapy product collection and administration.

C4.8.3.4 Documentation that external facilities performing critical contracted services have 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.

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. There may be other alternatives, but the contracting facility must establish that their contracted services are meeting requirements.

STANDARD:

C4.8.3.5 Chain of identity and chain of custody of cellular therapy products.

Explanation:
The chain of identity refers to the association of the cellular therapy product unique identifiers from procurement throughout the full product life cycle, including post treatment monitoring of the recipient. Whereas the chain of custody illustrates the guardianship of the cellular therapy product from origin to final disposition.

STANDARD:

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

Explanation:
If the Collection Facility participates in the collection of products for commercial manufacturers or regulatory agencies, they will most likely be asked to participate in audits of their procedures. The requests may be varied. It is responsibility of facility to ensure that such audits are handled in a consistent fashion.

STANDARD:

C4.9 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results and responsibility for the following activities at a minimum:

C4.9.1 Notification of the recipient, recipient's physician, processing staff, and any other facility in receipt of the cellular therapy product; and if relevant, the donor and the sponsor.

C4.9.2 Recipient follow-up.

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

C4.9.4 Documentation and investigation of cause.

C4.9.5 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 program to manage the aspects listed above. This requirement may be satisfied with a single policy or SOP or there may be separate documents. For each topic, SOPs should detail what action is to be taken, who is responsible to take the action (this might include the Clinical Program or the Processing Facility), and the expected timeframe of the actions. Different approaches to management may be acceptable if these approaches are consistently followed and meet regulatory requirements.

Policies and SOPs should cover investigation of the cause of the positive culture result, including at least evaluation of the collection and processing events for evidence of breach of sterility, determination if 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 cellular therapy product. Collection Facility personnel are responsible for investigation of the relevant collection events. Since a positive microbial culture is a deviation, all requirements for occurrences apply.

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.

In other cases, a positive result may only become known after the cellular therapy product has been administered. The Processing Facility is usually the first facility to be notified of a positive culture result. There should be timely notification of the Collection Facility, which should in turn investigate all records related to that collection to determine if anything in the collection process could have contributed to the positive culture result.

The decision to administer a cellular therapy product with a known positive culture is the responsibility of the Clinical Program.

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):
Examples of evidence of compliance to this requirement may include:

- Policy and/or SOP on management of cellular therapy 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.

Each area in a cellular therapy program may have responsibilities that do not apply to another area. In this case, there may be an over-arching policy for the management of cellular therapy products with positive cultures.

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 him/her of the infection and provide recommendations for care.

In the U.S., reporting regulations are detailed in 21 CFR 1271. A cellular therapy product with a positive microbial result must be reported to FDA only if the product is actually administered, whether the result was known prior to administration or only after administration. Marrow-derived products with positive microbial results do not need to be reported if used strictly to restore hematopoiesis. However, if the contaminated marrow is the source of a cellular therapy product that is extensively manipulated and is infused, it must be reported to FDA.

STANDARD:

C4.10 *The Quality Management 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:

A goal of a QM Program is to continuously improve processes. Monitoring occurrences and trends facilitates recognition of improvement opportunities. There must be policies, processes and procedures to detect, evaluate, take immediate action, document, and report occurrences in a timely fashion to key individuals, including the Medical Director of Collection Services, 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. Programs may use the definitions stated by applicable regulatory agencies; however, the definition should meet the intent of these Standards. See Part A (Definitions). Management of each of these types of occurrences is slightly different; however, the same steps (detection, evaluation/investigation, documentation, determination of corrective and preventive action, and reporting) apply to all types.

Evidence:
The inspector should expect to find a documented process for occurrences including detection, investigation, documentation, corrective action, preventive action, and follow-up. This should be reviewed by the Medical Director of Collection Services and Quality Manager and reported, as appropriate, 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:

C4.10.1 Detection.

Explanation:
Immediate action must be taken and documented to mitigate further risk to cellular therapy products, staff, or donor safety.

STANDARD:

C4.10.2 Investigation.

C4.10.2.1 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.

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

C4.10.2.3 Occurrences shall be tracked and trended.

Explanation:
Investigation of the cause(s) of any deviation is critical to determine what CAPA will most likely be effective. The focus of the investigation should be to learn and improve, not to cast blame or be punitive. Often "systems" play a role in causation. Serious events require more in-depth investigation to find the root cause. Collection Facilities should be encouraged to stratify deviations 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 systems, policies, or procedures that will correct the issue and prevent recurrence of the deviation.

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 cellular therapy product has been administered. The most common deviations encountered involve products from

ineligible donors. Specific issues regarding products from ineligible donors are addressed in the guidance for Standard C6.

Example(s):
Use of an ineligible donor may be an occurrence. The investigation of should focus on the documentation required for urgent medical need, including recipient notification, physician approval, and proper product labeling. Ineligible allogeneic donors for cellular therapy products that require a high degree of HLA matching are usually chosen based on HLA match. The small risk of CDJ when the best matched donor lives in Europe is generally acceptable.

STANDARD:

C4.10.3 Documentation.

C4.10.3.1 Documentation shall include a description of the occurrence, date and time of the occurrence, the involved individuals and cellular therapy product(s), when and to whom the occurrence was reported, and the immediate actions taken.

C4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Medical Director and Quality Manager.

C4.10.3.3 Cumulative files of occurrences shall be maintained and include written investigation reports containing conclusions, follow-up, corrective and preventive actions, 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/time, and actions are captured.

As in the investigation, documentation of the involved individuals in any occurrence should not be punitive. This information should be used for investigation and trending purposes to identify potential corrective and preventive actions, such as the need for additional training or staff resources.
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 reduce the risk of transmission of a communicable disease. Corrective action or process improvement must be implemented to prevent re-occurrence 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 Quality Manager, Medical Director of Collection Services, 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:

C4.10.4 Reporting.

C4.10.4.1 When it is determined that a cellular therapy product has resulted in an adverse event or reaction, the event and results of the investigation shall be reported to the donor's and recipient's physician(s), as applicable, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by Applicable Law.

C4.10.4.2 Occurrences shall be reported as required to other facilities performing cellular therapy product functions on the affected cellular therapy product.

C4.10.4.3 Occurrences shall be reported as required to the appropriate regulatory and accrediting agencies, registries, grant agencies, and Institutional Review Boards or Review Boards or Ethics Committees.

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, IDE, or BLA) 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, and IRBs or Ethics Committees).

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. 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.

Examples:
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 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. FDA guidance for such plans in the U.S. can be found in *Guidance for Industry: E2E Pharmacovigilance Planning* (2005) available at https://www.fda.gov/media/71238/download and *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005) available at https://www.fda.gov/media/71546/download.

STANDARD:

C4.10.5 Corrective and preventive action.

C4.10.5.1 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.

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

Explanation:

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

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

- Identification of the involved individuals and/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 corrective action.
- 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 The Quality Management 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:

One of the most important paper trails allows for tracking and tracing of information about the cellular therapy product at all steps between the donor and the recipient or final disposition. Documentation in the product collection record should include the identity and content of the cellular therapy product, the unique identification of the donor, the donation identification number (DIN), the donor eligibility status (for allogeneic donors), and the unique identity of the intended recipient. There should also be a means, direct or indirect, that will allow outcome information to be related back to a specific product and communicated to any other facilities involved in collection, processing, and/or distribution of the product. The final disposition of the

product must be documented whether the product was infused, destroyed, released for research, remains in storage, or another outcome. The process for product tracking must be defined by an SOP. Additionally, the identity of the individuals involved with each step of the product life cycle (from collection to final disposition) must be documented (chain of custody).

Evidence:
The inspector should review examples of specific cellular therapy products and determine if the chain of identity and the chain of custody from the donor selection through final disposition is unequivocally possible. Each critical step should identify the unique identifier of the product and the individual who performed the step or action and the date and time it was completed.

Review of the following documents may show evidence of product trackability and traceability:

- Collection orders showing recipient and donor information, including unique identification.
- Collection records showing the identity of the persons performing the procedure.
- Cellular therapy product receipt and distribution records showing donor identity, recipient identity, and unique product identifier.

STANDARD:

C4.12 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event collection 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 (see C5.1), 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, these 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 back up 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, or 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 if 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 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 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):
Examples include malfunctioning electronic records systems, drug shortages, power outages, equipment failures, or supply shortages. A contingency procedure would identify alternative supplies, sources of supplies, or preparative regimens.

STANDARD:

C4.13 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services relevant to the cellular therapy product.*

Explanation:
Quality can be maintained only if there is control over critical 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 Collection Facility, steps should be taken to verify supplier and vendor qualification had 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.

The Collection Facility must participate in site visits from the IND or BLA holder and provide the level of service required of that entity. FACT-accredited facilities that participate in manufacturing for external IND or BLA holders must provide inspectors evidence of complying with these requirements as required by Applicable Law.

Example(s):
For example:

- Critical documents include a document that is directly related to and could impact donor welfare and recipient care or cellular therapy product integrity.
- Updated software versions have the potential to materially affect performance of equipment.

Where purchasing is beyond the direct control of the Collection Facility, steps should be taken to verify supplier and vendor qualification had been performed by the parent organization.

For further definitions and examples of qualification, see the FACT *Quality Handbook* (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

STANDARD:

C4.13.1 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 minimum acceptance criteria. Supplier qualification must also confirm that vendors are compliant with Applicable Law and that there is a system in place that is consistent with these Standards, such that they can demonstrate process control. Suppliers of laboratory services, such as the Flow Cytometry Laboratory 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., ACD, NaCl) may consist of documented evidence of inspection of the reagent for discoloration and/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 apheresis machine.

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.

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, AABB, CAP or others.
- Remote audits by questionnaire.
- An ongoing dialogue 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 Collection Facility as evidence that deficiencies have been recognized and corrected.
- A documented review of the suppliers' past performance history.

STANDARD:

C4.13.2 Qualification shall be required following any significant changes to these items.

Explanation:
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:

C4.13.3 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Medical Director.

C4.13.4 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

Explanation:
This standard applies to situations where there are no suitable clinical or pharmaceutical grade reagents available for the collection of the cells. or for reagents being used under approved research purposes. Reagents meeting these criteria shall be qualified. This may include:

- Use under IND, IDE, or other exceptions approved by the appropriate regulatory agency.
- Evidence of extensive experience with the reagent and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.
- Extensive literature supporting use of the reagent for the specified purpose and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.

If a reagent is not of the appropriate grade, it must be of the highest grade (or purity) available and the Collection Facility must validate that the reagent is safe and effective for the specified purpose.

Example(s):
A cellular therapy product requires that cells from a primary tumor be collected into a proprietary medium essential for the cells to expand during processing, but the medium is labeled "Not for Clinical Use". The Collection Facility or the Processing Facility or third-party manufacturer, must qualify the medium to ensure that it is sterile, non-toxic, and supports the growth of the tumor cells.

STANDARD:

C4.14 The Quality Management 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 verification demonstrates that the products of a process meet the required conditions.

For further definitions and examples of validation, see the FACT *Quality Handbook* (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

STANDARD:

C4.14.1 Critical procedures to be validated shall include at least collection procedures, testing, labeling, storage, and distribution.

Explanation:

In the Collection Facility, the following (if used) should be validated at a minimum:

- The device for the intended use. Each type of machine should be validated for the process and procedures to be performed using it, including collection of cells and/or concurrent plasma. Subsequent machines of the same type may be qualified to document performance according to expected parameters, and a more limited verification of processes.
- The collection process. This validation should include all the variables used in the collection of each cellular therapy product, such as donor variables (e.g., blood volume, or 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. For collection, validation study results must be maintained for the duration the collection process is used.
- 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 I of these 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 facility reagents, supplies, and disposables are approved for human use. A manufacturer's certificate of analysis for each type of reagent should be available. If unapproved reagents are required for collection, these should be validated to work as expected, to cause no harm to the product, and to 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 these Standards to include hospital-based systems and clinical medical records. For further guidance see Standard C11.

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 Medical Director of Collection Services and the Quality Manager.

Example(s):
A change of equipment used for collection requires validation 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.

A requirement from a manufacturer that is outside of what is established in a program's SOP should be managed by a separate SOP applicable to manufacturer requirements.

STANDARD:

C4.14.2 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.

Example:
Examples of acceptable endpoints may include product volume, target cell collection goal, and contamination with RBCs, granulocytes, and platelets.

STANDARD:

C4.14.2.1 An approved plan, including conditions to be assessed.

C4.14.2.2 Acceptance criteria.

Explanation:
Marrow collection 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, but are not limited to, nucleated cell recovery, viability, and absence of microbial contamination.

STANDARD:

C4.14.2.3 Data collection.

C4.14.2.4 Evaluation of data.

C4.14.2.5 Summary of results.

C4.14.2.6 References, if applicable.

C4.14.2.7 Review and approval of the plan, report, and conclusion by the Medical Director and 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 Medical Director of Collection Services. 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 maternity 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:

C4.14.3 Significant changes to critical procedures shall be validated or verified as appropriate.

Example(s):
Use of a new system for collection of marrow would require validation to confirm the system performed as expected with no compromise of marrow product purity, potency, or safety.

STANDARD:

C4.15 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the evaluation of risk in changes to a process to assess the effect of the change elsewhere in the operation.

C4.15.1 Evaluation of risk shall be completed for changes in critical procedures.

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; recipient care; or the cellular therapy product integrity, sterility, viability, or recovery.

Evaluation of risk may be documented in a validation plan or exist as a separate document and may include:

- Identification of a risk.
- Context.
- Evaluation.
- Impact.
- Management Plan, including mitigation strategies.

Evidence:
The inspector should ask to see the SOP for evaluation of risk for changes to a practice, process, SOP, or environment and 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 successfully, the next step is identification and evaluation of potential risks 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 identity of the specific risk(s) should be included. After the risk(s) has been identified, it must be assessed on the potential of criticality or on their likelihood of occurrence and the 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.

Once the risk assessment is established then a risk management plan can be developed and implemented. It comprises 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 using another reagent or supply item of suitable grade.

Below is an example of a risk assessment matrix that combines the concept of likelihood and severity.

Risk Matrix

		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)
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:

C4.16 The Medical Director shall review the quality management activities with representatives in key positions in all areas of the cellular therapy program, at a minimum, quarterly.

C4.16.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

C4.16.2 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.

Quarterly meetings are not required but are highly recommended. 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.

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:

C4.16.3 The Medical Director shall not approve their own work.

Explanation:
Any person responsible for overseeing the QM activities should not be directly responsible for review of work solely performed by that person. It is important that the final review be non-biased, 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 Medical Director of Collection Services, or a person from the Processing Facility may be designated for review of these activities. It may be acceptable; however, for an individual to review his/her own work at a time and place removed from the actual performance of the work.

STANDARD:

C4.17 The Medical Director shall annually review the effectiveness of the Quality Management Program.

C4.17.1 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 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. If the Collection Facility is part of an integrated cellular therapy program, a single annual report is sufficient.

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 Medical Director of Collection Services 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. In addition to relevant measures addressed in B4.17.1, the Collection Facility may consider including the following measures:

- Collection efficiencies.
- Donor adverse events.
- Other events such as complaints or deviations.

C5: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

C5.1 Policies or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in C4 shall be established and maintained. These documents shall include all elements required by these Standards and shall address at a minimum:

Explanation:

Each Collection Facility must have written policies and SOPs that comprehensively address all important aspects of the facility. The facility is not required to have an SOP titled for every item on the list, provided that each item is addressed somewhere within an appropriate SOP. The items listed include the minimum requirements; a facility may exceed these requirements, but not omit any of these.

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.

Evidence:

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. This list should include the location within the SOP that the topic is addressed.

The inspector should verify 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.

The inspector will have a list of all SOPs with the pre-inspection material prior to the on-site inspection. The list should be examined for evidence of the existence of SOPs addressing each item listed in these 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 mockup scenario, and/or verbal conveyance of the SOPs.

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):
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 the emergency response to disasters. In cases where general institutional policies and SOPs are inadequate to meet 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 approval and review and approval of revisions every two years by the facility to ensure the most current version is in use and the applicability to all functions of the 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 (suitable 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.

STANDARD:

C5.1.1 Donor and recipient confidentiality.

Example(s):
Donor and recipient confidentiality include confidentiality of records. Such an SOP should indicate actions taken within the Collection Facility to maintain confidentiality.

STANDARD:

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

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.

STANDARD:

C5.1.4 Management of donors who require central venous access.

C5.1.5 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 should have low hematocrit and low platelet count.

STANDARD:

C5.1.6 Prevention of mix-ups and cross-contamination.

C5.1.7 Labeling (including associated forms and samples).

C5.1.8 Cellular therapy product expiration dates.

C5.1.9 Cellular therapy product 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.

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:

C5.1.10 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 product for administration, but also to releasing a 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 release 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:

C5.1.11 Packaging, transportation, and shipping.

C5.1.11.1 Methods and conditions to be used for distribution to external facilities.

C5.1.11.2 Use of additives for long duration of shipment.

Explanation:
If specified, ACD should be used as anticoagulant (may be combined with Heparin) when shipping cellular therapy products over a long duration of time for centralized manufacturing.

STANDARD:

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

C5.1.13 Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.

C5.1.14 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.

C5.1.15 Hygiene and use of personal protective equipment and attire.

C5.1.16 Disposal of medical and biohazard waste.

C5.1.17 Cellular therapy emergency and disaster plan, including the collection staff response.

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

Explanation:
Contingency planning for emergency and disaster events that may critically impact donor and recipient care must be included in Collection Facility 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 or disaster).

The Collection Facility must have a disaster plan that is specific for 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 is needed to augment the institutional policies (such as actions to take in response to an emergency or disaster occurring during a collection procedure or after a donor is prepared for 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 when a disaster occurs or what to do if cellular therapy products need to be moved.

Evidence:
The inspector will review the emergency and disaster plan, verifying that appropriate details are provided for collection personnel to follow.

Example(s):
Examples of disasters include fires, hurricanes, floods, earthquakes, or nuclear accidents. Specific natural disaster policies may be more pertinent dependent on geographic location. Infectious threats include failure of isolation facilities; outbreak of aspergillosis, 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 these Standards or where there are issues that are specific to the facility, the facility must develop its own policies and SOPs, including those addressing contingency procedures for circumstances of inadequate transportation, staffing, or supply availability issues. The article Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program (Wingard et all, 2006) provides a framework for disaster plans (available at https://www.astctjournal.org/article/S1083-8791(06)00520-9/fulltext).

The FDA offers information on its webpage titled, "The Impact of Severe Weather Conditions on Biological Products," at http://www.ncbi.nlm.nih.gov/pubmed/17085317.

STANDARD:

C5.2 A detailed list of all controlled documents, including title and identifier, shall be maintained for collection activities.

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 its 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. SOPs must be under document control as outlined in C4.

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 or divide policies and SOPs into several manuals by subject. A technical procedure manual in conjunction with a quality, a policy, and a 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:

This standard defines the minimum elements required in each SOP. SOPs are controlled documents and must comply with the requirements in C4.

Example(s):

The "SOP" may be limited to minimal work instructions and required elements such as a reference list may be found only in higher-level documents. The SOPs must describe the location within higher-level documents and be available during operations.

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, plasma volume, and absence of microbial contamination. The range for a given parameter can be determined within the facility by evaluating data from its own products.

STANDARD:

C5.3.4 A stepwise description of the procedure.

Explanation:
The procedure steps must be understandable by trained staff. The use of diagrams or figures can make a procedure easier to follow.

STANDARD:

C5.3.5 Donor age-specific issues where relevant.

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 may require 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 by apheresis from small donors requires several considerations, including at least extracorporeal volume, red blood cell depletion, 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 central venous catheters. In addition, collection of cellular therapy products from obese donors may present challenges, including dosing of mobilization agents (if used), and should be addressed on SOPs.

STANDARD:

C5.3.6 Reference to other Standard Operating Procedures or policies required to perform the procedure.

C5.3.7 A reference section listing appropriate and current literature.

C5.3.8 Reference to the 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 be attached to each SOP. The purpose of this standard is to assure 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. These documents must also be under document control in compliance with C4.

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 is listed.

STANDARD:

C5.3.9 Documented approval of each procedure by the Medical Director prior to implementation and every two (2) years thereafter.

C5.3.10 Documented approval of each modification to a Standard Operating Procedure by the Medical Director prior to implementation.

Example(s):
These forms need not necessarily be completed as an example, but it may be prudent to attach one or more completed forms to illustrate possible real-life scenarios.

STANDARD:

C5.4 Controlled documents relevant to processes being performed shall be readily available to the facility staff.

Explanation:

The written copy or electronic version (with provision of hardcopy as necessary) of controlled documents must be immediately available to all relevant employees in their working environment. 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.

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 Standard Operating Procedure.

Explanation:

The effective date of a controlled document is the date when all the required individuals have officially approved the document. However, a staff member may not perform the new or modified SOP until they have undergone documented review and training. Collection Facilities are not required to train all staff members before implementing a new policy or procedure but must document an individual's review and/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):
It is recommended that there be a specific signoff sheet for every policy and SOP and associated revisions to document that each staff member required to review them has done so. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each SOP and to any major revision also facilitate documentation of appropriate training of staff.

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. Documented review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

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 Medical Director and reviewed by the Quality Manager.

Explanation:
Planned deviations should be approved within a peer-review process (i.e., more than one individual), but approval from the Medical Director of Collection Services is required at a minimum. Processes set up for review of planned deviations are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately. Retrospective review must be performed in compliance with processes designed for deviations.

C6: ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

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

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 (if required) and to protect the recipient from the risks of transmissible disease.

Collection Facilities should endeavor to obtain voluntary and unpaid donations of cells. Donors may receive compensation, which is limited to reimbursement for the expenses and inconveniences (e.g., lost wages, travel) related to the donation. This is based on national and international standards for donation.

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.

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 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 require 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 he/she is:

- Free from risk factors for and clinical evidence of relevant communicable disease agents and diseases.
- Free from communicable disease risks associated with xenograft in the donor or in someone with whom the donor has had close contact.
- Tests 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 to be documented. Donor acceptability 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 are written, clearly defined, and are 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 making sure that there is an SOP for urgent medical need documentation and labeling for allogeneic 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, C, or 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 U.S. FDA Final Guidance ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products [HCT/Ps]", August 2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This Guidance Document is available at:
https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm091345.pdf.

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; Collection Facilities must obtain informed consent to perform the specific procedure. The essential elements of informed consent are that the donor or recipient is told, in terms she or he can reasonably be expected to understand, the reasons for the proposed therapy or procedure, the risks associated with the treatment or procedure, and 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 his/her satisfaction. The discussion that ensues is the 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 had been provided with satisfactory responses, and c) confirmed that all the information he/she has provided is true to the best of his/her 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 and/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 physician. 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 (as listed below) 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 Intent of the collection for treatment or research.

C6.2.1.3 Tests and procedures performed on the donor 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.

C6.2.2 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. 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 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 the planned cellular therapy. If the potential donor declines prior to donor workup, versus refusing after selection or on the day before the product is administered, 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 shall be obtained and documented by a licensed health care professional knowledgeable in the collection procedure and 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 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, 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 clinical team but is knowledgeable in the collection procedures.

STANDARD:

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

C6.2.7 In the case of a donor who is a minor, informed consent shall be obtained from the donor's legally authorized representative in accordance with Applicable 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 he/she 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.

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:

C6.2.8 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician or the recipient.

Explanation:
The purpose of this standard is to protect donor confidentiality regarding his or her health information. 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 that donor informed consent forms and recorded authorization to release relevant donor health information may document compliance. The date informed consent was obtained in relation to the date the donor's health information was released will be compared.

Example(s):
It is acceptable to obtain informed consent and authorization to release this information after donor screening and testing provided that 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:

C6.2.9 The donor shall be informed of the policy for cellular therapy product storage, discard, or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product.

C6.2.10 Documentation of consent shall be verified by the collection staff prior to the collection procedure.

Explanation:
Policies may differ between institutions and donor registries as to the fate of a donated cellular therapy product that is not or 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. Some registries that facilitate unrelated donations may

have requirements for what information is provided to the donor regarding product discard. In most cases, leftover cells after patient death can be discarded.

