PART A: TERMINOLOGY, TENETS, ABBREVIATIONS AND DEFINITONS

A1: Terminology

A2: Tenets

A3: Abbreviations

A4: Definitions

PART A: TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

A1 TERMINOLOGY

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

The phrase, "policies and Standard Operating Procedures," is used for ease of reading. When referring to a single document, either a policy or Standard Operating Procedure is sufficient.

A2 TENETS

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

A2.1 Where Applicable Law includes more stringent requirements than these Standards, Applicable Law supersedes the Standards. Conversely, when these Standards are more stringent than Applicable Law, the Standards shall be followed.

A2.2 Any activity can be delegated to an appropriate 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's organization.

A3 ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

ABO	Major human blood group including erythrocyte antigens, A, B, O
AC	Accompany
ACHC	Accreditation Commission for Health Care
AF	Affix
Anti-	Antibody to the designated antigen
APP	Advanced Practice Provider/Professional
ASHI	American Society for Histocompatibility and Immunogenetics
~~*ASTCT*~~	~~American Society for Transplantation and Cellular Therapy~~
AT	Attach
CAP	College of American Pathologists
CAPA	Corrective and preventive action
CFR	Code of Federal Regulations

CIBMTR	Center for International Blood and Marrow Transplant Research
~