STANDARD:

C6.3 Allogeneic and Autologous Donor Suitability for Cellular Therapy Product Collection

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 that relate 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, 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 regarding the collection process and ensure that is distributed to the individuals performing cellular therapy product collection.

STANDARD:

C6.3.1.1 The collection staff shall confirm that clinically significant findings are reported to the prospective donor with documentation in the donor 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 his/her role as a donor. Appropriate care of the donor requires that 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 these actions are documented in the donor's medical record.

Evidence:

The inspector should review documentation in the medical record that prospective donors were informed of the 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 prospective donor undergoing collection who had abnormal findings, 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 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:
The Clinical Program must identify an independent physician or health care professional for evaluating donor suitability to reduce potential bias of the recipient's health care professional(s). This individual must not be the primary health care professional of the recipient and should have knowledge of the risks of the donation procedures.

Medical literature supports the idea that having the allogeneic donor evaluated by a 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. The AAP and the ASTCT recommend this practice for related donations.

Evidence:
The Collection Facility 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. If the Clinical Program is responsible for donor workup, then the appropriate policy will reside with the program.

Example(s):
The donor's primary care physician, a general internal medicine clinic, or a clinic not directly associated with the cellular therapy program are options.

STANDARD:

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

Explanation:
When testing for autologous donors, even if tests not approved for donor screening are used and the results are positive, the appropriate warning statements must be on the label.

STANDARD:

C6.3.2 The risks of the cellular therapy product collection procedure shall be evaluated and documented.

Explanation:

The purpose of this standard is to evaluate the donor for potential risks associated with the collection.

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

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

Explanation:

Pregnancy testing is required since the donation of cells from peripheral blood may pose a risk to the fetus. Childbearing potential is meant to include all female donors from puberty through menopause, unless there is definite medical indication that pregnancy is impossible (e.g., past hysterectomy). The purpose of this standard is not to forbid collection during pregnancy but to prevent donor mobilization (if used) and recipient conditioning from occurring before finding out that the donor is pregnant.

Example(s):

A pregnancy test is required; serologic assays or urinalysis should be used.

If a cellular therapy product is collected from the donor and cryopreserved for future administration, the donor does not have to be retested for pregnancy prior to the recipient's preparation for administration.

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 has been no change in pregnancy status.

Additional information on procedural related risks can be found in the case series, *Therapeutic apheresis in pregnancy: General considerations and current practice* (Marson, Gervasi, et. Al, 2015), available at https://pubmed.ncbi.nlm.nih.gov/26621537/.

STANDARD:

C6.3.4 *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, which 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 United States FDA or as required by non-U.S. equivalent regulations. Note most products used for cellular therapy by programs accredited under these Standards will not be HPC products, so allogeneic donor testing should be within 7 days before the starting cells are collected.

Evidence:

The inspector may look for infectious disease testing results and verify they were performed according to Applicable Law.

Example(s):

Examples of relevant accreditation organizations in the U.S. include CLIA, CAP, ASHI, AABB, Joint Commission, and others.

STANDARD:

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

Explanation:

The decision to use a donor who does not meet Clinical Program donor safety criteria must be made by the donor's physician. However, a designee may document that decision. The Collection Facility must review this information on donor safety. This Standard also requires that if an allogeneic donor is selected for transplant who does 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:

C6.3.5.1 Issues of donor health that pertain to the safety of the collection procedure shall be available to the collection staff. Collection staff shall document review of these issues prior to collection.

Explanation:
Safety documentation is performed by the staff who conduct the donor health evaluation (in the Clinical Program or the Collection Facility). Responsibility should be defined in SOPs. Further, collection staff is required to document that donor health issues have been reviewed prior to collection.

STANDARD:

C6.3.6 There shall be a policy or Standard Operating Procedure for the management of collection-associated adverse events and follow-up of donors that includes routine management.

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 to ensure there are no immediate side-effects.

Example(s):
The guidelines for post-collection care of donors collected using apheresis may include the following short and long-term measures:

- Upon completion of the collection, the donors 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 may be defined as recommended elsewhere (e.g., WHO, EBMT).

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 are mentally incapacitated, as those terms are defined by Applicable Law.

Explanation:

A donor advocate is an individual distinct from the cellular therapy recipient's primary treating physician whose primary obligation is to help the donor understand the risks and benefits of donation and promotes the interests, well-being, and safety of the donor. According to Donor Registries for Bone Marrow Transplantation: Technology Assessment (NIH Office of Medical Applications of Research, 1985), 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 Collection Facilities collecting minor or mentally incapacitated donors, there must be documentation from the Clinical Program 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 is made to do so by the family or healthcare team.

Example(s):
Examples of donor advocates include chaplains, patient advocates, and social workers. "Family Donor Care Management: Principles and Recommendations," (van Walraven et al, 2010) provides recommendations for donor advocacy in the related donor setting. The ASTCT is also a source of information.

When Applicable Law define 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.

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

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.

Hemodilution is a decreased concentration of cells and solids in the blood resulting from gain of fluid. This is most likely to occur if a donor has received a large volume of fluids, blood, or plasma in the period before blood samples for infectious disease testing occurs. This is more likely if a cadaveric donor is used. The danger is that detection of relevant communicable disease agents might be missed if the test sample is too diluted. A test of blood volume analysis may help to identify hemodilution.

STANDARD:

C6.4.3 Collection staff shall comply with B6.4.6 through B6.4.6.7 when primarily responsible for donor screening for transmissible disease.

Explanation:
These 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 this screening. 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).

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 must be documented in the medical record.

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 the donor 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. When 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 in dealing with donors who had received smallpox vaccination. Donors must be screened for traveling to the area that would put them at risk for malaria, human transmissible spongiform encephalopathy, 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 and 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 the statements or biohazard label required for products positive for the agents listed in B6. However, there must be an SOP for communicating test results of donors who are positive or reactive for CMV antibody.

STANDARD:

C6.4.4 Collection staff shall comply with B6.4.7 through B6.4.11 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 B6.4.2 through B6.4.4 and B6.4.12 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, as defined by Applicable Law, is determined by a licensed health care provider after history, exam, medical record review, and testing before the donor begins the mobilization regimen, if mobilization is utilized.

Explanation:
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.

Donor eligibility determination may be made by a properly trained licensed physician or other health care professional such as an advanced practice professional or a nurse who is part of the Collection Facility or Clinical Program.

STANDARD:

C6.4.7 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., FDA requires that an accompanying statement of authenticity be present for records translated into English.

STANDARD:

C6.4.8 Collection of a cellular therapy product from an ineligible allogeneic donor, or from an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of urgent medical need that includes the rationale for the selection and documentation of the informed consent of the donor and the recipient.

Explanation:
This standard requires that if allogeneic donors are ineligible according to Applicable Law, or non-U.S. equivalent, 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 medical record by the 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.

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 results of infectious disease testing.

STANDARD:

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

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

C6.5.1 Allogeneic donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.

C6.5.2 Donor identification including name and date of birth.

C6.5.3 Age, gender, 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:
  - The donor identification (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 (e.g., for autologous donors), it does not need to be included in the donor records.
  - Consent/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 he/she does not meet donor safety criteria. For unrelated donations, when the organization responsible for procurement has limited access to recipient data, the treating organization must be provided with relevant donor data.
- All the records should be clear and readable, protected from unauthorized amendment and retained and readily retrievable throughout their specified retention period.
- Donor records required for full traceability must be kept for a minimum duration as dictated by institutional practice and/or 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 his/her knowledge.

C7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

STANDARD:

C7.1 ISBT 128 CODING AND LABELING

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

Explanation:
It is understood that FDA does not require ISBT 128 coding and labeling to be used for cellular therapy product labels. Therefore, a Collection Facility seeking accreditation under these

Standards may have existing products that are not named according to this terminology. After accreditation, FACT will require that the ISBT 128 coding and labeling system be used. We encourage Collection Facilities preparing for accreditation to use this system.

ISBT 128 is the international information standard for transfusion and transplantation. Initially, ISBT 128 was developed for blood and blood component transfusion to increase the capacity for electronic data, to increase security and accuracy, and to permit unique unit identification globally. ISBT 128 has now been extended to include cellular therapy products and tissues. ICCBBA is the not-for-profit organization (www.isbt128.org/standard-terminology) 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 CTCLAG includes international representation from FACT, JACIE, ISCT, ASTCT, EBMT, NMDP, WMDA, ISBT, APBMT, and AABB. CTCLAG was formed to recommend standard definitions for cellular therapy products and rules for future assignment of cellular therapy product codes, to draft labels and a labeling strategy for products, and to draft an implementation plan.

The two main pieces of the standard terminology 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 and/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 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 characterized in this standardized way can be labeled using common, well-defined terms that are printed in eye-readable format. The eye-readable terminology may be in the native language of the country in which the product is collected. The language also adapts to machine readable technologies such as bar codes. In this way, the products will be universally understood, and 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. Modifications in definitions and additions will occur. As the responsible body for the database development and maintenance, 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 the ICCBBA document *Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions*. Facilities should refer to Chapter Three, Cellular Therapy, for current terms and definitions related to cellular therapy.

If facilities have questions regarding ISBT 128 terminology, they can reference the ISBT 128 Standard Terminology document and view the ICCBBA website at www.isbt128.org/standard-

terminology or contact ICCBBA directly for additional information and assistance. 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.

To utilize ISBT 128 to its full advantage by using its technical database in the unique identification of cellular therapy products worldwide and in the use of common language, Collection Facilities must register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each product's unique alphanumeric identifier. 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 individually register and pay a nominal annual membership fee.

Evidence:
Inspectors will inspect the Collection Facilities according to the current ISBT 128 terminology and definitions. Inspectors should review Chapter Three, Cellular Therapy of the ISBT 128 Standard Terminology document before conducting an inspection. It would be helpful to have the document available for reference during the inspection.

Example(s):
The appropriate product name for HPC collected by apheresis is HPC, Apheresis. The acronym HPC(A), would be an abbreviation acceptable in documents, and possibly on partial labels. However, the U.S. FDA does not allow abbreviations on final product labels for licensed products.

Cellular therapy products with a biological license in the U.S. are subject to the bar code label requirements (21 CFR 201.25). The bar code, at a minimum, must contain the appropriate National Drug Code (NDC).

STANDARD:

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

Explanation:
The use of ISBT 128 for all cellular therapy products provides a uniform coding and labeling system internationally. Such standardization is even beneficial to, and thus required for, autologous products. The implementation of coding and labeling are supported by FACT and numerous other organizations in the field for cellular therapy. On the ICCBBA website (http://www.isbt128.org/standard-terminology).

Implementation of ISBT 128 is required for FACT accreditation, although as stated above, FACT does recognize that not all cellular therapy products being used at initial inspection will use this coding system. The most recent versions of the terminology are published, as well as resources to help centers implement ISBT 128.

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:

Labels can be prepared either by pre-printing sets of labels to be used during processing or by printing them "on demand". The use of any type 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 office. 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 or 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:

C7.2.2 Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Medical 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.
- Identity to source (original) label that has been approved for use by the Medical Director of Collection Services.

Inspection must include comparison with a label previously approved by the Medical Director of Collection Services.

The inspection of labels at receipt 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.

Evidence:
The inspector should review all relevant labeling SOPs (see C5.1). The inspector should 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 by the Medical Director of Collection Services 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.

The Collection Facility might conduct a risk assessment to determine if a label produced by the Processing Facility substantiates adherence with the approved labeling template.

STANDARD:

C7.2.2.1 Stocks of unused labels representing different 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 representing different cellular therapy products as well 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 products from one another (e.g., by color-coding, size, or location). It is not acceptable to have labels of different types and representing different products stored together with no separation.

Evidence:
The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors.

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:

C7.2.3 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 pre-printed labels must be documented to ensure that a label allocated to a particular cellular therapy product cannot be associated with the product, concurrent plasma, or related samples from 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. The reconciliation process applies to entire product labels, not to individual label components like separately printed DIN barcode copies.

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 donor collections. The method of destruction of unused labels should be verified.

Examples:
A form detailing the number of labels received, used, and passed to another unit or destroyed may be captured on collection worksheets, 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 Medical Director.

C7.2.4.1 Obsolete labels shall be restricted from use.

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 provided that 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 reference 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 first develop a validation protocol for implementation of "on-demand" computer software. Upon implementation of the process, the facility must confirm and document that the label printed meets the criteria of acceptability.

Evidence:
Validation studies of the print-on-demand labels must be available 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 these various elements and what constitutes a label version must be defined by the Collection Facility. Any change in the label or 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/storage 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 shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by Applicable 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 10 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 collection labeling/storage area.

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 prior to distribution of the cellular therapy product.

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, such as computer checks or barcoding, 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/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 vicinity of the donor and prior to distribution to the Processing Facility.

In addition to confirming correct content, the label verification should include:

- 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 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.

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.

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 the accuracy of the information rather than becoming solely dependent on the technology to work correctly.

STANDARD:

C7.2.6.3 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

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.

C7.2.8 Labeling elements required by Applicable Law shall be present.

Explanation:
Label elements that are required by governmental regulation must be clearly visible. The Collection Facility should review FDA, Health Canada, and/or 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 "NA."

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 water, 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 water, alcohol wipes, or sprays should be available to the inspector. The inspector should verify that all labels are completed clearly and legibly if a collection is carried out during the inspection.

Example(s):
Some Collection Facilities use post-collection cellular therapy product labels that are stuck over pre-collection labels and that contain all of the required label data. Others use labels with as many fields as possible containing preprinted data. 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 the labels 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 and a formal validation of the indelibility of the preferred pen's ink can be carried out.

STANDARD:

C7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

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 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.

STANDARD:

C7.2.12 The label shall be validated as reliable for storage under the conditions in use.

Explanation:

Adhesive labels affixed either directly on to a cellular therapy product bag or on 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. This includes while the product is in the control of the Collection Facility; on exposure to water, alcohol wipes, or sprays within the Processing Facility; or during periods of cold storage. The facility should determine the way in which the product bag is handled by the Processing Facility once it is in the Processing Facility's control. 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 identifier by which it will be possible to trace any cellular therapy product to its donor, all accompanying records, and its recipient or final disposition.

C7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.

C7.3.1.2 If a single cellular therapy product is stored in more than one (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 identifier on the pooled product 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 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 the chain of identity of 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 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 indicating how a unique identifier is assigned and tracked 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. If products are being pooled, the pool identifier 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 obtained at the time of cellular therapy product collection should be labeled in order to prevent misidentification. At a minimum, the labels must include the donor's name (except for the case of unrelated donors), donation unique 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, 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 labeling 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 identifier 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.

The ISBT 128 system uses the DIN together with the product code and division codes to identify multiple containers from the same collection.
Cellular therapy products with a biological license in the U.S. are subject to the bar code label requirements (21 CFR 201.25). The bar code, at a minimum, must contain the appropriate National Drug Code (NDC).

STANDARD:

C7.3.1.4 Supplementary identifiers shall not obscure the original identifier.

C7.3.1.5 The facility associated with each identifier shall be named in the documents to accompany the cellular therapy product.

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

Explanation:
The Collection Facility may assign additional identifier(s) 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. If a supplemental unique identifier is replaced with another identifier, records must link the current unique identifier to the previous one and to the facility associated with each identifier.

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 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:

C7.4 LABEL CONTENT

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

C7.4.2 Labeling at the end of collection shall occur before the cellular therapy product is removed 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 removing the product from the proximity of the donor. Labeling of the product before disconnecting it from the donor or in the proximity of the donor once the bag (or other collection 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.

Any change to the required process (e.g., label completion after the product bag 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 bag (or other collection container) has been disconnected from the donor identified and mitigated.

The label verification process should also include:

- Label is correctly affixed to the product (and/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 on associated forms and accompanying records and documents.
- The label is not damaged or defaced.

Evidence:
The inspector should verify that labeling at the end of collection occurs before the cellular product bag (or other collection container) is disconnected from the donor and contains the information listed in Appendix I. The inspector shall review the relevant documentation including the associated risk assessment if labeling at the end of collection is carried out in the proximity of the donor after the cellular therapy product bag (or other collection container) has been disconnected.

Example(s):
The collection equipment may typically display 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.

The use of print-on-demand post-collection labels containing the relevant label information including end-of-collection data may be affixed on top of the pre-collection product bag label before the cellular therapy product bag is disconnected 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 I.*

Explanation:
The required label content as specified in Appendix I represents minimum requirements and must be present as indicated at the various stages of cellular therapy product collection, processing, and distribution.

Accompanying paperwork should be packaged in a secondary bag with the cellular therapy product for distribution to the processing facility, third party manufacturing organization, or infusion site. It is not acceptable to distribute multiple product bags from different donors using partial labels with 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 organization. The Collection Facility must confirm with the third-party organization 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 organization. Recipient and donor identifiable data is placed on the cellular therapy product label prior to collection to ensure the product is being collected from the correct donor and put into a correctly labelled product bag. 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, and, for autologous collections, so that the product can be always associated with the recipient as it passes through the third-party organization and then is reissued back to the clinical facility for infusion.

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 anticipated processing facility, so that the Processing Facility will have an accurate determination of the age of the product and be able to apply the appropriate expiration date and time.

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 and/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; however, this information should be part of the processing record or be available to the Processing Facility if needed.

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 these Standards may serve as the prescription.

Evidence:
Prescreening of the labels by the FACT office will be performed and every effort made to correct any deficiencies prior to the on-site inspection. Examples of all labels in use by the applicant facility will be provided to the inspector prior to the on-site inspection. For applicant programs performing both allogeneic and autologous cellular therapy, examples of labels will include collection, processing, transport, and distribution labels for both types. In addition, labels

illustrating each cellular therapy product source handled by the Collection Facility should be included. Partial labels, if used, 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 office.

The inspector should examine labels to determine if deficiencies have been corrected and that confidential donor information is not included on the label or in accompanying documents. This will maximize the efficiency of the inspection by allowing the inspector to focus on elements that can only be verified on-site. However, 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 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 I. The inspector should further verify that labels are available for every type of cellular therapy product collected, with suitable 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 Collection 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 I.

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. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States" or other appropriate labels as required by Applicable Law.*

Explanation:
Table 2 of the inter-organizational *Circular of Information for Cellular Therapy Products* outlines when biohazard labels must be used. 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. Biohazard labels must not be applied indiscriminately.

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 I).

Communicable disease testing is not required for autologous donors in relation to cellular therapy product collection unless required by applicable laws or regulatory requirements, nor is there a requirement for donor eligibility determination. Some programs may decide to carry out communicable disease testing and eligibility determination in autologous donors to help standardize processes and so reduce the risk of error, and to 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. However, if autologous donor testing and screening is not performed, or is incomplete, the cellular therapy product label must contain the statement "Not Evaluated for Infectious Substances." In addition, if the autologous donor is tested or screened prior to collection and is found to be positive or at risk for a relevant communicable disease, the product label must bear a biohazard label and the appropriate warning statements. Since autologous recipients are not at risk of contracting a communicable disease from themselves (they already have the disease), the statement "Warning: Advise patient of communicable disease risk" is not required on autologous product labels even if donor testing results are positive, although a biohazard label is required.

If the complete allogeneic donor screening and testing is not performed, these cellular therapy products must be labeled with the statement "Not Evaluated for Infectious Substances." This statement must be also affixed or attached to the label of any product when either donor testing or donor screening for infectious disease risk has not been completed within the required timeframes by Applicable Law. The label of 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.

Cellular therapy products that are 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. Such products must obtain this statement, attached or affixed to the label or accompanying the product.

Note that residence in a country on the U.S. Department of Agriculture list as at risk of Bovine spongiform encephalopathy is considered to constitute a risk identified by donor screening. Thus, allogeneic cellular therapy products require a biohazard label and the statement "Warning: Advise Patient of Communicable Disease risks."

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" and other warning and biohazard labels for a variety of scenarios. The statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" must always be on the product if all donor eligibility requirements are not completed. For example, this statement must be on the following:

- 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 using approved donor screening test, but for which no official donor eligibility determination was made.

The use of the biohazard legend and the statement "WARNING: Reactive test results for (name of disease agent or disease)" is different. Any autologous cellular therapy product with the presence of risk factors for or clinical evidence of relevant communicable disease agents or diseases must have these labels, whether or not the regulations for donor eligibility determination were completely followed. If all donor eligibility requirements are not met, but the product is reactive for a relevant communicable disease, the product must be labeled with two warning statements: "WARNING: Reactive test results for (name of disease agent or disease)" and "NOT EVALUATED FOR INFECTIOUS SUBSTANCES".

Evidence:
The inspector should ask to see the SOP that defines the conditions for using a biohazard label and determine if the Collection Facility's SOPs are adequate and appropriate to prevent transmission of infectious disease.

The inspector should confirm that biohazard labels and warning statements are utilized as described in the Circular of Information Biohazard and Warning Labeling Table available at https://www.factglobal.org/education-and-resources/general/applicant-education-and-resources/resources/. Autologous cellular therapy product labels should be examined to confirm that "Not Evaluated for Infectious Substances" is present when the donor screening does not contain all elements listed.

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 Documents at Distribution table in Appendix III at the time of distribution.*

Explanation:
The FDA GTP regulations have specific requirements regarding the information that must accompany a cellular therapy product at the time of distribution. Requirements for products from allogeneic donors are listed in Appendix III. 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 that determination. This summary must include results of the donor screening for infectious disease risk and the communicable disease test results. The test and screening results must be listed with an interpretation of the values as positive or negative. There must also be a statement confirming that communicable disease testing was performed by a laboratory with the required

qualifications. For products that are distributed for administration, the product administration form can be used for this purpose. For products that are distributed to another facility, this information must be included in accompanying documents. If the Collection Facility is responsible for allogeneic donor eligibility determination, that facility is also responsible for distributing the above information to the Clinical Program and Processing Facility. If the Clinical Program determines allogeneic donor eligibility, the Collection Facility must obtain the information from the program so that it may accompany the product.

According to FDA and non-U.S. regulations, as applicable, there are many statements, results, and documents that must "accompany" the cellular therapy product at all times after the determination of allogeneic donor eligibility has been documented (see 21 CFR 1271.55).

The FDA Final Guidance "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)", August 2007 states that electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This Guidance Document is available at: https://www.fda.gov/media/73072/download.

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 I. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.*

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 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 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 was 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.

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. Urgent medical need documentation to release the product should also be present.

STANDARD:

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

Explanation:
For products collected for in-house Processing Facilities or third-party manufacturers operating under a BLA or IND, the label content is dictated by Applicable Law as listed in 21 CFR 312.6(a). To the extent possible, in-house and third-party manufacturers should be encouraged to follow the labeling requirements in Appendix I of these Standards.

STANDARD:

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

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 in Appendix I and state that the product is not for clinical use.

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. An example label reflecting these requirements can be found at https://www.iccbba.org/subject-area/cellular-therapy/faqs.

C8: PROCESS CONTROLS

STANDARD:

C8.1 *Collection of cellular therapy products shall be performed according to written Standard Operating Procedures.*

Explanation:

All SOPs should include elements outlined in standards C5.

Evidence:

The inspector should observe critical portions of a collection procedure to determine whether or not the personnel follow applicable SOPs. If there is no collection procedure scheduled for the day of an on-site inspection, the inspector should ask the Collection Facility staff to perform a mock collection, including all parts of the donor interview and consent for which that facility is responsible, and all labeling and storage steps. In addition, inspectors should 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 within proximity of the donor (or while collection tubing is still attached) 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 equipment required for each collection identified? How is cleaning and disinfection performed between collection procedures?

STANDARD:

C8.2 There shall be a process for inventory control that encompasses equipment, containers for transport and shipping, supplies, reagents, and labels.

C8.2.1 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.

C8.2.2 Each supply and reagent used to collect cellular therapy products shall be visually examined at receipt and prior to use for damage or evidence of contamination.

C8.2.2.1 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 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, and discoloration 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.

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 or evidence of tampering or contamination) and verification that it is the item actually ordered.

STANDARD:

C8.2.3 Supplies and reagents coming into contact with cellular therapy products during collection shall be sterile and of the appropriate grade for the intended use.

Explanation:
Supplies and reagents that contact the 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 facilities 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 are of pharmaceutical grade. Package inserts of reagents and supplies provide information regarding their intended use.

STANDARD:

C8.3 There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration.

C8.3.1 Equipment shall be maintained in a clean and orderly manner.

C8.3.1.1 Cleaning shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.3.1.2 Equipment shall be inspected for cleanliness and documented to be clean prior to use.

Explanation:
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.

STANDARD:

C8.3.2 Maintenance shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.3.2.1 The equipment shall be verified and documented to be in compliance with the maintenance schedule prior to use.

C8.4 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.

C8.4.1 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 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products collected since the last calibration.

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

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. There must be a schedule for equipment cleaning, maintenance, and quality control. Schedules may vary based on frequency of use, performance stability, or recommendations from the manufacturer.

Specified critical equipment must be calibrated by a qualified technician. 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.

If used, mobile collection sites must have SOPs that demonstrate compliance with these 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 (see C5.1) 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 (see C5.1). This should include an investigation of potential adverse effects on manufactured cellular therapy products using the equipment tracking system.

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 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, may still be helpful for any Collection Facility). See also 21 CFR 211.63-72.

STANDARD:

C8.6 *There shall be written documentation of an assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.*

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 (each day of collection). This does not require a complete history and physical examination by a physician for each 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 (or other) 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:

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

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 mobilization agents must supervise their 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 to mobilization agents and relevant laboratory tests should be performed, and dose adjustments made accordingly.

When parameters have been set by the Clinical Program that dictate when to (or when not to) administer mobilizing agents, the Collection Facility should have a mechanism in place to be certain 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 contraindicated for donors with sickle cell disease.

STANDARD:

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

Explanation:

The physician who evaluates the donor and makes the decision to proceed is not always the same physician who actually oversees or performs the collection. The collection 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. When relevant to the cells being collected, the written order should include:

- Identity of the donor.
- Identity of the allogeneic recipient.
- Timing of collection.
- Date and time the cells are needed by the recipient.
- Cell type to collect.
- Cell dose required for further processing.
- 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.

Collection timing may include a timeframe driven by target cells or specific date(s) and time(s). 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. 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 they were approved.

STANDARD:

C8.9 *Collection procedures shall include a process for assessing the quality of cellular therapy products to confirm product safety and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.*

C8.9.1 Methods for collection shall employ procedures that minimize the risk of microbial contamination and are validated to result in acceptable cell viability and yield.

Explanation:
Methods of collection must be validated to result in acceptable cell viability and recovery. 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.

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.

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.

STANDARD:
C8.10 Collection methods shall employ appropriate age and size adjustments to the procedures when required.

Explanation:
Specific adjustments to collection procedures may be required in circumstances where donor size is outside the norm, 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 the method applicable for pediatric donors, such as the use of blood prime with irradiated, CMV appropriate or equivalent red blood cell components and diluent when collection is via apheresis.

The written order for the product collection volume or cell dose should be appropriate for the age and/or size of the donor.

STANDARD:

C8.11 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 of applicable commercially disposable sets used by the Collection Facility.

STANDARD:

C8.12 Cellular therapy products shall be packaged in closed sterile containers appropriate for the product collected.

Explanation:

Sterile transfer bags designed for cellular blood products are required for the collection of cells by apheresis. 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.

Example(s):

Documentation of sterility of the transfer bag(s) from the manufacturer can be used as part of the qualification of the vendor. Inspection of collected cellular therapy products for a proper seal may be used as a product release criterion.

STANDARD:

C8.13 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

C8.13.1 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. 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.

If 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).

C9: CELLULAR THERAPY PRODUCT STORAGE

STANDARD:

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

C9.2 Collection policies or Standard Operating Procedures shall include the duration and conditions of short-term storage prior to distribution to a Processing Facility or Clinical Program.

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

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

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 C9.1 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 to require 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 Collection facility. Products that are awaiting release testing results (e.g., CD34 cell assessment by flow cytometry) 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 and/or on 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. The Collection Facility shall determine and assign expiration dates and times based on documented stability studies. 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.

Example(s):
An end-of-collection label with all the information printed, including storage temperature and duration, should be kept on-site.

C10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

STANDARD:

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

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 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/or shipping conditions and the responsibilities of each facility.

If the containers are appropriately validated to maintain acceptable temperature ranges and to protect the integrity of the products, and cellular therapy products are appropriately segregated, it may be possible to transport multiple products in the same transport container.

It is necessary that the cellular therapy product containers be securely sealed and packaged to protect them from potential harm during transit.

STANDARD:

C10.2 The primary cellular therapy product container shall be placed in a secondary container that is 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. When heat sealers are used on the tubing entering the primary container, a minimum of three (3) 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 cell product and concurrently collected plasma with the same identifier may be placed in a single secondary container.

Multiple primary bags from the same donor may be placed into a single secondary sealed container of adequate size. Human tissue, regardless of infectious disease testing, shall be considered potentially infectious. 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:

C10.3 The cellular therapy product shall be transported or shipped to the Processing Facility in a validated container within a temperature range defined in a Standard Operating Procedure or written agreement.

Explanation:

SOPs for transportation and shipping shall address issues of packaging, labeling, temperature, identification, safety, cellular therapy product integrity, and handling for 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:

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

C10.3.2 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.

C10.3.3 When a cellular therapy product is transported or shipped on public roads the outer container shall be secured.

Explanation:

The cellular therapy product temperature during transit is dependent upon variables, including the transport time, ambient temperature ranges, initial temperature, size of the product, and characteristics of the specific container system. The ideal transport temperature may range from 2-24°C. There shall be a prospective agreement among the collecting, processing, and receiving facilities regarding transport and/or 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 at 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, provided that the product is transported safely, a controlled temperature 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.

Examples(s):
Several reusable transport coolers are now available on the market that are used for shipping human blood and other biologics that may meet the requirements of these Standards, including some with nylon exteriors. Some are qualified for 2-8^{0}C, as well as 15-25^{0}C.

STANDARD:

C10.4 When a cellular therapy product is transported or shipped on public roads, the outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II A.

C10.4.1 There shall be a document inside the outer container that includes all the information required on the outer container.

C10.4.2 The cellular therapy product shall be transported or shipped with required accompanying records as defined in the transportation and shipping Standard Operating Procedures and in compliance with C7.4.5 and C7.4.6.

Explanation:
Accompanying documentation shall include all documentation of allogeneic donor eligibility as defined in Appendix III. 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 I and II.

STANDARD:

C10.4.3 The outer container shall be labeled in accordance with Applicable Law regarding the cryogenic material used and the transport or shipment of biological materials.

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

C10.6 Cellular therapy products transported internally shall be packaged in a qualified, closed, and protective outer container.

C10.6.1 The outer container for internal transport shall be labeled as defined in Appendix II B.

C10.7 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.

C10.8 There shall be contingency plans for alternative means of transport or shipping in an emergency.

C10.9 The cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.

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

Explanation:

Outer containers should not be opened during transport nor should they be exposed to gamma irradiation or X-Ray devices designed to detect metal objects. Such events could cause damage that may compromise cellular therapy product efficacy. 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. The inspector may look for documentation at receipt that containers had not been opened.

Example(s):
Examples of situations to investigate for possible compromise of the shipper include records of temperature outside of acceptable range, visible evidence that the container seal has been broken, volume of the container differs from the records, and shipping forms not included or attached. Outer containers should be secured using zip ties or locks.

C11: RECORDS

STANDARD:

C11.1 A record management system shall be established and maintained to facilitate the review of records.

Explanation:
Records are 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 provided that certain objectives are achieved. The record keeping system 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.

STANDARD:

C11.1.1 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

C11.1.2 For cellular therapy products that are to be distributed for use at another institution, the collection staff shall inform the receiving institution of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

C11.2 Good documentation practices shall be defined and used.

Explanation:
Good documentation practices are 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. Good documentation practices include:

- Data entry must be clear and legible.
- Use indelible blue or black ink; no gel pens, felt tip pens, or pencils.
- Make record entries at the time the task was performed (concurrently).
- Do not use ditto marks or arrows to include several data entry fields.
- Do not use correction fluid, correction tape, overlay of labels.
- Use the SLIDE RULE 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 Collection 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.

Example(s):
Slide Rule Examples:

discarded J.D. 11 Feb 13

- The vial was ~~dicrded~~* in error. Content …….

*misspelled J.D. 11 Feb 13

- Viability: ~~93.6%~~ Error J.D. 11 Feb 13
  98.6% J.D. 10 Feb 13

STANDARD:

C11.2.1 Records shall be accurate and legible.

C11.2.2 Written records shall be indelible.

C11.3 Records shall be maintained in such a way as to ensure their integrity, preservation, and retrieval.

C11.4 *Safeguards to secure the confidentiality of all records and communications among the collection staff, processing facilities and clinical facilities, and health care providers and their recipients and donors shall be established and followed in compliance with Applicable Law.*

Explanation:
Records may be maintained in more than one location, provided that the records management system is designed to confirm prompt identification, location, and retrieval of all records.

The Collection Facility must make provisions for all records to be maintained for the required time in the event that the facility ceases operation. Records that allow the tracking of a cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor must be maintained even when products are transferred to another facility.

Evidence:
The inspector should review the appropriateness of the storage of recent records, the adequacy of the system used for maintaining archived records, and the storage conditions for ensuring confidentiality and accessibility.

The inspector should acknowledge during the inspection that the Collection Facility is only responsible for compliance from the time of its initial FACT accreditation. Some Collection Facilities have not been accredited by FACT for a full 10 years. In these cases, the facilities are only held responsible for retaining records for the specified time since their initial accreditation.

Example(s):
It is recommended that recent records be kept on-site and that archived records are readily accessible within a reasonable period. Records may be maintained as original paper records, electronic files, photocopies, microfiche, or microfilm. Suitable equipment must be available for reading and/or photocopying records maintained on microfiche or microfilm. Electronic records must be backed up on a regular basis and stored to prevent their loss.

Secure storage may consist of maintaining the records in a locked room with access restricted to authorized personnel and/or the use of locked file cabinets. Examples of insecure storage include unsecured patient records; patient charts left unattended in areas where unauthorized personnel and/or visitors may have access, or unattended computer screens displaying patient information in such areas; indiscriminate discussion 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 and/or visitors; and release of confidential information without appropriate consent and approval.

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 cellular therapy product along with records of adverse reactions and post-donation complications, treatment interventions, and recovery.

STANDARD:

C11.5 Collection 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 or longer in accordance with Applicable Law.

Explanation:

Because QM documents provide evidence of compliance with the QM requirements, they should be maintained provided that 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 inspectors to reference when preparing for the inspection.

The inspector should review the Collection Facility's QM records, including documentation of periodic personnel training, cellular therapy product characteristics, and evidence of compliance with the facility's requirements. The inspector should also 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:

C11.5.1 Employee records shall be maintained in a confidential manner, as required by Applicable Law.

C11.5.2 Cleaning and sanitation records shall be retained for a minimum of three (3) years or longer in accordance with Applicable Law.

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 3 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.

STANDARD:

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

C11.6 Records to allow 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, whichever is latest. These records shall include product code, unique numeric or alphanumeric identifier, and collection date and time; and donor and recipient identification as far as known.

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.

This can be accomplished by selecting cellular therapy 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 cellular therapy product be retained indefinitely, as should records of adverse reactions and post-donation complications, treatment interventions, and recovery.

STANDARD:

C11.7 *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 ensures confidentiality and complies 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 the U.S., HIPAA regulations on confidentiality and data protection apply.

STANDARD:

C11.8 *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, and/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 and where these records are maintained and determine if an organized system is in place that allows timely retrieval of research records.

STANDARD:

C11.9 ELECTRONIC RECORDS

C11.9.1 There shall be a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum, systems under the control of the cellular therapy program that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

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 are listed in C4 and include collection procedures, labeling, storage conditions, and distribution.

It is not the intent of these 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 (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., calculation of total blood volume (TBV), collection efficiency) 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, for guidance to assess the validation procedures (https://www.fda.gov/media/75414/download), as well as the applicable requirements of HIPAA.

STANDARD:

C11.9.2 *For all critical electronic record systems, there shall be policies, Standard Operating Procedures, and system controls to maintain the accuracy, integrity, identity, and confidentiality of all records.*

C11.9.3 There shall be a means by which access to electronic records is limited to authorized individuals.

C11.9.4 The critical electronic record system shall maintain unique identifiers.

C11.9.5 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

C11.9.6 For each critical electronic record system, there shall be an alternative system for all electronic records to allow for continuous operation in the event that critical electronic record system is not available. The alternative system shall be validated, and collection staff shall be trained in its use.

C11.9.7 For all critical electronic record systems, there shall be written Standard Operating Procedures for record entry, verification, and revision.

C11.9.7.1 A method shall be established or the system shall provide for review of data before final acceptance.

Explanation:
Standards require that data is reviewed before final acceptance, but a second individual to verify the data is not required. Systems may be programmed to validate data (e.g., product numbers should only have a specified number of alphanumeric characters, date fields should follow a specific format).

STANDARD:

C11.9.7.2 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 may take the simple form of a log-in 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 log-in credentials.

STANDARD:

C11.9.8 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

C11.9.9 For all critical electronic record systems, there shall be validated procedures for and documentation of:

C11.9.9.1 Systems development.

C11.9.9.2 Numerical designation of system versions, if applicable.

C11.9.9.3 Prospective validation of systems, including hardware, software, and databases.

C11.9.9.4 Installation of the system.

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 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:

- 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 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 back-ups that include storage of back-up data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the back-up copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include all of 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 to assure 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 back-ups of records maintained electronically is in place.

STANDARD:

C11.9.9.5 Training and continued competency of personnel in systems use.

C11.9.9.6 Monitoring of data integrity.

C11.9.9.7 Back-up of the electronic records system on a regular schedule.

C11.9.9.8 System maintenance and operations.

C11.9.9.9 System assignment of unique identifiers.

C11.9.10 All system modifications shall be authorized, documented, and validated prior to implementation.

C11.10 RECORDS IN CASE OF DIVIDED RESPONSIBILTY

C11.10.1 A copy of all cellular therapy product records relating to the collection procedure shall be furnished to the facility of final disposition.

C11.10.2 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

Explanation:
In the event that two or more facilities participate in the collection, processing, or administration of a cellular therapy product, the records of each participating facility must clearly indicate the extent of each facility's responsibility. The facility's records should include relevant contracts and agreements. 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 Collection 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.

Records of documents showing areas of responsibilities must be documented and should include, but need not be limited to:

- Contracts and agreements.
- Donor work-up.
- Allogeneic donor eligibility and screening.
- Equipment maintenance.
- Staff education on the specific population being cared for.
- Patient outcomes reporting.
- Distribution and storage of cells.

Donor and recipient confidentiality must be maintained through the use of identifiers whenever the identity of the donor and recipient must remain anonymous. The location of each facility must be known to the relevant personnel at each facility, but donor identity should not be known to

the recipient, and recipient identity should not be known to the donor. Applicable Law regarding the sharing of confidential information must be followed.

It is the responsibility of the facility to furnish to all other facilities involved in the processing and/or administration of the cellular therapy product any data so far as it concerns the safety, purity, and potency of the product involved.

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.
The inspector should review the applicable SOPs regarding dissemination of collection data and verify that the process is in place.

Example(s):

For example, the Collection Facility may manufacture cellular therapy products for multiple clinical programs. A list of each facility showing its responsibility for collection, processing, or administration of the product should be provided for inspector review prior to the inspection. The facility record should indicate where the product was collected, stored, and/or infused but does not need to contain a record of the supply and reagent lot numbers used for steps performed at the Processing or Clinical Facilities.

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PROCESSING FACILITY STANDARDS

PART D

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 (bone marrow, umbilical cord blood, peripheral blood, or other tissue source). These Standards cover all processing in the Processing Facility regardless of product destination.

Processing Facilities are not restricted to serve only Clinical Programs or Collection Facilities that are FACT accredited; however, all organizations are encouraged to become accredited to demonstrate that they meet the minimum requirements for quality cellular therapy. Third parties who perform contracted services for the Processing Facility must comply with these Standards as they relate to the third party's interactions with the Processing Facility.

Evidence:

Processing Facilities will provide information to FACT 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 cells will most often be under IND or experimental studies approved by the IRB; however, unless otherwise stated, these Standards still apply to those cells and processing methods conducted within the Processing Facility. Separate facilities and laboratories in which cell processing takes place may be inspected and accredited separately.

STANDARD:

D1.2 The Processing Facility shall abide by Applicable Law.

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

Explanation:

Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with these Standards does not guarantee compliance with all Applicable Law. Governmental regulations must also be followed and supersede voluntary standards if those regulations are more stringent or inconsistent with voluntary standards. It is the responsibility of the individual Processing Facility to determine which laws and regulations are

applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the facility may also apply; for example, when a facility is sending or receiving cellular therapy products outside of its immediate location. Requirements also vary based upon the type of product processed or the stage of research.

Similarly, compliance with other organizations' standards or governmental regulations does not ensure that these Standards have been met. If a FACT standard is more stringent than a governmental regulation, the FACT standard must be followed.

Evidence:
Current certificates, registrations, permits, or licenses will demonstrate which areas of a facility have been authorized by governmental authorities.

A copy of a validated FDA registration document(s) will be submitted to FACT with the accreditation application. The inspector may also 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 can be obtained. It is not appropriate to request a faxed or scanned copy from the regulatory agency during the on-site inspection.

Example(s):
Cellular therapy products that are cultured prior to use, such as antigen-specific T cell lines or mesenchymal stromal cells, are considered to be extensively or substantially manipulated. In such cases, the processing would be regulated through an IND or IDE. When those requirements are more stringent than these Standards, the regulatory requirements must be followed.

In the U.S., minimally manipulated cellular therapy products from related donors are largely regulated under the 21 CFR 1271 GTP regulations, covered under section 361 of the Public Health Service Act., with the exception of products collected from marrow. Products from an unrelated donor, those that are extensively manipulated, combined with a device, or those with non-homologous use (does not perform the same function in the recipient as in the donor)are regulated under the Public Health Service Act section 351 and GMP regulations, including 21CFR 210 and 11. Most programs accredited under the FACT Common Standards fall in this category. The processing of HPC, Marrow should follow these Standards. It is the responsibility of the Processing Facility to verify that a contracting entity for whom it performs services possesses an approved IND , IDE, or BLA.

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. This team shall have been in place and 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 minimally one year, prior to initial accreditation. It is recognized that there may be minor staff changes during that one-year period, but the positions of major responsibility should have remained constant. Leadership changes may occur within a year of a renewal accreditation application. If a new or interim director (Processing Facility Director or Medical Director) with the required credentials specified in D3 is named, the facility is eligible for renewal accreditation.

During the 12-preceding initial accreditation, the Processing Facility must process enough cellular therapy products to validate its processes, train staff and maintain their competence, and demonstrate compliance with these Standards. The exact number of products required for initial accreditation is variable; FACT must be consulted for guidance in specific cases.

D2: PROCESSING FACILITY

STANDARD:

D2.1 There shall be secured and controlled access to designated areas for the processing procedure and for storage of equipment, supplies, and reagents.

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 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 or genetically modified products.

Explanation:

There must be clearly designated areas for cellular therapy product receipt, processing, and storage that are adequately segregated. 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.

Depending upon how open the processing procedure is, and the nature of the products being processed, there may be more rigorous requirements for minimizing the risks of contamination or cross-contamination. These may include the need for a higher level of personal protective equipment (PPE) (e.g., clean room (bunny) suits), stricter air quality standards (e.g., single pass hepa-filtration, ≤ ISO 5 air quality), buildings designed for better cleaning (e.g., sealed ceilings, washable epoxy paint), individual processing suites, one directional personnel flow, pass-through windows, and the use of ante rooms for dressing and undressing, to reduce the risks of cross-contamination. For products that are reaching the stage of requiring a BLA and are in phase III clinical trials, the degree of adherence to full GMP requirements is increased. Full adherence to GMP is more than just the physical environment, it includes process control, personnel training, and a strong quality management program similar to that described in these Standards.

A cleanroom is an isolated environment, strictly controlled with respect to but not limited to:

- Airborne particles of viable and non-viable nature.
- Temperature.
- Humidity.
- Air pressure.
- Air flow.
- Air motion.
- Lighting.

The cGMP for Finished Pharmaceuticals provides information about clean rooms from 21 CFR 600 through CFR 680. These give important requirements for biological products.

Cellular therapy programs are advised to consult with regulatory agencies early in product development to determine if or when upgrade to clean room facilities may be required.

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.

When an accredited Processing Facility is to be relocated, qualification and validation must be performed to confirm the new space meets these Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT accreditation policies (available on the FACT website). The Processing Facility is expected to submit a description and floor plans of the new facility, QM documents, and expected relocation date. Most relocations will be assessed during regularly scheduled inspections or interim audits; however, if there are any concerns with the information submitted by the facility, a relocation inspection may be necessary.

Example(s):
A cluttered Processing Facility without a defined workflow may be evidence that the facility does not have adequate space, is poorly designed, or is not under proper control. The inspector should be able to identify where receiving, processing, labeling, storage, and record- keeping take place.

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.

For cellular therapy products processed in clean room facilities, review of air monitoring results (during use and inactive), building layout, and observing how staff, materials, and products move through the facility should be part of the inspection. Look for evidence of room cleaning between products and look for systems in place to keep different product types separate when in the same facility.

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:
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 cellular therapy 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. If the location of the liquid nitrogen freezers prohibits limited access (e.g., is a shared facility with other users), individual freezers containing cellular therapy products for recipients must be securely locked.

This standard also applies to cellular therapy products stored overnight as fresh samples in refrigerators (quarantine or non-quarantine) before further processing or distribution.

Evidence:
Processing Facility personnel can be asked to demonstrate the process for release of a cellular therapy product in quarantine to confirm that such products cannot be released without proper approvals.

Example:
Where applicable, 21 CFR 211.42(b) in the U.S. requires that facilities have adequate space and measures for product segregation and for the orderly placement of equipment and materials to prevent mix-ups and/or contamination between different components, including cellular therapy products. Separate or defined areas, or other control systems, must be in place for the operations as necessary to prevent contamination or mix-ups.

STANDARD:
D2.2 The Processing Facility shall provide adequate lighting, ventilation, and access to sinks for hand washing and to toilets to prevent the introduction, transmission, or spread of communicable disease.

Explanation:
The layout and design of the Processing Facility must minimize the risk of error and permit effective cleaning and maintenance 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 cellular therapy products and allows personnel to perform their duties safely.

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 minimize the risk of introduction, transmission, or spread of communicable disease. 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.

STANDARD:
D2.3 Oxygen sensors shall be appropriately placed and utilized in 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.

Evidence:
The inspector should confirm that oxygen sensors are present in all areas where liquid nitrogen is present. Both visible and audible alarms are needed. The facility must define the low oxygen level in order to set the alarm at a safe level to allow sufficient time for evacuation.

Examples:
Risks to asphyxiation are real, and dangerously low levels of oxygen do occur. As reported in the article, *Deputy dead, several taken to hospital in liquid nitrogen incident,* from WJBF 6 News in Augusta Georgia, a liquid nitrogen incident claimed the life of a deputy and risked the lives of several others after responding to an activated freezer alarm. The article can be found at https://www.wjbf.com/news/georgia-news/liquid-nitrogen-leak-at-georgia-poultry-plant-kills-6/. An oxygen concentration below 19.5% is considered a hazardous atmosphere (exposing employees to risk of acute illness or death) according to a document of the OSHA (https://www.osha.gov/laws-regs/regulations/standardnumber/1926/1926.1202). The minimum safe level of atmospheric oxygen can range between 15 to 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 affected areas.

STANDARD:

D2.4 *Processing Facility parameters and environmental conditions shall be controlled to protect the safety and comfort of personnel.*

D2.5 *There shall be a written assessment of critical Processing Facility parameters that may affect cellular therapy product viability, integrity, or contamination or cross contamination during processing, storage, or distribution.*

D2.5.1 *The written assessment shall include temperature, humidity, air quality, and surface contaminants at a minimum.*

D2.5.2 *Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.*

Explanation:
The Processing Facility must 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 as well as conditions that would diminish equipment or personnel performance, such as extreme humidity. Some but not all, equipment has defined operating limits that should not be exceeded.

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 acceptable range for control parameters for maintenance of appropriate environment in the facility. The acceptable range of temperature for example may range between 20-24 degree Celsius and humidity may range between 15 to 75%. Most importantly the facility needs to justify their acceptable range for environmental parameters with documented evidence of maintenance. Whether environmental parameters are controlled by the laboratory or a central facility, there must be a mechanism to control any variations with 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 while on site to determine if the facility parameters affecting cellular therapy product viability, integrity, contamination, or cross-contamination identified by the facility are appropriate. 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 Accreditation Committee.

The Processing Facility should document when the humidity and cellular therapy product temperature went out of 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 did impact 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:

D2.5.3 *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 and/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 and/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 such as that provided by processing in a clean room. 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 suitable 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. These parameters should be defined by an SOP and compliance documented through quality records. If this review reveals problems, the inspector may recommend that the facility itself needs to be upgraded to achieve better environmental control.

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 EN/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:
D2.6 The Processing Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.

Explanation:
Processing Facility cleaning and sanitation must be performed on a regular basis to prevent contamination and cross-contamination of cellular therapy products. The methods used must be specified by an SOP (see D5.1). While the bench-top, 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 who performs the

sanitation procedures, the methods used, and the schedule. Facility cleaning must be documented, and the records maintained for at least three (3) 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, confirming that 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 Public Health Service (PHS) Act) can be found in 21 CFR parts 210, 211, 820, and 610.

A review of FDA reports of laboratory inspections revealed a number of facilities cited for the presence of dirt, dust, or mold growing in or around hoods or other equipment.

STANDARD:

D2.7 *The Processing Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, visitors, and volunteers.*

D2.8 *The Processing Facility shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, 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 Applicable Law regarding safety. Processing Facilities should post warning signs for biohazards and wherever radioactive materials are in use. Safety, infection control, or biohazard waste disposal procedures that are unique to the facility must be covered in SOPs. The use of electronic training programs that cover safety and infection control is acceptable, but there must be evidence that the staff has reviewed this information.

All persons who may encounter human blood or body fluids must wear appropriate personal protective equipment. This includes those exposed to cellular therapy products. The type of exposure that may be encountered will determine the appropriate suitable 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. The use of personal protective clothing must be defined by an SOP (see D5.1).

For patients receiving frozen cellular therapy products, the staff members involved in identification and infusing the products should be informed about potential danger of liquid nitrogen exposure. 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.

Activities such as eating, drinking, putting on makeup, smoking and recapping needles must be prohibited in the Processing Facility.

Evidence:
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 Applicable Law 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 CDC), for handling cellular therapy products, is a requirement of OSHA in the U.S. Equivalent regulations apply in other countries.

STANDARD:

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

Explanation:

An "Institutional Biosafety Committee" is a committee that reviews, approves, and oversees projects in accordance with NIH guidelines. The Institutional Biosafety Committee (IBC) must comprise at least five members so selected that they collectively have experience and expertise in recombinant or synthetic nucleic acid molecule technology and the capability to assess the safety of recombinant or synthetic nucleic acid molecule research and to identify any potential risk to public health or the environment.

The requirements of the biosafety plan are based on the hazardous characteristics of each agent or toxin used in the facility. The plan must include methods to prevent cross-contamination when multiple agents are used and work methods to prevent dissemination outside of primary containment areas. Methods of disposal must be defined. The IBC will review the plan and will determine the appropriate level of biocontainment necessary based on the agent and amount of agent used.

Evidence:

The inspector should review the biosafety plan and the approval from the IBC for each applicable genetically modified product.

STANDARD:

D2.10 All waste generated by Processing Facility activities shall be disposed of in a manner that minimizes 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/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 (see D5.1) 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. General waste that contains confidential information such as paper, CDs, or disks should be stored in a secured container before disposal and ultimately shredded or destroyed (see D5.1).

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

Example(s):
Contaminated materials soiled with biohazards may be typically discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, through the use of a sanitary landfill. Sharps like needles and blades, whether or not they are contaminated, should be considered highly hazardous health care 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:

D2.11 Personal protective equipment, including gloves and protective clothing, shall be used while handling biological specimens. Such protective equipment shall not be worn outside the work area.

Explanation:
Processing Facilities must follow their institutional policy regarding appropriate personal protective equipment (e.g., gowns, goggles, plastic apron, gloves) that must be worn when handling potentially hazardous substances. To prevent the spread of hazardous substances, personal protective equipment must be removed before leaving the workspace. This requirement must be outlined in an SOP as defined in Standard D5.1.

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 leaves the Processing Facility until it is received by the collection staff.

D2.12.2 Identity of the supplies and reagents including manufacturer, lot number, and expiration date shall be documented for each collection.

D2.12.3 Supplies and reagents shipped to the collection staff from the Processing Facility shall be in an outer container validated to maintain the designated temperature range.

Explanation:
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 Processing Facility 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 Processing Facility for the use and storage of the collection kit, and the documentation that the kit was correctly used and stored.

Example:
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.
- During return to the Processing Facility.

D3: PERSONNEL

STANDARD:

D3.1 PROCESSING FACILITY DIRECTOR

D3.1.1 There shall be a Processing Facility Director with a medical degree, doctoral degree, or equivalent degree in a relevant science, qualified by a minimum of two (2) years training and experience for the scope of activities carried out in the Processing Facility.

Explanation:
The Processing Facility Director must be an individual with a medical degree, doctoral degree, or an equivalent degree in a relevant science. A non-physician director may hold a doctoral degree in any of the biological sciences and must have practical and relevant experience in cellular therapy product processing including adherence to GxP.

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 his/her responsibilities. The director should

understand the procedures, identify critical points where extra precautions are needed, know 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, he/she must have practical training, experience, and be knowledgeable for each new procedure that is introduced into the facility, even if he/she is not responsible for performing the procedure (e.g., DC vaccines, MSC culture, flow cytometry). Experience requirements may exceed those required by these Standards based on Applicable Law including operating under GxP when that is required.

The Processing Facility Director may also serve as the Processing Facility Medical Director, if appropriately credentialed.

Evidence:
The Processing Facility Director is required to submit a CV that demonstrates two years of combined training and/or 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 where experience was obtained. 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):
Training consists of a total of two years of formal postdoctoral training in processing or clinical laboratory training following fellowship. 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 or a Ph.D. with experience in animal models of immunotherapy who is actually functioning day-to-day in a cell processing role for two years are examples of relevant experience.

STANDARD:

D3.1.2 The Processing Facility Director shall be responsible for all Standard Operating Procedures, administrative operations, and compliance with the Quality Management Program of the Processing Facility, 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 these Standards and with all other Applicable Law. Specific duties of the director required by these Standards include:

- Development of and compliance with the Quality Management 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 he/she or a designee should be available to Processing Facility personnel at all times. The director's active involvement in the laboratory is strongly encouraged. Knowledge of day-to-day activities in addition to the specific duties listed above allows for the director to be aware of overall operations in the facility. Facilities that process a large number of cellular therapy products or perform complex processing should ideally employ a director with a minimum of 50 percent effort committed to the laboratory. 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.

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 records requiring director review to confirm that he/she is available to the Processing Facility personnel when needed. Evidence should also be present to confirm that the responsibilities of the director are performed by the designated individual, and in a timely fashion.

STANDARD:

D3.1.3 The Processing Facility Director shall participate in a minimum of ten (10) hours of educational activities annually.

D3.1.3.1 Continuing education shall include, but is not limited to, activities related to cellular therapy product processing or the applicable therapeutic disease area.

Explanation:

The Processing Facility Director must participate regularly in educational activities related to the processing or use of cellular therapy products 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 his/her 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.

To assess the appropriateness of the amount and type of continuing education in which the Processing Facility Director participated, the following information must be submitted for each of the completed continuing education activities within each accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, meeting, grand round).
- 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. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

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, cell enrichment or cell depletion, gene editing or insertion, quality management related to cellular therapy, immunotherapy, and GxP.

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 on-line 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.

A downloadable Educational Activities form is available on the FACT website at https://www.factglobal.org/education-and-resources/general/hematopoietic-cellular-therapy-library/. The use of this form is not required but can be used to document compliance with continuing education requirements.

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 postgraduate 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 these Standards based on Applicable Law including GxP.

Practical relevant experience might mean day-to-day interaction in the preparation of and clinically relevant attributes of cellular therapy products, attending scientific conferences with clinical and cell processing content, or clinical and cell processing regulatory activities.

Evidence:
To fulfill this standard, the Processing Facility Medical Director must provide a photocopy of his/her current national and/or local governmental license and a current CV. Since documentation of the medical degree is required to obtain a medical license, the license will 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/or 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 Fellowship or post-doctoral training but must include at least one year of experience in performing or supervising cell processing procedures relevant to cellular therapy.

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 he/she or a designee must be available to Processing Facility personnel at all times. The director's responsibilities should be outlined in a job description.

Evidence:
Evidence of availability may be confirmed by examining documents, processing records, audits, and other records requiring the Facility Medical Director's review to confirm that the director is available to the facility personnel when needed.

Example(s):
Adverse reactions may occur after cellular therapy administration. The Processing Facility Medical Director must be available to assess the potential role of the product in the adverse event.

STANDARD:

D3.2.3 The Processing Facility Medical Director shall participate in a minimum of ten (10) hours of educational activities annually.

D3.2.3.1 Continuing education shall include, but is not limited to, activities related to cellular therapy product processing or the applicable therapeutic disease area.

Explanation:
The Processing Facility Medical Director must participate regularly in educational activities related to the processing and use of cellular therapy products 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 his/her 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.
To assess the appropriateness of the amount and type of continuing education in which the Processing Facility Medical Director participated, the following information must be submitted for each of the completed continuing education activities within each accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, meeting, grand round).
- 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. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Example(s):
Evidence of compliance may include either formal or informal study. Educational activities do not necessarily require large financial resources or a major commitment of time. 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.

Examples of appropriate continuing education activities include:

- The annual meetings of professional societies that include information directly related to the field. Both in-person and virtual meetings apply.
- 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 on-line 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 offers an Online Learning center that hosts recordings from its many educational events. These can be accessed at https://learn.astct.org/.

A downloadable Educational Activities form is available on the FACT website at https://www.factglobal.org/education-and-resources/general/hematopoietic-cellular-therapy-library/. The use of this form is not required but can be used to document compliance with continuing education requirements.

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 the performance of the Processing Facility, these Standards, or Applicable Law.

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 Quality Management. The title held by this individual may differ among facilities and is not relevant provided that the duties include those described in these 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 quality management.

The Quality Manager has responsibility for preparing, reviewing, approving, and implementing QM policies and SOPs and must confirm that they are compliant with these Standards and 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 and these Standards.

Quality units provide an objective review of the cellular therapy product processing, unbiased by work performed themselves. Although this review is independent, the quality unit must still have regular interaction with the Processing Facility Director and personnel, and provide regular updates and information related to the performance of the QM Program.

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 these Standards may play an active role in reviewing the work of the technologists, including QM procedures. The director is 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 these 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.

For Processing Facilities that perform minimal manipulation (e.g., 361-designated products) and have a low processing volume, these Standards do not prohibit the Quality Manager from participating in other facility operations. Many facilities or institutions may

not be large enough to support QM staff solely for the Processing Facility. However, the Quality Manager should not review or approve technical procedures for which he/she is solely responsible. In such cases, that review must be delegated. The Quality Manager may review SOPs where he/she has contributed to the activity following a reasonable time 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 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 Facility policies or Quality Management Plan. The independence of Quality Manager from manufacturing does not prevent interaction with the Processing Facility Director, but independence in approving/rejecting cell therapy quality control measures must be demonstrated in records. 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 or rejecting materials and equipment not compliant with pre-defined acceptance criteria. The role of Quality Manager extends to approving/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 provided that there is evidence of external review of his or her activities (e.g., by the institutional quality department or 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. where technical responsibilities do not allow time for the activities of QM supervision and the complexity is restricted to minimal manipulation of homologous use products.

STANDARD:

D3.3.3 The Processing Facility Quality Manager shall participate in a minimum of ten (10) hours annually of educational activities.

D3.3.3.1 Continuing education shall include, but is not limited to, activities related to cellular therapy, cell processing, and Quality Management.

Explanation:

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

There are many ways to meet this standard, and the standard is not meant to be prescriptive. A total of 10 hours in combination of these topics is required. Each topic does not need to be covered in 10 hours individually. The inspector should assess the documented number and

content of continuing education activities and use his/her judgment to determine if a QM Manager meets this standard.

Evidence:
To assess the appropriateness of the amount and type of continuing education in which the QM Manager participated, the following information must be submitted for each of the completed continuing education activities within each accreditation cycle:

- Title of activity.
- Type of activity (e.g., webinar, meeting, grand round).
- Topic of activity (e.g., cell administration).
- Date of activity.
- Approximate number of hours of activity.

Example(s):
Evidence of compliance may include either formal or informal study. Educational activities do not necessarily require large financial resources or an excessive time commitment. 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.

Examples of appropriate continuing education activities include:

- The annual meetings of professional societies that include information directly related to the field. Both in-person and virtual meeting are acceptable.
- 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 on-line 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 offers an Online Learning center that hosts recordings from its many educational events. These can be accessed at https://learn.astct.org/.
Cell therapy standards and Quality Management related resources including webinars are also available from Foundation for the Accreditation of Cellular Therapy (FACT) web site (http://www.factglobal.org).

A downloadable Educational Activities form is available on the FACT website at https://www.factglobal.org/education-and-resources/general/cord-blood-bank-library/. The use of this form is not required but can be used to document compliance with continuing education.

STANDARD:

D3.4 STAFF

D3.4.1 The number of trained processing personnel shall be adequate for the number of procedures performed and shall include a minimum of one (1) designated trained individual with an identified trained 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 these Standards and other 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 including the use of necessary equipment. Their continued competence must be documented.

Although some Processing Facilities may have only 1 full time staff member, it is unlikely that staff member will always be available due to illness, vacations, or unexpected emergencies. Therefore, it is important to have additional qualified individuals to process cellular therapy products and prepare them for administration. Such back-up help does not need to be directly employed by the facility but does need to be fully trained and must maintain competency for the procedures they are to perform.

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 and should specifically review the training and competency records of such individuals. 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:

A member of another laboratory, such as a research laboratory or an HCT processing laboratory, can be cross trained to perform specific tasks in the Processing Facility accredited under these Standards. A technician from the laboratory that initially developed the immunotherapy may be most easily trained.

STANDARD:

D4.1 There shall be a Quality Management Program that incorporates key performance data.

D4.1.1 The Processing Facility Director shall have authority over and responsibility for ensuring that the Quality Management 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 quality management activities required in these Standards.

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, or have a stand-alone QM program.

STANDARD:

D4.2 The Processing Facility shall establish and maintain a written Quality Management 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 does not have to be fully described in the QM Plan but must be referenced within the plan and linked to the appropriate document 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 these Standards and clarify the nature and extent of participation by other areas and/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.

STANDARD:

D4.2.1 The Processing Facility Director shall be responsible for the Quality Management 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 Processing Facility. A designee must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. Delegation of a 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 and designee's (if applicable) 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 he/she could be a member of the 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) may have a distinct individual responsibility for QM, provided that there is a mechanism for sharing information to all participating entities.

STANDARD:

D4.3 The Quality Management 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 Quality Management 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 for the Processing Facility and the QM Program. In addition, these charts must illustrate relationships to Clinical, Collection, and Processing Facilities that meet these Standards. Such an organizational

chart is required, but, depending upon program size and complexity, it may be necessary to have a separate chart showing the relationships that directly pertain to quality management activities.

The inspector will verify that the organization and daily function is as described in the chart and QM Plan (e.g., meetings, participants, schedule, reporting, and documentation). Lines of responsibility and communications must be clearly defined in a way that is understood by all involved.

If a Processing Facility contracts any of its processing service to an outside entity, the organizational chart must include the contracted service and summarize the reporting structure in the QM Plan.

Remote Directors or Medical Directors is those with professional responsibilities in more than one metropolitan geographic area, or those whose residence is outside of the metropolitan geographic area of the accredited facility. 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 any 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 these 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 quality management 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 these Standards. Documentation of director involvement in these responsibilities must be available on-site for review.

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.

Documentary 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.
- Investigation report review.
- Qualification/validation studies: plan and final report review and approval.
- Planned deviation pre-approval.
- Cellular therapy product release authorization.

Example(s):
Organizational charts for matrix programs, where an individual may report to different people for different duties (e.g., to the Processing Facility Supervisor for technical duties and to the QA Director for quality duties), should reflect the sphere of influence of individuals rather than just the lines of legal authority.

STANDARD:

D4.4 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Processing Facility. Personnel requirements shall include at a minimum:*

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. These must include all individuals responsible for critical elements of the Processing Facility. Documentation of training for all key personnel must include all procedural skills routinely practiced. These requirements are detailed in D3 and 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 as described in D4.4.
The inspector should review the records of one or more employees to confirm that all required elements are documented.

Example(s):
Although only one job description is needed for each key position, documentation for staff members 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 his/her 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.

STANDARD:

D4.4.1 A current job description for all staff.

D4.4.2 A system to document the following for all staff:

D4.4.2.1 Initial qualifications.

Explanation:
Initial qualifications generally include minimal educational requirements, formal training that is either required or preferred, and licensing or certification.

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, institutional policies, and 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, and in accordance with Applicable Law.

Explanation:
Initial training documentation must include all specific procedures that an individual staff member will perform (as defined in the job description). Such documentation 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 (e.g., GMP training).

Example(s):
Training and its documentation may be accomplished in a variety of formats. Training may be formal or informal presentations, self-learning by reading suggested materials on the topic, or reviewing previously presented audio/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 Part A for the definition of "critical").

Evidence:
The inspector will review policies or SOPs describing the elements of continued competency as described in D4.4 and the records of one or more employees to determine whether all of the required elements are documented. The inspector should review records of employees' initial and annual competency.

Example(s):
An annual competency assessment may be performed in conjunction with performance reviews during which a staff member's collective competencies and behaviors are evaluated to determine if the individual is meeting expectations and to identify areas of needed improvement. Competency may be assessed by direct observation, the use of written tests, successful completion of proficiency surveys, review of processing procedure endpoints, or other ways as determined by the Processing Facility.

STANDARD:

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

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.

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; 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 the Applicable Law for a particular jurisdiction. Comprehensive training on every aspect of GxPs each year is not expected; rather, there must annually be some training based on a GxP topic.

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 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.
- Current Good Manufacturing Practice (GMP or cGMP) on a sliding scale.
- Good Documentation Practice (GDP) and data integrity practices.

The *Guide to the Quality and Safety of Tissues and Cells for Human Application* (4th edition, 2019), published by the European Directorate for the Quality of Medicines and HealthCare (EDQM, Council of Europe), 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, immune effector cellular therapy, and other novel cellular therapies. It is available online at www.edqm.eu/freepub.

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 suitable educational opportunities for staff related to their duties, such as quality-related meetings, webinars, and/or FACT training sessions, if applicable.

Example:
There are topic overview educations sessions associated with the annual meetings of both ISCT and ASTCT/CIBMTR that might be well targeted to laboratory staff.

STANDARD:

D4.5 The Quality Management 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 these 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.

In this context, "policies and SOPs" means that a single document, either a policy or SOP, could suffice. Documents serve multiple purposes for the QM Program and can consist of different document types, such as policies, SOPs, or forms. Documents provide the structure needed for quality assurance through policies and SOPs, demonstrate quality control using forms and worksheets, and substantiate QM activities with audit reports, occurrence trends, outcomes analyses, training records, and others. 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 shall comply with the document control system requirements. Controlled documents shall include at a minimum:

D4.5.1.1 Policies and Standard Operating Procedures.

D4.5.1.2 Worksheets.

D4.5.1.3 Forms.

D4.5.1.4 Labels.

Explanation:

The QM Program must maintain identification of the types of documents considered critical. For example, all SOPs required by these Standards are considered to be critical documents and must be controlled. Processing Facilities may call documents different names and may identify additional types of documents as critical within the scope of the document control system.

Evidence:

The inspector should review a listing of which documents fall under the document control system.

STANDARD:

D4.5.2 There shall be policies or Standard Operating Procedures for development, approval, implementation, distribution, review, revision, and archival of all critical 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 these Standards. The inspector will observe how the Processing Facility controls modifications of documents and whether retrospective review is possible.

STANDARD:

D4.5.3 The document control system shall include:

D4.5.3.1 A standardized format for critical documents.

Explanation:
The Processing Facility should be consistent in the format or design of controlled documents.

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.

Examples:
Labels may present a challenge to ensure they meet the requirements of the document control system described in this series of sub-standards, especially since labels may be printed on demand using commercially available software packages that limit the information that can appear on the label. One method may involve creating a template containing a copy of the actual label that does not require that all that data to appear on the actual label.

STANDARD:

D4.5.3.2 Assignment of a numeric or an alphanumeric identifier and a title to each document and document version regulated within the system.

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, alphanumerical). Worksheets and forms must also be controlled documents and contain a title and unique identifier.

Evidence:
The inspector must verify that controlled documents are consistently 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 the effective date.

Explanation:
The effective date is when the previous version of a document has been recalled or archived, and the new version that is available has been implemented.

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 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:
Regular record review should alert the Processing Facility to areas needing improvement, particularly specific elements that are repeatedly missing or contain errors. This allows forms, worksheets, or SOPs to be revised and improved. The process should specify who reviews the records and the time interval for review.

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.

Example(s):
If controlled documents are associated with an SOP, the document review may occur in conjunction with the SOP review. If this is done, a separate review process for each controlled document is not required. Controlled documents could also be reviewed independently provided that they are reviewed and updated at a minimum every two years and when relevant to changes in procedures.

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 changes 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 these Standards and Applicable Law, risk and impact assessment on existing processes and controlled documents, approval of change, revision of documents, communication or training on the change as applicable, and implementation of the change. Change 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 he or she has reviewed the SOP and 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 Archival of controlled documents including policies and Standard Operating Procedures, the inclusive dates of use, and their historical sequence for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

Explanation:
Documentation is especially important for the investigation of occurrences since these investigations are frequently retrospective in nature. If outcomes change over time, one needs to be able to go back to previous versions of controlled documents to determine if an operational change is the cause.

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, and title).

Example(s):
The archival system may contain items such as date removed, version number, reason for removal, and identification of the person who performed removal.

STANDARD:

D4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

Explanation:
Hard copies of controlled documents may exist, and when documents are updated, there needs to be a secure process in place to ensure that any hard copies are not used beyond their expiry date.

Example(s):
Processing Facilities may have forms and worksheets that are printed and distributed. There should be a system in place to recall/remove these obsolete documents to prevent unintended use. A clear statement could be printed on hard copies that they may not be the current version, which can only be reviewed by going to the source library.

STANDARD:

D4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for 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. This standard does not apply to entities within the Processing Facility's institution. Agreements are also required when critical services are provided by the Processing Facility to external parties.

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

Example(s):
It is recommended that a Processing Facility have a contingency plan should it be unable to provide services as intended (e.g., significant personnel change or 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 external facilities) used for the storage of cryopreserved cellular therapy products or for laboratories performing testing of cellular therapy products.

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 health and safety of the donor or recipient.*

Explanation:
It is the Processing Facility's responsibility to determine whether entities providing critical contracted services are external or internal.

Documented agreements must clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements must be dated, reviewed, revised, and approved by both parties and legal counsel, if necessary, on a regular basis as defined by the program, and at least every two years. Agreements must also describe the maintenance or transfer of records and cellular therapy products following termination of the agreement.

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 signature), but which are relevant to the clinical care of the patient or donor or impact the cellular therapy product.

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 processing, testing, storage, distribution, or administration to maintain required accreditations, and to comply with these Standards and Applicable Law.

Explanation:

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.

Example(s):

When formulating written agreements either for clinical trial cellular therapy products or licensed products, the Processing Facility can add language to require that it be notified of information such as:

- Whether initial incoming material did not meet the appropriate cell (e.g., target cell) dose. Receiving this information as feedback allows the facility to investigate the collection failure.
- Potential issues that impact scheduling and production.

Additionally, if providing critical 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:

- How is updated donor eligibility information communicated?
- Is the facility required to provide notification of breaches in aseptic collection?
- How should post-donation information be communicated (e.g., donor contacts the facility two days after donation that they have an infection or identifies a risk that impacts donor eligibility)?
- What changes in operational availability or regulatory status must be communicated?

STANDARD:

D4.6.4 Agreements shall be dated and reviewed on a regular basis, at a minimum every two (2) years.

Explanation:
This standard does not require that agreements be renewed every two years, only that they have been reviewed to ensure that the needed requirements are met. This review should also confirm that the signatories to the agreement are the appropriate individuals.

Evidence:
The inspector should ask to review agreements and the documentation of regular review as required.

Example(s):
A master list of written agreements and a checklist could assist with appropriate review and ensure that important elements are included, and a designee in the Processing Facility is notified when changes are made.

STANDARD:

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

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 products can be demonstrated to produce a desired or intended function. Therefore, the assessment of outcome analysis requires input from the Clinical Program as well as product data from the Processing Facility.

Cellular therapy product efficacy based on patient outcome may be more difficult to document for products other than HPCs, and that assessment will differ for each product type. Minimally, the QM Plan must address the need for the development of a validated potency assay as regulated products enter the later stages of clinical trials. Validation of product potency assays has become a significant issue as more therapies enter phase III trials and although the FDA is aware of the difficulties for certain product types (e.g., MSCs) the need for a test of product potency is still required. The development of potency assay methods should begin early in product development.

Evidence:
The inspector should confirm documentation of all activities from definition of expected outcome to process improvement and potency assay development, 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, minutes of meetings, and Processing Facility review of the data including the personnel in attendance and where data are presented.

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:

It is the responsibility of Processing Facilities to assess the impact of cellular therapy processing on outcomes to identify trends. When HPC products are being used for nonhomologous use (e.g., HPC, Marrow for the treatment of cardiac failure), 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 recipient outcome is required to confirm that the highest quality product has been manufactured and distributed. Any unexpected outcomes must be investigated, including 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 failed persistence of the cells, if relevant.

If a Processing Facility provides cellular therapy products to one or more Clinical Programs, it is the responsibility of the facility to document outcome data from each program. There must be evidence of ongoing analysis of outcome data in addition to mere data collection.

When the Processing Facility is 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 microbial contamination, and cell type.

Example(s):

A measurable reduction in lymphoma tumor size may indicate that the infused CAR-T cells are effective.

STANDARD:

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

Explanation:

Outcome analysis should include each individual cellular therapy 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 of a similar product be assessed together for efficacy, safety, trends, and opportunities for improvement. However, outcome analysis should not only be performed on individual products, but also on all products of a given product type to identify overall trends. Product characteristics, especially cell dose and the role of cryopreservation (if relevant), should also be considered in such analysis. These data can be used to identify changes that might require further investigation.

Example(s):

Outcome analysis may be performed by grouping data based on cellular therapy product source (e.g., marrow, peripheral blood, or cord blood) or 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 number of recipients limit the number of groups that can be assessed.

STANDARD:

D4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:

Explanation:

The responsibility for the processing 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.

Evidence:

The inspector should confirm documentation of all activities from definition of expected outcome to process improvement, when indicated. The inspector should ask to see the data and/or minutes of meetings, including the personnel in attendance, where data are presented.

STANDARD:

D4.7.3.1 An endpoint of clinical function as approved by the Clinical Program Director.

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

Explanation:
An endpoint of clinical function may include safety and efficacy endpoints, depending on the product and the phase of clinical trial. Endpoints could include reduction in tumor burden, adverse reaction rates, length of hospitalization or other measures ad defined by the Clinical Program in addition to overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy. The measures may include overall outcomes in certain groups of recipients, which may be compared to existing internal or published data.

STANDARD:

D4.7.4 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, or distribution of the cellular therapy product.

Explanation:
Because patient outcome data are 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 are dependent on these data to adequately assess their practices. Data should be shared quarterly at a minimum.

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 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.

STANDARD:

D4.8 The Quality Management 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 Quality Management Program, operational policies and Standard Operating Procedures, these Standards, and Applicable Law.

Explanation:
Audits represent one of the principal activities of the QM Program. An audit is a documented, independent inspection and retrospective review of an establishment's activities to determine if they are performed according to written SOPs. Compliance is verified by examination of objective

evidence. Audits are conducted to be sure that the QM Program is operating effectively and to identify trends and recurring problems in all aspects of Processing Facility operation. Processes to be audited should include those where lack of compliance would potentially result in a nonconforming cellular therapy product or an adverse event.

The QM Manager should identify areas to be audited and audit frequency. The audit process should occur throughout the year 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 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.

A schedule of prospective audits is expected. There may be other audits required in response to specific events.

Further information is available in the FACT *Quality Handbook* (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

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 corrective and preventive action 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):
Audit schedules can be flexible and can be created through use of an Excel spreadsheet or table. Other examples of audits within the Processing Facility include:

- Adherence to policies and SOPs (e.g., correct labeling SOPs).
- Presence in the Processing Facility of written medical orders prior to processing and administration of products.
- Equipment maintenance performed according to schedule.
- Microbial culture results present in the processing record.
- Documentation of facility cleaning before, after, and between products.

These audits may be on-site inspections by contracting personnel or self-assessments performed by the Processing Facility or other members of the program.

Audit reports are an important tool to provide inspectors evidence regarding adherence to standards and effectiveness of implemented CAPAs; provide management guidance on future actions and decisions; and document the evaluation process and decisions made in response to issues detected. An acceptable audit report contains the following elements:

- Audit title.
- 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.
- Name and title of staff assigned to complete the audit.
- Audit period (date range).
- Audit purpose.
- Audit scope.
- Audit plan.
- Date audit started and completed.
- Audit findings and recommendations: if errors were found but not included in the final analysis, an explanation must be provided.
- Summary (includes assessment/evaluation of results): identifying the underlying cause (root cause) of the errors guides a program to develop an appropriate CAPA, which should be included in the audit report to demonstrate that appropriate action was implemented.
- Timeline for follow-up: a CAPA is required when errors are found. Should an organization determine that a CAPA is not required, this should be documented along with why it arrived at that conclusion. When a CAPA is implemented, follow-up audits should be performed to assess the effectiveness of the corrective actions and demonstrate improvement in the area where the original deficiency occurred.
- Signatures and Comments.
    - Auditor signature and date.
    - Quality Manager signature, date, and comments.
    - Processing Facility Director signature, date, and comments.
    - BMT quality committee chair signature, date, and comments.
- Documented staff review (initials) 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 or 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 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:

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

Explanation:

The individual(s) performing an audit does not need to be external to the Processing Facility, but he/she should not have performed the actions being audited.

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

Example(s):

Processing Facilities may have a designated position for an individual who performs such audits. Some facilities share auditors with the Clinical Program especially if the Clinical Program Quality Manager is a different individual from the Processing Facility Quality Manager. It is also possible to use a laboratory member with other responsibilities who also has sufficient expertise. For example:

- Clinical Program staff with audit experience could also audit Processing Facility processes.
- Data management staff can audit forms completed by Processing Facility staff. This encourages discussion among staff and facilitates learning.
- A separate HCT Processing Facility could audit activities in the non-HCT Facility and vice versa.

STANDARD:

D4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions in a timely manner.

Evidence:

The 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, cellular therapy 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:

D4.8.3 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 includes at least the required audits shown in the standards below, annually. Other processes should be chosen for audits at the discretion of each individual facility or identified by risk assessment. Audits that continuously fail to identify potential problems or opportunities for improvement can be replaced on the schedule by a new audit topic.

Example(s):
An example of another recommended audit is a gap analysis when a new version of these Standards has been published.

STANDARD:

D4.8.3.1 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 Processing Facility's defined responsibilities.

STANDARD:

D4.8.3.2 Infectious disease resulting from cellular therapy product collection, processing, or administration.

D4.8.3.3 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

Explanation:
Audits must 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 also after there has been a change in the agreement or in Applicable Law that pertains to the agreement.

Audits of external facilities may be accomplished by reviewing the facilities' internal and external audit reports, performing on-site inspections for compliance, or by receiving periodic performance reports from the facility. There may be other alternatives, but the contracting facility must establish that their contracted services meeting requirements.

STANDARD:

D4.8.3.4 Chain of identity and chain of custody of cellular therapy products.

Explanation:

The chain of identity refers to the association of the cellular therapy product's unique identifiers from procurement throughout the full product life cycle, including post treatment monitoring of the recipient. The chain of custody documents the guardianship of the cellular therapy product from origin to final disposition. The Processing Facility will likely be an intermediate step in both processes but must ensure that it is able to follow the chains from beginning to end.

STANDARD:

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

Explanation:

The Processing Facility will most likely be asked to participate in audits of their procedures performed by or for commercial manufacturers or regulatory agencies. The requests may be varied. The processing facility is responsible to ensure that such audits are handled in a consistent fashion.

STANDARD:

D4.9 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results and responsibility for the following activities at a minimum:

D4.9.1 Documentation and product labeling.

D4.9.2 Cellular therapy product quarantine.

D4.9.3 Criteria for cellular therapy product release.

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

D4.9.5 Notification of the recipient, recipient's physician, collection staff, and any other facility in receipt of the cellular therapy product; and if relevant, the donor and the sponsor.

D4.9.6 Recipient follow-up.

D4.9.7 Follow-up of the donor, if relevant.

D4.9.8 Documentation and investigation of cause.

D4.9.9 Reporting to regulatory agencies, as required by Applicable Law.

Explanation:
The Processing Facility shall monitor all cellular therapy products, minimally after processing, for microbial contamination. For cells that are infused fresh, without culture or cryopreservation, the results of such testing will not generally be known prior to administration. Preliminary or final culture results should be available for cryopreserved or cultured products prior to administration.

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 the particular area (Clinical Program, Collection or Processing Facility) is responsible. This requirement may be satisfied with a single policy or SOP or there may be separate documents. For each topic, SOPs should detail what action is to be taken, who is responsible to take the action, and the expected timeframe of the actions. Different approaches to management may be acceptable if these approaches are consistently followed and meet regulatory requirements.

These documents should cover investigation of the cause of the positive culture result, including at least evaluation of the collection and processing events for evidence of breach of aseptic technique, determination if 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 cellular therapy product that might explain the positive result. Since a positive microbial culture is a deviation, all requirements for occurrences apply.

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 of the Clinical and Collection Facility, which should in turn investigate all records related to that collection to determine if anything in the collection process could have contributed to the positive culture result. Notification of clinical staff of the positive culture result is critical so that appropriate patient care

can be delivered to the donor, and, if the cellular therapy product has already been administered, to the recipient. If the product has been shipped or transported to another facility, that facility must also be notified.

There should be a policy or SOP 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. The Clinical Program is typically responsible for recipient notification and consent and must assist with urgent medical need documentation. Biohazard label and warning statements must be used as required by D7 and Applicable Law.

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 D4.9 and the regulatory requirements of the FDA must be met.

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):
It is recommended that cellular therapy products with a known positive culture be labeled in a fashion similar to that used for products from donors with a positive infectious disease test result. These products should be kept in quarantine due to possible cross-contamination. Although, this standard indicates a contaminated product might be released, for cellular therapy products that are cultured, or have undergone extensive manipulation, it is unlikely such a product would be considered safe to infuse. A process for release of a known contaminated product is generally part of the product IND, and that process would have to meet FDA approval.

In the U.S., regulations for 351 and 361 products should be followed and the cellular therapy program should have policies that cover responsibility for reporting.

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

- Review of processing records for any indication of breech 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 viable and non-viable 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.

- Follow up of the recipient for adverse reaction to administration, infection by the contaminating organism, or other adverse event.

Evidence of investigation of cause, outcome analysis, and any preventive/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 minutes of QM meetings.

STANDARD:

D4.10 The Quality Management 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:

A goal of a QM Program is to continuously improve processes. Monitoring occurrences and trends facilitates recognition of improvement opportunities. There must be policies, processes, and procedures to detect, evaluate, take immediate action, document, and report occurrences in a timely fashion to key individuals, including the Processing Facility Director, Processing Facility Medical Director, Processing Facility Quality Manager, appropriate 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 Part A (Definitions). Management of each of these types of occurrences is slightly different; however, the same steps (detection, evaluation/investigation, documentation, determination of corrective and preventive action, and reporting) apply to all types.

Evidence:

The inspector should expect to find a documented process for occurrences that include detection, investigation, documentation, corrective action, preventive action, and follow-up. This should be reviewed by the Processing Facility Director and Quality Manager and reported, as appropriate, to the Medical Director of Collection Services, the Clinical Program Director, appropriate governmental agencies, and other third parties involved in the manufacture of the cellular therapy product.

STANDARD:

D4.10.1 Detection.

Explanation:
Immediate actions must be taken and documented to mitigate further risk to cellular therapy products, staff, or patient safety.

STANDARD:

D4.10.2 Investigation.

D4.10.2.1 A thorough and timely investigation shall be conducted by the Processing Facility in collaboration with all entities involved in the collection, manufacture, testing, or administration of the cellular therapy product, as appropriate.

D4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective and preventive action as warranted.

D4.10.2.3 Occurrences shall be tracked and trended.

Explanation:
Investigation of the cause(s) of any deviation is critical to determine what CAPA will most likely be effective. The focus of the investigation should be to learn and improve, not to cast blame or be punitive. Often "systems" play a role in causation. Serious events require more in-depth investigation to find the root cause. Processing Facilities should be encouraged to stratify deviations 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 systems, policies, or procedures that will correct the issue and prevent recurrence of the deviation.

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 product has been administered. The most common deviations encountered involve products from ineligible donors.

Example(s):
Use of an ineligible donor may be an occurrence. The investigation of should focus on the documentation required for urgent medical need, including recipient notification, physician approval, and proper product labeling. Ineligible allogeneic donors for cellular therapy products that require a high degree of HLA matching are usually chosen based on HLA match. The small risk of CDJ when the best matched donor lives in Europe is generally acceptable.

STANDARD:

D4.10.3 Documentation.

D4.10.3.1 Documentation shall include a description of the occurrence, date and time of the occurrence, the involved individuals and cellular therapy product(s), when and to whom the occurrence was reported, and the immediate actions taken.

D4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Processing Facility Director, Medical Director, and Quality Manager.

D4.10.3.3 Cumulative files shall be maintained and include written investigation reports containing conclusions, follow-up, corrective and preventive actions, 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/time, and actions are captured.

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

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 reduce the risk of transmission of a communicable disease.

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.

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:

D4.10.4 Reporting.

D4.10.4.1 When it is determined that a cellular therapy product has resulted in an adverse event or reaction, the event and results of the investigation shall be reported to the donor's and recipient's physician(s), as applicable, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by Applicable Law.

D4.10.4.2 Occurrences shall be reported as required to other facilities performing cellular therapy product functions on the affected cellular therapy product.

D4.10.4.3 Occurrences shall be reported as required to the appropriate regulatory and accrediting agencies, registries, grant agencies, and Institutional Review Boards or Ethics Committees.

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 cellular therapy 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, and IRBs or Ethics Committees).

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. 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.

Examples:
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 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. FDA guidance for such plans in the U.S. can be found in *Guidance for Industry: E2E Pharmacovigilance Planning* (2005) available at https://www.fda.gov/media/71238/download and *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (2005) available at https://www.fda.gov/media/71546/download.

STANDARD:

D4.10.5 Corrective and preventive action.

D4.10.5.1 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.

D4.10.5.2 Follow-up audits of the effectiveness of corrective and preventive actions shall be performed in a timeframe as indicated in the investigative report.

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

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

- Identification of the involved individuals and/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 corrective action.
- 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 *The Quality Management 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:
One of the most important paper trails allows for tracking and tracing of information about the cellular therapy product at all steps between the donor and the recipient or final disposition. Documentation in the processing record should include the identity and content of the product, the unique identification of the donor, and a unique identity of the product. There should also be a means, direct or indirect, that will allow outcome information to be related back to a specific product and communicated to any other facilities involved in collection, processing, and/or distribution of the product. The final disposition of the product must be documented whether the product was infused, destroyed, released for research, remains in storage, or another outcome. The process for product tracking must be defined by an SOP. Additionally, the identity of the individuals involved with each step of the product life cycle (from collection to final disposition) must be documented (chain of custody).

Evidence:
The inspector should 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 (chain of identity) and recipient identification is possible. All critical steps should identify who performed the procedure and when they were completed (chain of custody). 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 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, provided that 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 facility removes specimens from a 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 product.

STANDARD:

D4.12 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event the Processing Facility's 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 (see D5.1), 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, these 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, a HVAC supply interruption, or shortage of a critical reagent. The plan should reflect differences between specific 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 back up 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, or 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 if 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. This should include a mechanism to determine and document critical values for determining cellular therapy product release criteria and appropriate product labeling.

Evidence:
The inspector should review policies and forms to be used in case the electronic record system is unavailable.

Example(s):
Examples include malfunctioning electronic records systems, critical reagent shortages, power outages, equipment failures, and supply shortages. A contingency procedure would identify alternative supplies, sources of supplies, or alternative validated processing or testing procedures. For example, a backup flow cytometer should be validated to use for cellular therapy products that require a defined cellular content before release.

STANDARD:
D4.13 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services relevant to cellular therapy product.

Explanation:
Quality can be maintained only if there is control over critical 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 Processing Facility, steps should be taken to verify supplier and vendor qualification had 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.

In the U.S., when using a licensed or research cellular therapy product, the IND or BLA holder is responsible for verifying that any facility performing a step of manufacturing complies with GMP and GTP requirements as applicable (see 21 CFR 1271.150(c)(1)(iii)). If the IND or BLA is held internally by a FACT-accredited facility, the facility must perform this qualification and provide documentation to inspectors. If the IND or BLA is external, i.e., held by a third-party investigator or manufacturer, this qualification is outside the scope of FACT accreditation and the FACT-accredited facility is not required to provide documentation of this type of qualification.

The Processing Facility must participate in site visits from the IND or BLA holder and provide the level of service required of that entity. FACT-accredited facilities that participate in manufacturing for external IND or BLA holders must provide inspectors evidence of complying with these requirements as required by Applicable Law.

Example(s):
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 cellular therapy product integrity.
- Updated software versions have the potential to materially affect performance of equipment.

Where purchasing is beyond the direct control of the Processing Facility, steps should be taken to verify supplier and vendor qualification had been performed by the parent organization.

For further definitions and examples of qualification, see the FACT *Quality Handbook* (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

STANDARD:

D4.13.1 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 vendors are compliant with Applicable Law and that there is a system in place that is consistent with these Standards, such that they can demonstrate process control. 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., ACD, NaCl, PlasmaLyte) may consist of documented evidence of inspection of the reagent for discoloration and/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.

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, AABB, CAP, or others.
- Remote audits by questionnaire.
- An ongoing dialogue 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 Processing Facility as evidence that deficiencies have been recognized and corrected.
- A documented review of the suppliers' 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 and 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.

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.

STANDARD:

D4.13.2 Qualification shall be required following any significant changes to these items.

Explanation:
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 cellular therapy product efficacy.

STANDARD:

D4.13.3 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Processing Facility Director.

D4.13.4 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

Explanation:
This standard applies to situations where there are no suitable clinical or pharmaceutical grade reagents available for the processing that is being conducted or for reagents being used under approved research purposes. Reagents meeting these criteria shall be qualified. This may include:

- Use under IND, IDE, or other exceptions approved by the appropriate regulatory agency.
- Evidence of extensive experience with the reagent and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.
- Extensive literature supporting use of the reagent for the specified purpose and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.

If a reagent is not of the appropriate grade, it must be of the highest grade (or purity) available and the Processing Facility must validate that the reagent is safe and effective for the specified purpose.

DMSO not approved for clinical use must undergo lot-to-lot functional qualification. It is a critical reagent that actually performs a function (i.e., it protects the cells). Should a lot of DMSO not function as expected, there would be dire consequences to the cellular therapy product and its intended recipient.

Example(s):
Qualification of a new reagent used in processing (washing, freezing, or other product manipulation) can be achieved by review of the certificate of analysis and microbial testing. The Certificate of Analysis should list contents and concentration of the reagent and if the reagent is sterile and safe for human use.

DSMO lot-to-lot qualification could be accomplished by reserving two extra, small samples from each of several cellular therapy products for comparison. This method requires a very small percentage of cells collected. One sample can be cryopreserved and the other would not. A comparison of the two can then be performed to determine the effects of the DMSO. Advantages of this method are that no normal donors are required, no patient is at risk, and qualification data can be obtained. Generally, IRBs or ethics committees do not consider reagent qualification to be research, so special donor or recipient consent is not normally required. This would need to be confirmed with local requirements.

STANDARD:
D4.14 The Quality Management 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.

For further definitions and examples of validation, see the FACT Quality Handbook (https://www.factglobal.org/education-and-resources/general/quality-management-resource-center/).

STANDARD:
D4.14.1 Critical procedures to be validated shall include at least processing techniques, cryopreservation procedures, testing, labeling, storage, distribution, and preparation for administration.

Explanation:
In the Processing Facility, the following should be validated or verified:

- Processing procedures. All processing procedures must be validated. A published procedure adopted from another processing facility (e.g., hetastarch sedimentation for RBC depletion) may be verified provided that the conditions under which it is used are like those validated elsewhere. In processing, the results of the validation study must be kept as long as there are products in storage collected or processed using the procedure in the validation study. Staff from collection and processing facilities should have a process for communicating with one another to ensure that validation studies are not discarded prematurely.
- 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 manufacture would require a more extensive validation study.
- The intended use of reagents made on site and those not approved for clinical use. Must be validated. A novel reagent used for RBC removal would be validated to show that RBCs are depleted to the required degree from each product type and under all the conditions. Each new lot of the reagent would be verified to perform similarly using more limited testing.
- Labels. The validation of the label would demonstrate that the labels in use were checked against an approved template to contain all of the required elements as listed on the label table (see Appendix I), were approved for use, maintain integrity during use, remain affixed or attached during storage as required, are readable, and that any hand-written elements were made with indelible ink. Validation of the labeling process should demonstrate completeness and correctness of each data point, absence of blank data spaces, and 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, including temperature and storage duration.
- Distribution of the product. This may include transportation or shipping, within or between facilities, and preparation for administration. Preparation may include removal of cryoprotectant or medium used during processing (washing) such as culture medium or other medium not approved for administration, and the final label and product checks needed to ensure product integrity and identity.
- Electronic records system, if applicable.

When possible, reagents and supplies 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, or safety) or to the recipient of the product. Examples of acceptable endpoints may include but are not limited to nucleated cell recovery, viability, red blood cell reduction., or lack of microbial contamination.

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 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 results meet acceptance criteria, outcome and conclusions are documented, and that both the finalize validation plan and validation study report have been reviewed and approved by the Processing Facility Director and Quality Manager.

Example(s):
A change of reagents used for processing, such as cryopreservation, requires validation to verify maintenance of cellular therapy product cell recovery, viability, potency, and absence of microbial contamination. are maintained within acceptable limits. The potential for adverse reactions and comparison of product function should also be examined.

Another example of a change requiring validation is a change to a different method of red blood cell reduction. Documentation of red blood cell content remaining in the cellular therapy products, nucleated cell recovery, and viability should be included in evaluation of the new method.

Specific manufacturer's requirements that are not part of the facility's SOP should be managed by a separate SOP applicable to manufacturer's requirements.

STANDARD:

D4.14.2 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, conduct 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 and to 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 include nucleated cell recovery, viability, red blood cell reduction., and lack of microbial contamination.

STANDARD:

D4.14.2.1 An approved plan, including conditions to be assessed.

D4.14.2.2 Acceptance criteria.

D4.14.2.3 Data collection.

D4.14.2.4 Evaluation of data.

D4.14.2.5 Summary of results.

D4.14.2.6 References, if applicable.

D4.14.2.7 Review and approval of the plan, report, and conclusion by the Processing Facility Director and Quality Manager.

Explanation:
Review and approval must be completed at a minimum by two individuals: the Quality Manager and the Processing Facility Director. Designees are acceptable according to the policies of the Facility.

STANDARD:

D4.14.3 Significant changes to critical procedures shall be validated or verified as appropriate.

D4.15 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the evaluation of risk in changes to a process to confirm that the changes do not create an adverse impact or inherent risk elsewhere in the operation.

D4.15.1 Evaluation of risk shall be completed for changes in critical procedures.

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, or the cellular therapy product integrity, sterility, viability, or potency. Critical procedures include processing, distribution, labeling, and storage.

Evaluation of risk may be documented in a validation plan or exist as a separate document and 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 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 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 identity of the specific risk(s) should be included. After the risk(s) has been identified, it must be assessed on the potential of criticality or on their likelihood of occurrence and the 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.

After the risk assessment is established, a risk management plan can be developed and implemented. It is comprised of 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 using another reagent or supply item of suitable grade.

Below is an example of a risk assessment matrix that combines the concept of likelihood and severity.

Risk Matrix

Severity of Incidence	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)
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:

D4.16 *The Processing 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.*

D4.16.1 *Meetings shall have defined attendees, documented minutes, and assigned actions.*

D4.16.2 *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.

Multidisciplinary meetings involve several academic disciplines or key personnel in an approach to make recommendations to a topic or problem.

Quarterly meetings are not required but are highly recommended. 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.

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 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:

D4.16.3 The Processing Facility Director shall not approve their own work.

Explanation:
Any person responsible for overseeing the QM activities should not be directly responsible for review of work solely performed by that person. It is important that the final review be non-biased, and that there has been sufficient time away from the work for the review to be objective. Alternatively, in small Processing 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 for review of these activities. It may be acceptable, however, for an individual to review his/her own work at a time and place removed from the actual performance of the work.

STANDARD:

D4.17 The Processing Facility Director shall annually review the effectiveness of the Quality Management Program.

D4.17.1 The annual report and documentation of the review findings shall be made available to key personnel, the Clinical Program Director, the Collection Services personnel, and staff of the program.

Explanation:
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 Plan, 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. If the Processing Facility is part of an integrated cellular therapy program, a single annual report is sufficient.

The annual report should also contain trending information related to key indicators that are monitored, recipient 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. In addition to relevant measures addressed in B4.17.1, the Processing Facility may consider including the following measures:

- Product outcomes (cell counts, viabilities, recovery data, absence of microbial contamination).
- Facility and environmental monitoring data.
- Other events such as complaints or deviations.

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 and SOPs that comprehensively address all important aspects of the facility and operations. 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. These Standards allow the facility to create its document hierarchy based upon 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 and/or SOP required for each item on the list provided that each item is addressed somewhere within an appropriate document. The items listed in D5.1 include the minimum requirements; a facility may exceed these requirements, but not omit any of these.

Policies and SOPs must comply with the document control system 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 these Standards. The list should be assessed by the inspector for evidence of SOPs addressing each item before arriving at the inspection site in order to reserve limited on-site time for verification of implementation of written SOPs and other activities that can only be verified in person. 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. This crosswalk should include the location within the SOP where each topic is addressed.

If a Processing Facility is operated as part of a larger organization or institution (e.g., transfusion services) and shares some SOPs or policies with another service or organization, 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. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, the emergency response to disasters, and patient confidentiality. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for initial approval and review and approval of revisions every two years by the facility to ensure the most current version is in use and the applicability to all functions of the facility. If general institutional policies and SOPs are inadequate to meet standards or where there are issues that are specific to the cellular therapy facility, the facility must develop its own policies and SOPs to supplement those of the institution.

Some Processing Facilities may handle cells as starting material or as final cellular therapy products for third party manufacturers. These third-party manufacturers may require processes different from those 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 (suitable 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.

STANDARD:

D5.1.1 Donor and recipient confidentiality.

Example(s):
Donor and recipient confidentiality include confidentiality of records. Such an SOP should indicate actions taken within the facility to maintain confidentiality.

STANDARD:

D5.1.2 Cellular therapy product receipt.

D5.1.3 Processing and process control.

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

D5.1.4 Processing of ABO-incompatible cellular therapy products to include a description of the indication for and processing methods to be used for plasma and red blood cell reduction.

Explanation:

ABO incompatibility between donor and recipient may be significant if the product contains red blood cells at the time of infusion. There is a risk of hemolytic infusion reaction if significant volumes of incompatible red cells are infused with a cellular therapy product. A potential risk also exists if ABO incompatible plasma is infused with a cellular therapy product. This standard requires that procedures be in place for the management of those products that may conclude significant amounts of incompatible red cells or plasma. There are various methods to deplete the red cells or plasma from various products prior to infusion to minimize risk.

Example(s):

Cellular therapy products vary in the content of red cells and plasma. Bone marrow products typically contain significant volumes of red cells at the end of collection. Several methods of reduction of red cells prior to infusion, including sedimentation in hydroxyethyl starch or centrifugation methods may be sufficient to permit safe infusion of the product. Similarly, cord blood collections typically contain significant volumes of red cells at the end of collection but may be processed prior to cryopreservation to minimize risk at infusion. If not red cell reduced prior to cryopreservation, cord blood units require dilution or washing prior to administration.

In contrast, apheresis products typically contain very small volumes of red blood cells in the final product. Likewise, highly processed products may contain few if any red cells at infusion. Similarly, many products covered under these Standards, including those more than minimally manipulated ex vivo, contain few if any red cells, and the considerations of incompatibility are nor relevant.

This standard requires that policies and SOPs be in place to manage those scenarios where ABO incompatibility is relevant.

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 to include alternative storage if the primary storage device fails.

D5.1.9 Release and exceptional release.

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

Explanation:
Processing facilities should have an SOP for both transportation and shipping, even if the Processing Facility does not routinely perform these distribution methods.

STANDARD:

D5.1.11 Cellular therapy product recall, to include 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 failure.

D5.1.15 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.

D5.1.16 Environmental control to include a description of the environmental monitoring plan.

D5.1.17 Hygiene and use of personal protective equipment and attire.

D5.1.18 Disposal of medical and biohazard waste.

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

D5.1.19 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, 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 and what to do if cellular therapy products need to be moved. Institutional policies typically do not include issues of inventory management or immediate product management.

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, 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 these 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 et all, 2006) provides a framework for disaster plans that can be customized for individual programs: http://www.ncbi.nlm.nih.gov/pubmed/17085317.

The U.S. FDA offers information on its webpage titled, "The Impact of Severe Weather Conditions on Biological Products," at
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ProductSecurity/ucm147243.htm.

STANDARD:

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

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 Processing Facilities have adopted an electronic method of compiling its controlled documents. 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. SOPs must be under document control as outlined in D4.

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 a quality, a policy, and a database manual 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:
This standard defines the minimum elements required in each SOP. SOPs are controlled documents and must comply with the requirements in D4.

Evidence:
The inspector should review the Processing Facility's SOPs to verify that each of the items required in this standard is present in the individual SOPs.

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.

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 for each procedure. Examples include nucleated cell recovery, viability, hematocrit, DMSO concentration, plasma volume, and absence of microbial contamination. The range for a given parameter can be determined within the facility by retrospective analysis of its own data or reference ranges

established in published literature. Determination of a mean ± 1 or 2 standard deviations from analysis of past procedures may be used to define an acceptable range.

STANDARD:

D5.3.4 A stepwise description of the procedure.

Explanation:
The procedure steps must be understandable by trained staff. The use of diagrams or figures can make a procedure easier to follow.

STANDARD:

D5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

D5.3.6 A reference section listing appropriate and current literature.

D5.3.7 Documented approval of each procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation and every two (2) years thereafter.

Explanation:
These 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 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.

STANDARD:

D5.3.8 Documented approval of each modification to a Standard Operating Procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation.

D5.3.9 Reference to the current version of orders, worksheets, reports, labels, and forms.

Explanation:
Copies of 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 being performed shall be readily available to the facility staff.

Explanation:
The written copy or electronic version 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 him/her for reference when needed.

If an electronic manual is used, there must be an appropriate mechanism to access the SOPs at all times, even if the network is not available. A hard copy of the SOP manual or a backup electronic version on a downtime computer could provide such access.

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 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 Standard Operating Procedure.

Explanation:
Before a staff member is allowed to perform new and revised policies and SOPs, he/she must have reviewed and/or received training on the new document. 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 and/or training before that person uses the revised policy or SOP.

Example(s):
It is recommended that there be a specific signoff sheet for every policy and SOP and associated revisions to document that each staff member required to review a policy or procedural revision has done so prior to performing the tasks described. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each SOP and to any major revision also facilitate documentation of appropriate training of staff.

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. Review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

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 appropriate Processing Facility Director or Medical Director and reviewed by the Quality Manager.

Explanation:
Planned deviations should be approved within a peer-review process (i.e., more than one individual), but approval from the Processing Facility Director is required at a minimum. A planned deviation should include an assessment of risk. Processes set up for review of variances are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately. Retrospective review must be performed in compliance with processes designed for deviations.

D6: EQUIPMENT, SUPPLIES, AND REAGENTS

STANDARD:

D6.1 *Equipment, supplies, and reagents used to process 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. If equipment must be shared, there should be an agreement related to maintenance, calibration, cleaning, and other responsibilities. It is not acceptable to share equipment with other laboratories or to process cellular therapy products for different recipients using the same equipment under conditions in which the sterility, integrity, and/or viability of the product may be compromised.

For critical pieces of equipment (e.g., biological safety cabinets or centrifuges), there should be back-up equipment immediately available, or a well described back-up plan should exist in the case of primary equipment failure (see D5.1). 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 back-up 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. Frequent "emergency" orders would suggest that an inadequate supply of material is being kept in inventory. A policy or SOP outlining material management, including how availability and adequacy are ensured, must be verified.

Example(s):

Examples of adequate equipment and practices that are acceptable include:

- Dedicating a biological safety cabinet to use for cell processing only.
- Having a policy or SOP preventing staff from performing different procedures on multiple cellular therapy products in the same biological safety cabinet simultaneously.

- Dedicating or reserving a cell counter to be available for immediate processing.
- Using a refrigerator and/or freezer for cellular therapy products or reagents that is not used for food or beverages.

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 provided that this practice can be confirmed by the inspector as having the desired result.

STANDARD:

D6.3 Supplies and reagents used in processing, testing, cryopreservation, and storage shall be controlled by a materials management system that includes requirements for the following, at a minimum:

D6.3.1 Visual examination of each supply and reagent used to manufacture cellular therapy products for damage or evidence of contamination upon receipt and acceptance into inventory.

D6.3.2 Records of receipt that include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.

D6.3.3 Storage of materials 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 in a manner that preserves their function and minimizes the risk of contamination or cross-contamination. For items requiring storage at defined specifications such as temperature and humidity, the environmental conditions of the storage area must be monitored and documented. Evaluation of the environment during transport should also be included.

Locally sourced reagents used in cellular therapy product processing requiring GMPs must also be GMP grade, have an appropriate Certificate of Analysis, or reference a relevant Drug Master File. If not GMP grade, reagents must be part of an IND and be qualified for use.

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 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, compromise product integrity, or pose a risk of contamination or cross-contamination.

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. Outdated supplies and reagents and those not intended for clinical use should be stored separately from those designated for clinical use. When this is not possible, outdated or research material must be clearly distinguished from clinical material and appropriately labeled as not for clinical use.

STANDARD:

D6.3.4 Use of supplies and reagents coming into contact with cellular therapy products during processing, storage, or administration that are sterile and of the appropriate grade 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 certified to be free of microbial contamination. For the types of products processed by Processing Facilities accredited under these Standards, it is recognized that in many situations reagents not approved for human use were used during product development. For products produced under IND or IDE for early phase studies (Phase I or Phase I/II) the FDA may allow the use of research grade supplies and reagents. However, as the studies progress to Phase II and Phase III, it is expected that supplies and reagents be of the highest quality. It is advisable to qualify clinical and pharmaceutical grade reagents early in product development to ensure the resulting cellular therapy product are comparable.
If no suitable, equivalent substitute can be identified for the specified purpose, the supply or reagent must be qualified (see D4.13 and its guidance) and its use approved by the FDA.

Evidence:
The inspector should request COAs or manufacturer documentation that the supply or reagent meets pre-determined specifications. Policies or SOPs should be available that define supply and reagent specifications and qualification.

Example(s):
Often a company will produce cytokines to identical standards but only qualify part of the batch for clinical or GMP use. This is due to the high costs of the testing required to certify the reagent

for clinical use. During early phase studies FDA often allows the use of the non-qualified reagent but will expect the fully qualified reagent to be used in later phase studies.

STANDARD:

D6.3.4.1 Reagents shall undergo initial qualification for the intended use.

D6.3.4.2 Where there are no suitable clinical or pharmaceutical grade reagents available, reagents shall undergo lot-to-lot functional verification.

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

Explanation:
There is no specific definition of what makes a reagent clinical or pharmaceutical grade. Therefore, the Processing Facility must review package inserts, labeling, and COAs in the context of cellular therapy to determine if the reagents will maintain the integrity of the cellular therapy product and the safety of the recipient.

Typically, reagents of clinical or pharmaceutical grade comply with the United States Pharmacopeia (USP) or EU-Pharmacopeia (Ph.Eur.) requirements and are manufactured in compliance with GMPs. For these reagents, initial qualification for the intended use is required. As with all significant changes to materials or procedures, any significant change to a reagent (e.g., different reagent, different manufacturer) requires additional qualification to demonstrate there are no adverse effects to processes.

Where there are no suitable clinical or pharmaceutical grade reagents available for the processing, or when reagents are used under approved research protocol, Processing Facilities must perform more extensive qualification that demonstrates that the reagent is the only option available, safe for the intended use, and approved by the applicable regulatory authority. This may include:

- Use under IND, IDE, or other exceptions approved by the appropriate regulatory agency.
- Evidence of extensive experience with the reagent and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.
- Extensive literature supporting use of the reagent for the specified purpose and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.

Reagents, including DMSO, that are not clinical or pharmaceutical grade or do not have regulatory approval for the indication (such as a license), must undergo lot-to-lot functional verification. DMSO is specifically mentioned because it is a critical reagent that performs a critical function (i.e., it protects the cells from damage during cryopreservation). Should a lot of DMSO not function as expected, there would be dire consequences to the cellular therapy product and its intended recipient.

If a facility is using clinical or pharmaceutical DMSO and they document their qualification criteria after qualifying their supplier/vendor, they are not required to perform lot-to-lot verification every time.

Example(s):
Qualification of a reagent used in processing (washing, freezing, or 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./USP) Non pyrogenic cryopreservative solution."
- "Complies with USP" or "Complies with Ph.Eur."
- "This batch complies with the specifications of the USP and Eur.Ph."
- "Grade: USP" or "Grade: Ph.Eur."
- "Cryoprotectant for the cryopreservation of human cells and tissues for transplantation."

When DMSO lot-to-lot verification is required as described above, the study may be accomplished by reserving two extra, small samples from each of several cellular therapy products for comparison. A comparison of the new lot of DMSO with the current lot of DMSO can be performed. Generally, IRBs or ethics committees do not consider reagent qualification to be research, so special donor or recipient consent is not normally required. This should be confirmed with local requirements.

STANDARD:

D6.3.5 Cleaning and sterilizing of non-disposable supplies or instruments using a procedure verified to remove infectious agents and other contaminants.

Explanation:
For some specialized processing procedures, equipment or instruments that contact 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. When available, single use supplies or instruments are preferred.

Evidence:
The inspector should review the records of this verification process.

Example(s):
Surgical equipment for tissue manipulation such as scissors, forceps, or scalpel handles are examples of non-disposable supplies or instruments that may be included in processing procedures.

STANDARD:

D6.3.6 Use of supplies and reagents 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, or serum components i could meet this requirement.

STANDARD:

D6.3.7 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 facilitate identification of the location or disposition of a specific lot of a supply or reagent if 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, and if it facilitates location or disposition of each lot of supplies and reagents..

Example(s):

A first expired, first out system is frequently used, and can be tracked on paper or electronically.

STANDARD:

D6.4 There shall be a system to uniquely identify and track all critical equipment used in the processing of cellular therapy products. The system shall identify each cellular therapy product for which the equipment was used.

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.

It is also important that the system in use allows for the identification of all cellular therapy products 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 has a unique identifier, 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):
Equipment can be identified by using a pre-existing serial number, but it may be better to assign a unique identifier that is easily 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/consumables log in the processing record could be used.

STANDARD:

D6.5 *Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.*

D6.6 *Equipment shall be inspected for cleanliness and verified to be in compliance with the maintenance schedule prior to each use.*

Explanation:
Equipment used for processing or cellular therapy product testing must be located to allow access for maintenance and calibration at Processing Facility-described intervals. It is also important to maintain a schedule of equipment cleaning, sanitation, and disinfection that is described by an SOP (see D5.1).

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 10 uses). Manufacturers' recommendations should always be followed at a minimum.

STANDARD:
D6.7 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 critical parameters are maintained within acceptable limits at all times. There must be a schedule for equipment maintenance and quality control.

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 (see D5.1). 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 QC be readily available for each piece of equipment.

STANDARD:

D6.7.1 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 US) reference thermometers, stop watches, and tachometers. Other vendors may provide similar reference 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:

D6.7.2 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products manufactured since the last calibration.

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 be conforming to specification or corrective action has been documented. This should include an investigation of potential adverse events 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 notified.

STANDARD:

D6.8 There shall be a Standard Operating Procedure that addresses the actions to take in the event of equipment malfunction or failure.

D6.9 Equipment shall conform to Applicable Law.

Evidence:

Where applicable, the inspector should review documentation of relevant regulation for CE/UL marking.

Example(s):

In the U.S., Nationally Recognized Testing Laboratories (NRTL) are testing facilities recognized by OSHA and are primarily private-sector organizations that provide product safety testing and certification services to manufacturers. Underwriters Laboratories Inc. (UL), a recognized NRTL, 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.

NRTLs 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.

STANDARD:

D6.10 Lot numbers, expiration dates, manufacturers, and key equipment identifiers 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, and/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.

STANDARD:

D6.11 The Processing Facility shall use an inventory control system to document the availability and identity of critical reagents and supplies. This shall include at a minimum:

D6.11.1 A system to uniquely identify and track all critical reagents and supplies used to manufacture cellular therapy products.

D6.11.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.

D6.11.3 A system to maintain adequate stocks of reagents and supplies for the procedures to be performed.

Explanation:
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 list 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, provided that the information can be easily obtained.

Evidence:
The inspector should verify through review of records that supplies and reagents used in manufacturing can be traced to cellular therapy products manufactured using a specified reagent or supply.
A method to do this might include selecting a lot number of a reagent from the critical supplies and inventory list and asking for manufacturing records from cellular therapy products that are in inventory or have been released.

Example(s):
For situations in which there is a product recall of a lot of human serum albumin (HSA) found to be contaminated, 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 suitable 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.

D7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

STANDARD:

D7.1 ISBT 128 CODING AND LABELING OPERATIONS

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

Explanation:

It is understood that FDA does not require ISBT 128 coding and labeling to be used for cellular therapy product labels. Therefore, a Processing Facility seeking accreditation under these Standards may have existing products that are not named according to this terminology. After accreditation, FACT will require use of ISBT 128. Processing Facilities preparing for accreditation are encouraged to begin using this system.

ISBT 128 is the international information standard for transfusion and transplantation. Initially, ISBT 128 was developed for blood and blood component transfusion to increase the capacity for electronic data, to increase security and accuracy, and to permit unique unit identification globally. ISBT 128 has now been extended to include cellular therapy products and tissues. ICCBBA is the not-for-profit organization (www.isbt128.org/standard-terminology) 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 CTCLAG includes international representation from FACT, JACIE, ISCT, ASTCT, EBMT, NMDP, WMDA, ISBT, APBMT, and AABB. CTCLAG was formed to recommend standard definitions for cellular therapy products and rules for future assignment of product codes, to draft labels and a labeling strategy for products, and to draft an implementation plan.

The two main pieces of the standard terminology 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 and/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 cellular therapy product. The intent is to capture relevant characteristics

about the product from donor and collection through the final processing. In some settings, such as where multiple additives are used, the additional information is part of the accompanying documentation, especially where label space is limited. 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 characterized in this standardized way can be labeled using common, well-defined terms that are printed in eye-readable format. The eye-readable terminology may be in the native language of the country in which the product is collected. The language also adapts to machine readable technologies such as bar codes. In this way, the product label will be universally understood, and 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. Modifications in definitions and additions will occur. As the responsible body for the database development and maintenance, ICCBBA is the appropriate authority for maintaining publications on current terminology. Facilities must use the terminology as defined in the ICCBBA document *Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions,* which is available at www.isbt128.org/standard-terminology. Facilities should refer to Chapter Three, Cellular Therapy, for current terms and definitions related to cellular therapy. Inspectors will inspect the facilities according to the current ISBT 128 terminology and definitions. Inspectors should review Chapter Three, Cellular Therapy, in this document before conducting an inspection. It would be helpful to have the document available for reference during the inspection as well.

If Processing Facilities have questions regarding ISBT 128 terminology, they can reference the Standard Terminology document, view the ICCBBA website at www.isbt128.org/standard-terminology, or contact ICCBBA directly for additional information and assistance. 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.

To utilize ISBT 128 to its full advantage by using its technical database in the unique identification of cellular therapy products worldwide and in the use of common language, facilities must register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each product's unique alphanumeric identifier. Facilities in or affiliated with hospitals may find that their Blood Bank has registered, and a unique facility code already exists. Stand-alone facilities can individually register and pay a nominal annual membership fee.

Evidence:
Inspectors should examine the labels on site and the labeling process and SOPs to verify the appropriate use of ISBT 128 terminology for class and attributes.

Example(s):
The acronym HPC(A), would be an abbreviation acceptable in documents, and possibly on partial labels. However, the U.S. FDA does not allow abbreviations even on partial labels for licensed products.

Cellular therapy products with a biological license in the U.S. are subject to the bar code label requirements (21 CFR 201.25). The bar code, at a minimum, must contain the appropriate National Drug Code (NDC).

STANDARD:

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

Explanation:
The use of ISBT 128 or Eurocode for all cellular therapy products provides a uniform coding and labeling system worldwide. Such standardization is even beneficial to, and thus required for, autologous cellular therapy products.

Implementation of ISBT 128 is required for FACT accreditation, although as stated above, FACT does recognize that not all cellular therapy products being used at initial inspection will use this coding system. The implementation of coding and labeling are supported by FACT and numerous other organizations in the field for cellular therapy. On the ICCBBA website (www.isbt128.org/standard-terminology), the most recent versions of the terminology are published, as well as resources to help centers implement ISBT 128.

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 can be prepared either by pre-printing sets of labels to be used during processing or by printing them "on demand". The use of any type 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 office. 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 or 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:

D7.2.2 *Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Processing Facility Director 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.
- Correct bar-code scanning.
- Identity to source (original) label that has been approved for use by the Processing Facility Director.

Inspection must include comparison with a label approved by the Processing Facility Director.

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.

Evidence:
The inspector should review the process to confirm that the intended labels are being generated.

Example(s):
A log(s) or form(s) is 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:

D7.2.2.1 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 representing different cellular therapy products as well 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.

Evidence:
The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors.

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:

D7.2.3 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 pre-printed labels must be documented to ensure that a label allocated to a particular cellular therapy product cannot be associated with the product, concurrent plasma, or related samples from 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 Processing Facility, the number of labels used, and the number of labels passed to another unit or destroyed shall be used. The reconciliation process applies to entire product labels, not to individual label components like separately printed DIN barcode copies.

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 donor collections. The method of destruction of unused labels should be verified.

Examples:
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 the 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.

D7.2.4.1 Obsolete labels shall be restricted from use.

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), includes test cases to demonstrate the system works as intended for use.

The SOP should include each of the following:

- Lay-out of the labels.
- Transfer of information to the label.
- Verification of accuracy.
- Proper storage.
- Version control.
- Destruction of obsolete or unusable labels.

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.

STANDARD:

D7.2.5.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by Applicable 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 10 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 collection labeling/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 prior to distribution of the cellular therapy product.

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, such as computer checks or barcoding, is used. New labels are usually generated only when the cellular therapy product is being processed or to preserve donor confidentiality in the case of unrelated donors. Facility SOPs must include details on how to prevent errors during relabeling. When transferring a product, labeling of new containers or samples shall meet the labeling requirements of these 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:

- 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 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. 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 accuracy of the information rather than becoming solely dependent on the technology to work correctly.

STANDARD:

D7.2.6.3 *Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.*

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:

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 governmental regulation must be clearly visible. The Processing Facility should review FDA, 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 a label must be complete; fields for which information is not required must be filled as "NA."

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:
Indelible ink must be used to record any information entered manually on the label. Inks and labels must be resistant to water, alcohol wipes, or sprays if they are likely to be subjected to such liquids 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 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.

STANDARD:

D7.2.12 The label shall be validated as reliable for storage under the conditions in use.

Explanation:
Labels must have been validated to assure 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.

Example(s):
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.

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, all accompanying records, and its recipient or final disposition.

D7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.

D7.3.1.2 If a single cellular therapy product is stored in more than one (1) container, there shall be a system to identify each container.

D7.3.1.3 If cellular therapy products from the same donor are pooled, the identifier on the pooled product 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 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 the chain of identity of 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, except for 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.

Processing Facilities must have a 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.

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, 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 and tracked to distribution and then to administration of the product. The Processing Facility SOP for labeling shall be sufficiently detailed to permit the inspector to match the processing records to a uniquely identified collected product and to the donor and recipient.

Example(s):
The donor or recipient registry number, such as the GRID number (WMDA), 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, provided that each cellular therapy product can be uniquely identified.

The ISBT 128 system uses the DIN together with the product code and division codes to identify multiple containers from the same collection. If products are being pooled, the pool identifier must allow tracing to the original products. For this example, the Collection Facility and the Processing Facility have their own ICCBBA registrations and ISBT 128 assigned DINs. If product W036320050376 was pooled with a second day of collection product W036320050379 for processing, the pool identifier would be W377620100196 provided that the new identifier is traceable to the original identifiers through the Processing Facility records.

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 accredited sources.

STANDARD:

D7.3.1.4 Supplementary identifiers shall not obscure the original identifier.

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 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 product, verify the original identifier is not obscured, and 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, that 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 identity can be linked to the new identifier so that the Processing Facility and staff responsible for assigning new identity is 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:
D7.4 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.

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.

Example(s):
Cellular therapy products from unrelated donors shall contain the donor identification number supplied by the registry with or without the identification of the collection center, according to Applicable Law.

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 I.

Explanation:
The required label content as specified in Appendix I represents minimum requirements and must be present as indicated at the various stages of cellular therapy product collection, processing, and distribution.

Accompanying paperwork should be packaged in a secondary bag with the cellular therapy product for distribution to third party manufacturing organization or infusion site. It is not acceptable to distribute multiple product bags from different donors using partial labels with the additional information on a single inventory sheet.

Labeling must be consistent with Applicable Law. Local interpretations may differ. The identity and address of the collection facility or registry and identity and address of the Processing Facility, as applicable, must be part of labeling at issue. The name of an unrelated donor is not included in labeling due to confidentiality. This may be extended to the collection site per some interpretations of Applicable Law.

Evidence:
Prescreening of the labels by the FACT Accreditation Coordinator will be performed and every effort made to correct any deficiencies prior to the on-site inspection. Examples of all labels in use by the applicant organization will be provided to the inspector prior to the on-site inspection so they can confirm that deficiencies have been corrected. For organizations performing both allogeneic and autologous cellular therapies, examples of labels will include collection, processing, transport, and distribution labels for both types of therapies. 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 in advance.

Onsite, the inspector should examine labels to confirm that confidential donor information is not included on the label or in accompanying documents. As per Applicable Law the inspector should confirm 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.

Evidence:
The inspector should verify that labeling during processing, at the completion of processing, and at distribution contains all the information listed in Appendix I and contains appropriate biohazard and warning statements as specified in the Circular of Information Biohazard and Warning Label Table available at: https://www.factglobal.org/education-and-resources/general/applicant-education-and-resources/resources/.

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 III.

STANDARD:

D7.4.4 *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. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States," or other appropriate labels as required by Applicable Law.*

Explanation:
Table 2 of the inter-organizational *Circular of Information for Cellular Therapy Products* outlines when biohazard labels must be used. 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. Biohazard labels must not be applied indiscriminately.

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 I).
Communicable disease testing is not required for autologous donors in relation to cellular therapy product collection unless required by applicable laws or regulatory requirements, nor is there a requirement for donor eligibility determination. Some programs may decide to carry out communicable disease testing and eligibility determination in autologous donors to help standardize processes and so reduce the risk of error, and to 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. However, if autologous donor testing and screening is not performed, or is incomplete, the cellular therapy product label must contain the statement "Not Evaluated for Infectious Substances." In addition, if the autologous donor is tested or screened prior to collection and is found to be positive or at risk for a relevant communicable disease, the product label must bear a biohazard label and the appropriate warning statements. Since autologous recipients are not at risk of contracting a communicable disease from themselves (they already have the disease), the statement "Warning: Advise patient of communicable disease risk" is not required on autologous product labels even if donor testing results are positive, although a biohazard label is required.

If the complete allogeneic donor screening and testing is not performed, these cellular therapy products must be labeled with the statement "Not Evaluated for Infectious Substances." This statement must be also affixed or attached to the label of any product when either donor testing or donor screening for infectious disease risk has not been completed within the required 7-day period. The label of 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.

Cellular therapy products that are 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." Such products must contain this statement attached or affixed to the label or in accompanying documents.

Note that residence in a country on the U.S. Department of Agriculture list as at risk of 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 Patient of Communicable Disease risks."

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" and other warning and biohazard labels for a variety of scenarios. The statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" must always be on the product if all donor eligibility requirements are not completed. For example, this statement must be on the following:

- 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 using approved donor screening test, but for which no official donor eligibility determination was made.

The use of the biohazard legend and the statement "WARNING: Reactive test results for (name of disease agent or disease)" is different. Any autologous cellular therapy product with the presence of risk factors for or clinical evidence of relevant communicable disease agents or diseases must have these two labels, whether or not the regulations for donor eligibility determination were completely followed. If all donor eligibility requirements are not met, but the product is reactive for a relevant communicable disease, the product must be labeled with two warning statements: "WARNING: Reactive test results for (name of disease agent or disease)" and "NOT EVALUATED FOR INFECTIOUS SUBSTANCES".

Evidence:
The inspector should ask to see the SOP that defines the conditions for using a biohazard label and determine if the Processing Facility's SOPs are adequate and appropriately safe to prevent transmission of infectious disease.

The inspector should confirm that biohazard labels and warning statements are utilized as described in the Circular of Information Biohazard and Warning Labeling Table available at

https://www.factglobal.org/education-and-resources/general/applicant-education-and-resources/resources/. Autologous cellular therapy product labels should be examined to confirm that "Not Evaluated for Infectious Substances" is present when the donor screening does not contain all of the elements listed.

STANDARD:

D7.4.5 *A cellular therapy product collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix III at the time it leaves the Processing Facility.*

Explanation:

The FDA GTP regulations have specific requirements regarding the information that must accompany a cellular therapy product at the time of distribution. Requirements for products from allogeneic donors are listed in Appendix III. 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 that determination. This summary must include results of the donor screening for infectious disease risk and the communicable disease test results. The test and screening results must be listed with an interpretation of the values as positive or negative. There must also be a statement confirming that communicable disease testing was performed by a laboratory with the required qualifications. For products that are distributed for administration, the product administration form can be used for this purpose. For products that are distributed to another facility, this information must be included in accompanying documents. If the Collection Facility is responsible for allogeneic donor eligibility determination, that facility is also responsible for distributing the above information to the Clinical Program and Processing Facility. If the Clinical Program determines allogeneic donor eligibility, the Processing Facility must obtain the information from the program so that it may accompany the product.

According to FDA and non-U.S. regulations, as applicable, there are many statements, results, and documents that must "accompany" the cellular therapy product at all times after the determination of allogeneic donor eligibility has been documented (see 21 CFR 1271.55).

The FDA Final Guidance "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps"), August 2007 states that electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This Guidance Document is available at: https://www.fda.gov/media/73072/download.

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 Processing Facility and is transported to another institution for further processing, storage, or administration.

STANDARD:

D7.4.6 *Any container bearing a partial label at time of distribution shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix I. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.*

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:

D7.4.7 *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 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:

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

Explanation:
For products collected for in-house Processing Facilities or third-party manufacturers operating under a biologic product license or IND, the label content is dictated by the applicable regulations as listed in 21 CFR 312.6(a). To the extent possible, in-house and third-party manufacturers should be encouraged to follow the labeling requirements in Appendix I of these Standards.

For cellular products in clinical trials, ISBT 128 provides clinical trial label standards and is encouraged. These labels must conform to Applicable Law.

Evidence:
Labels should meet FACT requirement unless the clinical trial has other requirements.

STANDARD:

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

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. An example label reflecting these requirements can be found at https://www.iccbba.org/subject-area/cellular-therapy/faqs.

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 assure their safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such tests and procedures shall become part of the permanent record of the product processed.

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 (see D5.1). All test results that are available at release must be present in the processing record. Certain tests on the product or the donor are required to be performed by these Standards when appropriate, including:

- ABO group and Rh typing on samples obtained on two occasions from an allogeneic donor when the product contains red blood cells.
- Microbial testing after processing for all products.
- Post-processing TNC and viability for processing procedures that affect TNC or viability.
- Post processing CD34 cell assay on HPC products for processing procedures that affect CD34 cell content.
- Assay of target cell population for products that have been enriched or depleted.

Only the results of those tests defined by the Processing Facility Director need to be maintained in the facility records. HLA typing results, when that is required, should be part of the Clinical Program patient records. The results of this testing or other testing designated by the director may not always be required for release from the facility, although samples should have been obtained prior to release unless otherwise specified in SOPs. Other tests may be appropriate depending upon the cellular therapy product, in particular tests to measure the potency of the final product.

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 TNC (required for all processing that affects TNC), microbial culture (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.

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.

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.

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), and 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):
Wash supernatant or culture medium may be considered representative of the cellular therapy product for certain assays. For example, the supernatant of a CAR-T cell product at the time of the last wash for administration could be used for microbial culture if cells are limited. Supernatant from processing steps further upstream before cryopreservation would not be considered representative of the final product because contamination could occur during subsequent steps. Supernatant would not be considered representative of the product for purposes of TNC or CD3 analysis; samples for these tests must come from the final product itself.

STANDARD:

D8.1.3 *There shall be established, appropriate, and validated assays and test procedures for the evaluation of cellular therapy products.*

Explanation:
Test methods that are used for these assays are not specified by these 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 must be qualified, and controls should be used when required. In the event an assay is unavailable, defined release criteria such as those specified in an IND must be utilized.

Evidence:
The inspector must utilize his or her 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, that there is a record of method validation, that reagent and instrumentation controls are used, and that 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 for example, flow cytometry, endotoxin and mycoplasma testing, cell selection, or 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.

STANDARD:

D8.1.3.1 For all cellular therapy products, cell enumeration and viability assays shall be performed for clinically relevant cell populations.

D8.1.3.2 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:
Total product viability and cell enumeration are of importance, but assessment of the target relevant cells is most important. Target 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 total nucleated cells (e.g., after density gradient separation for mononuclear cell preparation), testing for the affected cell type(s) must be performed at the end of processing and prior to administration or cryopreservation.

STANDARD:

D8.1.4 For tests required by these Standards performed within the Processing Facility:

Explanation:
Requirements of the Processing Facility providing these required 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. Suitable 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/or tests that they perform. While separate accreditation for the tests performed by the facility may be available, it is not

required by these Standards. However, performance of such testing should be consistent with these Standards of other such accrediting bodies.

STANDARD:

D8.1.4.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

D8.1.4.2 New reagent lots shall be verified to provide comparable results to current lots or to give results in agreement with suitable reference material before or concurrently with being placed into service.

Example(s):

Reference material for reagent and/or 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-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.

For CE-marked reagents, it is acceptable to use the Certificate of Analysis, datasheets, and visual inspection of the reagent as verification. The inspector should review the policy and SOP for evidence of good stock control.

STANDARD:

D8.1.4.3 Where available, controls shall be used each day of testing and shown to give results within the defined range established for that material.

D8.1.4.4 Function checks shall be performed for testing instruments prior to testing donor, recipient, or cellular therapy product samples.

D8.1.4.5 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, Communicable Disease Center, 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-based assays such as 7-AAD using the same samples. Total nucleated cell count for products whose function is dependent on cell dose is sometimes an appropriate surrogate for viability measurement.

STANDARD:

D8.1.5 Tests required by these Standards, and 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 certification certificates are not required to be on-site at the Processing Facility, they should be readily available for review.

STANDARD:

D8.1.6 Infectious disease testing required by these Standards shall be performed using screening tests that are 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. There may be regions where this requirement is not applicable.

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 those 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:

D8.1.7 *Cellular therapy products that do not meet allogeneic donor eligibility requirements, or for which allogeneic donor eligibility determination is not yet complete, shall be distributed only if there is documented urgent medical need for the product. Documentation shall include, at a minimum, the approval of the recipient's physician and the Processing Facility Medical Director.*

D8.1.8 *Notification of the recipient's physician of nonconforming cellular therapy products and approval for their release shall be documented.*

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 this must be clearly indicated on the medical order.

For cellular therapy products that are in early phase studies, the clinical protocol may specify dose escalation for a defined number of patients. The dose to be administered may not be known at the time processing begins. Therefore, orders for administration should be written at the time of infusion and must clearly indicate the dose to be infusion.

For standard processing procedures, precise parameters do not have to be indicated on the medical order provided that 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 specify 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 on the written request include the number of target cells required, preferred volume, and cryopreservation.

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(s) 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 donor eligibility be confirmed. This eligibility determination is usually performed by the Clinical Program or Collection Facility, and not the Processing Facility.

For allogeneic donors not meeting eligibility requirements, the reason must be provided and the criteria for urgent medical need must have been met, including approval of the physician overseeing the recipient. In some cases, a cellular therapy product may be needed before donor eligibility determination has been completed. In those situations, the attending physician must be notified that testing and screening has not been completed. See Appendix III 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 and/or ongoing evaluation of processing results, data analysis, establishment of expected ranges and means and/or medians, and periodic documentation that the procedure is yielding results within the expected range.

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 (with consent), 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.

Validation of the quality of the cellular therapy product is ultimately determined by the clinical outcome of the recipient. However, there should be *in vitro* studies of efficacy demonstrating that the desired endpoints of the processing procedure were achieved.

In some cases, the Processing Facility may implement a processing procedure or process that has been validated by an external facility and/or has been published. In such cases it may not be necessary to perform a full validation study; rather the facility may verify that the procedure or process results in comparable cellular therapy products when performed locally. It is important that a formal process for verification 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 these 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 these 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 red blood cell depletion protocols.

STANDARD:

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

D8.4.3 Preparation for administration of cellular therapy products manufactured by third parties shall follow the instructions provided by the manufacturer.

D8.4.3.1 The Processing Facility should verify the preparation procedures utilizing practice materials similar to the cellular therapy product intended for administration when feasible.

D8.4.3.2 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 accredited programs. 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 SOP, processes, and training needs to be established.

Labeling and accompanying documentation of prepared products must follow the manufacturer requirements. Many third-party products will not follow FACT Standards and may not comply with ISBT 128 label requirements. The Processing Facility should not modify manufacturer requirements without permission. If the manufacturer does not provide instructions, labeling should follow established facility practice. The elements listed in Appendix I 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 or label format) may not be feasible since the facility 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, and/or wash cellular therapy products with which the facility has little or no experience. In these cases, the facility's ability to perform a validation study 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.

Evidence:
Inspectors may verify compliance with this standard by reviewing processes and SOPs for cellular therapy product preparation for administration, occurrence management, validation/verification studies including documentation of practice runs, and product records.

Example(s):
Investigational 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 manufacturer requirements even if not consistent with FACT 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 or Product Code).

FDA regulations require that manufacturers of cellular therapy products validate the thaw procedure and provide instructions to the program administering the product. Cell therapy laboratories that receive cellular therapy products such as CB units and only prepare these products for administration are not manufacturers. Processes such as thawing, dilution, or washing are considered "preparation for infusion" of the product. It is recommended that the manufacturers' instructions be followed; however, facilities with experienced staff may choose to perform their own validated method of preparation of a product for administration.

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, those 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. SOPs also define 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 to reduce the likelihood of microbial contamination during processing. The use of a sterile connecting device when moving cells from one bag to another, adding reagents, and removing samples, can help keep systems closed.

GTP regulations specifically forbid the pooling of products from more than one donor during processing to reduce the risk of communicable disease transmission. Administration of products from more than one donor should proceed sequentially as is routine for double cord blood transplantation.

For some cellular therapy products processed under approval by regulatory agencies as specified in INDs, IDEs, or equivalent approval pathway, pooled cells may be part of the manufacturing process. This step would have been reviewed by the competent authority and would thus be allowed under these 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 and/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 in a timely manner of any positive microbial cultures.

Explanation:
It is a requirement of these Standards that microbial testing be performed post-processing at a minimum. More frequent testing may be required by regulatory agencies.

It is the responsibility of the Processing Facility to confirm that the recipient's physician has been notified of positive culture results in a timely manner. The timeframe for notification of positive microbial cultures should be defined in an SOP. For products produced under IND, IDE, or other approvals, there shall be a plan in case a product becomes contaminated.

Policies and SOPs for the management of cellular therapy products with positive microbial culture results are required in D4.

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 review the microbiology report and audit results.

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 may 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 show the test results and the interpretation of each result, where appropriate.*

Explanation:
Records such as worksheets and batch records must be used during cellular therapy product processing and must be completed in real time as the procedure is performed. If an error or adverse event results during or as a consequence of processing, it is important to perform an investigation in a timely manner. It must be possible to investigate each critical step, including identification of the individual responsible, and the reagents and equipment utilized from the appropriate worksheet.

The worksheet design must be such that the identity of the individual performing each significant step, or the same step over time, can be easily determined. The worksheets also must serve as documentation that each step was performed as specified in the SOP and contain the results of in-process testing and calculations required for the next step to be performed. All personnel must be well informed of the procedures to follow when endpoints are not met.

Since potency and efficacy may be affected by the competency of the individual(s) performing the processing, testing, cryopreservation, storage, administration, or disposal of a cellular therapy product, it is critical that the responsible individual(s) be identified for each significant step.

Evidence:
The inspector should examine paperwork to determine if adequate records are maintained that identify the responsible individual(s) for all significant steps of processing.

Example(s):
For example, cryopreservation of a bone marrow harvest may include: 1) receipt of the cellular therapy product into the Processing Facility with label and integrity checks, initial sampling, and cell counts, 2) a red cell depletion step (buffy coat preparation, density gradient separation, or other step), 3) washing or suspension of the cells in cryopreservation medium, and 4) the actual controlled rate freezing. Each of these is a discrete step that may be performed by different individuals. It is recommended that these critical calculations be performed at least twice and then re-checked by a second individual not involved in that processing step before proceeding to the next step.

Identifying the responsible individual(s) for each significant step is most easily accomplished by including places for initials or other identification on relevant worksheets and forms.

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 assure that isolated and/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. Review of processing records may occur on several levels.

Other records may be reviewed within a reasonable time after processing. 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 these are 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., disease reduction, GVHD, or infection) and notification of appropriate individuals.

Examples(s):
Records that should be reviewed immediately include:

- Calculation of cell doses.
- Labeling records.
- Planned deviations from Standard Operating Procedures.
- Determination of reagent concentrations or administration dose.

Records that may be reviewed after processing is completed include:

- Microbial culture results (A positive result must be reviewed and reported immediately).
- Flow cytometry results.
- Chart review.
- Analysis of freeze curves.
- Reagent and supply lot number recording.

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 corrective and preventive actions 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 Institutional Review Board, Ethics Committee, or equivalent and the Institutional Biosafety Committee or equivalent shall be maintained.

D8.12.2 The Processing Facility shall adhere to Good Manufacturing Practice regulations 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 these 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.

For cellular therapy products in the US, manufacturers of HCT/Ps regulated as medical devices must comply with the Quality System regulations (21 CFR part 820) and applicable CGTP requirements. The Guidance for Industry - 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 provides a list of CGTPs that are applicable to HCT/Ps regulated as devices, drugs, and/or biological products. The guidance is available at https://www.fda.gov/media/82724/download.

Evidence:
For procedures other than those considered to be minimal manipulation, the inspector should inquire if IRB and the appropriate IND or IDE approval has been obtained. If participating in the manufacturing but not the IND holder, the entity who holds the IND is responsible for informed consent.

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 red blood cells at the time of administration sufficient to cause a transfusion reaction:

D8.13.1 Results for donor and recipient 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 When relevant, results for a red blood cell antibody screen on the recipient shall be available.

Explanation:
ABO group and Rh typing is performed on blood 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 a measure of patient safety from gross hemolytic reactions and/or late hemolytic reactions that might result from engraftment of B-lymphocytes producing anti-A, anti-B, or anti-Rh antibodies. It is not intended to be a primary 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.

These 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, independent donor identification, and if possible, different phlebotomists). 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 personnel. The cellular therapy program determines who collects the samples and who performs the testing. 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.

These Standards do not dictate how ABO and Rh mismatched cellular therapy products should be processed. ABO typing may not be required for most cellular therapy products produced by Processing Facilities accredited under these Standards since most products will not contain allogeneic red blood cells or plasma. However, the Processing Facility must have a policy regarding management of products that are ABO and/or Rh mismatched between 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. Processing protocols must clearly state how to achieve the stated guidelines for ABO and Rh mismatched products. The policy should also include instructions for recipients and donors with positive antibody screens (other than ABO antibodies). There must be protocols indicating what the facility's responsibilities are and what should be done with the product in the case of an adverse reaction that is suspected to be the result of red blood cell antibodies.

Evidence:
The inspector will look for records of ABO and Rh typing results and antibody screening in the processing chart records when relevant.

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

Explanation:
This standard requires that one or more samples of individual cryopreserved cellular therapy products be available 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 of 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 and/or investigative purposes. Applicable Law may prohibit the use of stored aliquots for research unless IRB approval has been obtained.

The Processing Facility Director should verify that 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, 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 and/or low cellular content of the final product. In such situations, a cell-free sample that represents 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 the 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 to represent not only the product freezing conditions but also the storage conditions.

It is also recommended, but not required, to store the samples(s) minimally 10 years after the final disposition (administration, transfer, or discard) of the cellular therapy product or until the patient expires. 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 be secured and controlled to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products.*

D9.2 *STORAGE DURATION*

D9.2.1 *Conditions and duration of storage of all cellular therapy products shall be validated.*

D9.2.2 *Processing Facilities processing, storing, or releasing cellular therapy products for administration 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.

For cellular therapy products processed internally that are not cryopreserved, the stability of the starting product and the product at the end of processing must also be assessed. The Processing Facility Director should determine the steps in processing where stability should be tested and the duration over which the testing period spans.

Example(s):
The manufacturing of a clinical T cell line recognizing a virus may start with whole blood that is then separated into fractions for processing. The maximum time from blood collection to the initiation of processing needs to be established since the temperature and duration of storage can affect the initial fractionation results. Once fractionation occurs, a fraction containing T cells is put into culture. The conditions of culture are validated, but the time from removal from culture and preparation for administrations to the actual administration also needs to be determined. Since the cellular therapy product is no longer in culture, the viability and potency of the product needs to be tested until one or both are below release criteria.

STANDARD:

D9.2.3 There shall be a written stability program that annually evaluates the viability and potency of cryopreserved cellular therapy products.

Explanation:
The maximum duration of storage of cryopreserved cellular therapy products that maintains potency is unknown and may be affected by various factors in the collection, processing, cryopreservation, or storage conditions. The purpose of a stability program is to assess cellular therapy products over time in storage for potency and viability. Products from each processing and storage method must be assessed.

The stability program must evaluate cellular therapy products each year with predefined criteria. Standards are not prescriptive in terms of the number of products to assess, which products are tested in a given year, or other details. 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. Products stored for various periods may be assessed; however, the oldest products in storage for each processing method must be included in the assessment.

Retrospective studies are acceptable. For HPC products, potency is generally measured by CD34 recovery, and total nucleated cell viability. For cellular therapy products in early phase trials, the stability program should be in place but may not have mature data available. Early in the process, even before clinical trials are initiated, samples from preclinical studies using methods to be used clinically should be banked for future stability assessments. The stability program for all cellular therapy products should assess characteristics that affect the safety and efficacy of the product including container and label integrity, and other product characteristics as defined by the Processing Facility.

The assessment of cellular therapy products in the stability program must include pre-determined acceptance criteria for potency and viability. It may be that thawed products need to undergo an initial period of expansion for potency to be assessed. The stability program should also define actions to take if 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.

The inspector should review results of the stability testing for cryopreserved cellular therapy products and the establishment of expiration dates and times after products are prepared for infusion.

Example(s):
Stability testing can be performed using cellular therapy products stored for more than a year that are scheduled to be discarded and/or could be performed with samples from products that were frozen and stored under the same conditions as the actual product. Processing Facilities are encouraged to discontinue any use of research-grade reagents and adopt single platform flow cytometry technology 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.

An example would be to establish the stability of cryopreserved mononuclear cells from the initial collection to establish a virus specific T cell line to be used clinically.

STANDARD:

D9.3 TEMPERATURE

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

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

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

Explanation:
The Processing Facility must establish a process to assure that cellular therapy products are stored in a manner that maintains their integrity and potency. 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.

Short term 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., cell assessment by flow cytometry) 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., 1-8˚C). Temperature ranges and duration must be determined for each type of product and should be based on the medical literature and/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 ≤ - 150˚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 does not have to be assigned to cryopreserved products if storage conditions are shown to be adequate based on the medical literature and/or are justified by validation studies, where applicable.

Storage temperatures for cellular therapy products from third party manufacturers must be defined by the manufacturer.

In the case of autologous and/or related donations, donors, recipients, and associated clinical programs should be informed of the conditions of storage and storage duration, preferably before cellular therapy product collection.

Evidence:
Processing Facility policies or SOPs must define storage criteria. 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):
Informing donors, recipients, and associated clinical programs may be accomplished by informed consent, contractual agreement, or other legal means.

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 the container, number of containers, required storage conditions, or inclusion of any related sample aliquots.

Example(s):
Cord blood units are one example of a cellular therapy product for which special arrangements should 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 the cellular therapy products.

D9.4.2 For cellular therapy products immersed in liquid nitrogen, procedures to minimize the risk of cross-contamination of products shall be employed.

D9.4.3 Processes for storing cellular therapy products in quarantine shall be defined in Standard Operating Procedures.

D9.4.3.1 Quarantined cellular therapy products shall be easily distinguishable and stored in a manner that minimizes the risks of cross-contamination and inappropriate distribution.

D9.4.3.2 All cellular therapy products with positive infectious disease test results for relevant communicable disease agents or positive microbial cultures shall be quarantined. Disposition shall be documented.

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 RS, Zuckerman MA, Goldstone AH, Hawkins AE, Fielding A, Briggs EM, Irwin D, Blair S, Gorman AM, Patterson KG, Linch DC, Heptonstall J, Brink NS: Hepatitis B transmission from contaminated cryopreservation tank. Lancet 346:137-140, 1995).

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 contamination or cross-contamination when unusual patterns are seen and report to the proper authority as required by 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., microbiological cultures) is required. Quarantine does not require physical segregation of such products but does require a mechanism to minimize the potential for cross-contamination of communicable disease agents and to prevent product distribution when release has not been 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.

Whenever possible cellular therapy products should be stored in bags approved for cryopreservation and not in tubes with screw caps. The use of bags makes the handling of products during thawing for infusion safer by avoiding open steps.

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 but may not be limited to 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, labelled 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 frozen. 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 continuously and that temperatures be recorded at not less than four-hour intervals for LN_2 vapor phase storage. Temperature records of stored cellular therapy products, including alarm conditions, must be reviewed prior to product distribution. Failure of a storage device to maintain the target temperature represents a deviation that must be documented, including the appropriate investigation and follow-up actions required to determine the integrity and potency of the products has not been compromised. The Processing Facility should establish critical values that, if exceeded, require documentation for those products in the storage freezer that did not maintain target temperature. In the case of suspected thawing of cryopreserved products, the recipient's primary attending physician must be notified. The attending physician, in collaboration with the Processing Facility Director, must determine if the products remain in storage for future use.

STANDARD:

D9.5.2 There shall be a mechanism to confirm that levels of liquid nitrogen in liquid nitrogen freezers are consistently maintained to assure that cellular therapy products remain within the specified temperature range.

Explanation:

For cellular therapy products stored in the liquid phase of liquid nitrogen, continuous temperature monitoring is not required. Processes must be sufficient to ensure that the liquid nitrogen level does not fall below set limits. The objective is to confirm that products are continuously maintained at the target storage temperature. Validation studies may be especially important to assure that the level limits that trigger alarms are suitable 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.

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 back-up power systems (battery- or generator-based) to confirm they are continuously active.

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:

D9.6.2 *Alarm systems shall have audible and visible signals or other effective notification methods.*

D9.6.3 *Alarm systems shall be checked periodically for function.*

D9.6.4 *If trained personnel are not always present in the immediate area of the storage device, a system shall be in place that alerts responsible personnel of alarm conditions on a 24-hour basis.*

D9.6.5 *Alarms shall be set to activate at a temperature or level of liquid nitrogen that will allow time to salvage products.*

D9.6.6 *Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.*

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.

Example(s):
Instructions may include information on "who to contact," and is 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 trouble-shooting flowchart located at the freezer device for quick reference and immediate response by the technical staff.

STANDARD:

D9.6.6.1 Instructions shall include a procedure for notifying processing personnel.

D9.6.7 Storage devices of appropriate temperature shall be available for cellular therapy product storage if the primary storage device fails.

Explanation:

Back-up 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 and time to intend use of the product.

STANDARD:

D9.7 The storage device shall be located in a secure area and accessible only to personnel authorized by the Processing Facility Director.

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

D9.8.1 Cellular therapy product unique identifier.

D9.8.2 Recipient name or unique identifier.

D9.8.3 Storage device identifier.

D9.8.4 Location within the storage device.

Explanation:

There must be a mechanism by which the storage location of cellular therapy products and sample vials from the products can be identified 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 location of the cellular therapy product within the storage container is identified. The inspector should also review the processes in place to make changes in inventory entries when products are added or removed to assure 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 (e.g., imminent administration). This process must include container validation and courier qualifications.

It is necessary that the product container be securely sealed and packaged to protect it from potential harm during transit.

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.

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 these 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 these Standards. Inspectors should verify the process and container validation is adequate to maintain product security and integrity during expected transit time and ambient temperature conditions.

STANDARD:
D10.2 The primary 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 TIC 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.

STANDARD:
D10.3 Cellular therapy products that require a temperature-controlled environment and that are transported or shipped over an extended period of time shall be transported or shipped in a container validated to maintain the appropriate temperature range.

Explanation:
These SOPs must include maintenance of optimal temperature during distribution. 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. 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, among 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.

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 extremes of temperature, 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 cellular therapy 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.

Processing Facilities using shipping containers from a third-party manufacturer should verify 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 and/or shipping.

Frozen products may be placed in the dry shipper surrounded by material such as Styrofoam to absorb impacts during shipping.

TNC count and cell viability are examples of data on which temperature ranges should be established.

STANDARD:

D10.4 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

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 (i.e., fresh unfrozen 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:

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 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 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.

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 II A.

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 II 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 IIA and Appendix III.

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 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 if the accompanying paperwork is lost or destroyed. To safeguard unrelated donor and recipient anonymity, neither the donor nor recipient name should be on the transport or shipping label; however, unique identifiers are acceptable.

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.

STANDARD:
D10.6 Cellular therapy products transported internally shall be packaged in a qualified, closed, and protective outer container.

Explanation:
The conditions for transport on public roads and shipping have been described in D10.5. 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 outer container must be closed and 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.

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.

Example(s):
A number of reusable transport coolers are now available on the market that are used for shipping human blood and other biologics that may meet the requirements of these Standards, including some with nylon exteriors. Some are qualified for 2-8^{0}C, as well as 15-25^{0}C.

STANDARD:
D10.6.1 The outer container for internal transport shall be labeled as defined in Appendix II 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:
D10.7 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:
If the cellular therapy product to be administered is essential for the recipient's survival, it may be important that the product be entrusted to a knowledgeable individual who accompanies it from the distributing facility to the receiving facility.

STANDARD:

D10.8 There shall be plans for alternative means of transport or shipping in an emergency.

D10.9 The cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.

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 cellular therapy product efficacy. 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.

STANDARD:

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

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 I. 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 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 facility shall have ready access, are defined in Appendix III.

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 these Standards and should verify that the quarantine process is defined in SOPs and physical or electronic systems are in place to support quarantine functions.

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 Processing Facility should 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, 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 There shall be Standard Operating Procedures to maintain cellular therapy products in quarantine until they have been determined to meet criteria for release from quarantine.

D11.1.6 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.

D11.1.7 The receiving facility shall have readily available access to a summary of documents used to determine allogeneic donor eligibility.

D11.1.7.1 For cellular therapy products received from an external facility, there shall be documented evidence of donor eligibility screening and testing in accordance with Applicable Law.

Explanation:

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 these Standards, "manufacturer" refers to whoever produced the cellular therapy product, such as a laboratory or a facility that banks biological products. 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:

D11.1.8 When cellular therapy products are returned to the Processing Facility after distribution for administration, there shall be documentation in the Processing Facility records of the events requiring return, the temporary storage temperature when at the clinical facility, the results of inspection upon return, and subsequent action taken to protect product safety and viability.

D11.1.8.1 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 Processing 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 processing 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 outside of 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 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, logically as part of the facility's SOP for release and exceptional release SOP (see D5.1).

Evidence:

The inspector should verify the Processing Facility SOP for cellular therapy product return and 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 recipient has an unanticipated reaction to an initial portion of the planned infusion or when a scheduled treatment is delayed.

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 and 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 these Standards, the facility's own SOPs, and Applicable Law. 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.
- 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 that donor eligibility determination was completed.
- 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.

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 cellular therapy 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:
These Standards require that there be predefined release criteria for distributed cellular therapy products and that there be provisions for exceptional release when a given 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 cellular therapy products that meet all release criteria, the Processing Facility Medical Director or another suitable 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 a release criteria).

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 D11.1.2 and the regulatory requirements of the FDA must be met. Facilities outside of the U.S. must follow Applicable Law.

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 identity as indicated by appropriate labeling.

D11.2.3.1 A cellular therapy product shall not be released when the container is compromised or recipient, donor, or product information is not verified unless the Processing Facility Director gives specific authorization for the product's release.

Explanation:

The processing record of cellular therapy products issued under exceptional release must include documentation of consent from the recipient's physician. 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.

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 must include all cell types that are in use. The facility may wish to issue a "Circular of Information" with each administration although this is not required by these Standards. The circular must be available to personnel at the sites where administrations are performed. Like all controlled documents, these circular 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 the information required by these Standards 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. This document provides the information listed in D11.1.4 for commonly used hematopoietic cellular therapy products and may be used to satisfy the requirements of this standard for most HCT programs. Please note, when a FACT standard is stricter than the Circular of Information for the Use of Cellular Therapy Products, the FACT standard must be followed. A copy of the consensus Circular of Information may be downloaded from the FACT website at https://www.factglobal.org/education-and-resources/general/applicant-education-and-resources/resources/. For most Cellular Therapy Programs accredited under these Standards, individual instructions for administration will be required.

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 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 cellular therapy product was distributed.

D11.3.1.7 Date and time 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, cellular therapy product identifier(s), the proper product name(s) and any attributes of the product(s), the identity of the distribution facility, and documentation of allogeneic donor eligibility, if applicable and if provided to the Processing Facility. If the 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 "product administration form," a copy of which can be maintained in the Processing Facility record. 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 these 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 is contained in the consent for the collection of products.

In the case of autologous and/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: Death of the recipient, identification of cellular therapy products for the recipient, or notification of the recipient's responsible physician, must be documented by the storage facility 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/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 in 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/or to the FACT Standards, whichever is more stringent.

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 responsible attending 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 strongly advises 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 to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.

Explanation:

Transfer of cellular therapy products should comply with Applicable Law. These Standards do not require the Processing Facility to identify an alternative storage facility.

STANDARD:

D12.1.3 Documentation of no further need for the cellular therapy product before any product is discarded.

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 facility.

The clinical team does not have to write a specific note stating death; 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 index in the U.S. The institution registry or the governmental regional registries are also adequate sources. Secondary sources of information, such as newspaper articles alone, 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):

The Medical Director of the Processing Facility and the recipient's physician must agree 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 to the Processing Facility for disposal 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 and medical waste.

Explanation:
Cellular therapy products derived from human tissue are 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 following institutional 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 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 and/or disposal, or 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 identity of the product, date of discard or transfer, disposition, and method of disposal or transfer.

D13: RECORDS

STANDARD:

D13.1 A record management system shall be established and maintained to facilitate the review of records.

Explanation:

Records are 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 provided that certain objectives are achieved. The record keeping system 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.

STANDARD:

D13.1.1 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

D13.1.2 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 at or before the time of product distribution.

Explanation:

The intent of this standard is to track the identity of the cellular therapy product to the final recipient. The Processing Facility must inform the receiving institution of the identifiers necessary to complete the tracking.

STANDARD:

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

Explanation:
Good documentation practices are 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. Good documentation practices include:

- Data entry must be clear and legible.
- Use indelible blue or black ink; no gel pens, felt tip pens, or pencils.
- Make record entries at the time the task was performed (concurrently).
- Do not use ditto marks or arrows to include several data entry fields.
- Do not use correction fluid, correction tape, overlay of labels.
- Use the SLIDE RULE 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.

Example(s):
Slide Rule Examples:

discarded J.D. 11 Feb 13

- The vial was ~~dicrded~~* in error. Content …….

*misspelled J.D. 11 Feb 13

- Viability: ~~93.6%~~ Error J.D. 11 Feb 13

98.6% J.D. 10 Feb 13

STANDARD:

D13.2.1 Records shall be accurate and legible.

D13.2.2 Records shall be indelible.

D13.3 Records shall be maintained in such a way as 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:

D13.4 *Safeguards to secure the confidentiality of all records and communications among the collection staff, processing facilities, clinical facilities, and health care providers and their recipients and donors shall be established and followed in compliance with Applicable Law.*

Example(s):
Breaches in policy that might compromise confidentiality include: unsecured patient records; patient charts left unattended in areas where unauthorized personnel and/or visitors may have access, or unattended computer screens displaying patient information in such areas; indiscriminate discussion 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 and/or visitors; and 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 and/or the use of locked file cabinets. The Processing Facility must have SOPs describing the maintenance of donor and recipient confidentiality (see D5.1).

STANDARD:

D13.5 ELECTRONIC RECORDS

D13.5.1 The Processing Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum, systems under the control of the Processing Facility that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

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 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 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 these 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. Personnel then use this printed record 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 these 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 (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 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., when electronic records are used as a substitute for paper, the inspector should refer to the FDA document Part 11, Electronic Records; Electronic Signatures - Scope and Application, for guidance to assess the validation procedures (https://www.fda.gov/media/75414/download).

STANDARD:

D13.5.2 *For all critical electronic record systems, there shall be policies, Standard Operating Procedures, and system controls to maintain the accuracy, integrity, identity, and confidentiality of all records.*

D13.5.3 *There shall be a means by which access to electronic records is limited to authorized individuals.*

D13.5.4 *The critical electronic record system shall maintain unique identifiers.*

D13.5.5 *There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.*

D13.5.6 For each critical electronic record system, there shall be an alternative system for all electronic records to allow for continuous operation of the Processing Facility in the event that a critical electronic record system is not available. The alternative system shall be validated, and Processing Facility staff shall be trained in its use.

D13.5.7 For all critical electronic record systems, there shall be written Standard Operating Procedures for record entry, verification, and revision.

D13.5.7.1 A method shall be established or the system shall provide for review of data before final acceptance.

Example(s):
Standards require that data be reviewed before final acceptance, but a second individual to verify the data is not required. Systems may be programmed to validate data (e.g., product numbers should only have a specified number of alphanumeric characters, date fields should follow a specific format).

STANDARD:

D13.5.7.2 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 may take the simple form of a log-in 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 log-in credentials.

STANDARD:

D13.5.8 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

D13.5.9 For all critical electronic record systems, there shall be validated procedures for and documentation of:

D13.5.9.1 Systems development.

D13.5.9.2 Numerical designation of system versions, if applicable.

D13.5.9.3 Prospective validation of systems, including hardware, software, and databases.

D13.5.9.4 Installation of the system.

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 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:

- 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]), 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 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 back-ups that include storage of back-up data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the back-up copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include all of 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 to assure 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 back-ups of records maintained electronically is in place.

STANDARD:

D13.5.9.5 Training and continued competency of personnel in systems use.

Explanation:
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 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:

D13.5.9.6 Monitoring of data integrity.

D13.5.9.7 Back-up of the electronic records system on a regular schedule.

D13.5.9.8 System maintenance and operations.

D13.5.9.9 System assignment of unique identifiers.

D13.5.9.10 All system modifications shall be authorized, documented, and validated prior to implementation.

D13.6 RECORDS TO BE MAINTAINED

D13.6.1 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 or date of the cellular therapy product's distribution, disposition, or expiration, whichever is latest, or according to Applicable Law.

D13.6.1.1 Employee records shall be maintained in a confidential manner, as required by Applicable Law.

D13.6.1.2 Facility maintenance records pertaining to facility cleaning and sanitation shall be retained for at least three (3) years or longer in accordance with Applicable Law.

D13.6.1.3 Validation study records for a processing procedure shall be retained for a minimum of ten (10) years after distribution of the final products manufactured using that procedure.

D13.6.2 Records to allow tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after administration, distribution, disposition, or expiration of the cellular therapy product, or as required by Applicable Law. These records shall include collection and processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product code, and donor and recipient information as known.

D13.6.3 All records pertaining to the processing, testing, storage, or distribution of cellular therapy products shall be maintained for a minimum of ten (10) years after the date of administration, or if the date of administration is not known, then a minimum of ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, or the creation of the cellular therapy product record, whichever is most recent, or according to Applicable Law or institutional policy, whichever is latest.

Explanation:
The standards in this section detail what records must be maintained and the minimum 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 10 years after their creation include:

- QM records: validation and qualification studies; equipment maintenance reports; the results of audits; errors, accidents, and adverse reaction 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 (e.g., 15 years for genetically modified products in the U.S.). 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 and/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 and/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; and confidentiality and data protection requirements.

An exception to the 10-year requirement for retention of Processing Facility maintenance records is for the documentation of cleaning and sanitation. These records need only be retained for at least 3 years after creation but should include cleaning schedules, methods, and identification of personnel responsible for cleaning. There should also be documentation of initial training and retraining of personnel as needed.

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 10 years old.

The inspector should acknowledge during the inspection that the Processing Facility is only responsible for compliance from the time of its initial FACT accreditation. Some facilities have not been accredited by FACT for a full 10 years. In these cases, the facilities are only held responsible for retaining records for the specified time since their initial accreditation.

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 cellular therapy product along with records of adverse reactions and post-donation complications, treatment interventions, and recovery.

STANDARD:

D13.6.4 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, and/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 and where these records are maintained and determine if an organized system is in place that allows timely retrieval of research records.

STANDARD:
D13.7 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

D13.7.1 The Processing Facility shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a cellular therapy product.

D13.7.2 The Processing Facility shall provide to the facility of final disposition a summary of all records relating to the collection, processing, and storage procedures performed and concerning the safety, purity, or potency of the cellular therapy product.

Explanation:
The Processing Facility shall have an applicable SOP or policy that describes the dissemination to other collection and/or clinical facilities of summary records that concern safety, purity, and potency of the cellular therapy product. Quantity and control of the product should be evident within these records.

Evidence:
The inspector should determine if divided responsibility occurs 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 occur in different departments of the same institution. There must be documents clearly defining the responsibilities of each department. It must be possible to identify these responsibilities when reviewing the documents. In addition, there should be a written policy or agreement between both departments that defines the responsibilities and the documents to be shared between both departments.

STANDARD:

D13.7.3 If two (2) or more facilities participate in the collection, processing, or distribution of the cellular therapy product, the records of the Processing Facility shall show the extent of its responsibility.

Explanation:

In the event that two or more facilities participate in the collection, processing, storage or administration of a cellular therapy product, the records of each participating facility must clearly indicate the extent of each facility's responsibility. The Processing Facility's records should include relevant contracts and agreements and the Processing Facility is responsible for compliance with these 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 or clinical facilities. 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.

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.

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APPENDIX I

CELLULAR THERAPY PRODUCT LABELING

Each label shall include at least the elements detailed in the following table[1]:

Element[2]	Label at completion of collection	Label at completion of processing	Partial label at distribution for administration[4]	Label at distribution for administration[3]
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	-	-	-
Approximate volume	AF	AF	AF	AF
Name and quantity of anticoagulant and other additives	AF	AF	AF	AF
Recommended storage temperature range	AF	AF	AF	AT
Donor identifier and (if applicable) name	AT	AT	AC	AC
Biohazard and Warning Labels (as applicable, see C7.4.4, D7.4.4).	AT	AT	AC	AC
As applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" Statement "WARNING: Advise Patient of Communicable Disease Risks" Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"	AT AT AT	AT AT AT	AC AC AC	AT AT AT
Identity and address of processing and distribution facility(ies)	-	AC	AC	AC
Statement "Do Not Irradiate"	-	AT	AC	AF
Expiration Date (if applicable)	-	AC	AC	AF
Expiration Time (if applicable)	-	AC	AC	AC
ABO and Rh of donor (if applicable)	-	AC	AC	AC
RBC compatibility determination (if applicable)	-	-	AC	AC
Statement indicating that leukoreduction filters shall not be used.	-	-	AC	AF
Statement "FOR AUTOLOGOUS USE ONLY" (if applicable)	AT	AT	AC	AF
Date of distribution	-	-	AC	AC

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

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

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

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

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

[5]Product proper names and attributes must also be identified in words and are listed in Chapter Three of the ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. Available at: www.isbt128.org/standard-terminology.

This includes all potential attributes, in addition to the core attribute referenced in this table (Anticoagulant, Volume, Storage Temperature): Intended Use, Manipulation, Cryoprotectant, Blood Component from Third Party Donor, Preparation, Genetically Modified, Irradiation, Modification, Mobilization, Pooled Single, Cultured, Enrichment, and Reduction.

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

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APPENDIX II

A: CELLULAR THERAPY PRODUCT LABELS FOR SHIPPING AND TRANSPORT ON PUBLIC ROADS

Each container for shipping or 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, if appropriate	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 Warning Labels (as applicable, see C7.4.4, D7.4.4).	AC	-
If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" Statement "WARNING: Advise Patient of Communicable Disease Risks" Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"	AC AC AC	-

AC= Accompany, AF=Affix

[1]Time 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 include an internal transport label with at least the elements detailed in the following table.

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

AF=Affix

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APPENDIX III

ACCOMPANYING DOCUMENTS AT DISTRIBUTION

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

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 infused until completion of the donor-eligibility determination, except under condition of urgent medical need	-	-	X
Listing of any required screening or testing that has not yet been completed	-	-	X
Results of donor screening 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

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

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

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

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

[5]Access to the Clinical Program SOPs and forms could suffice when the distributing and clinical facilities are within the same institution.

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ACKNOWLEDGEMENTS

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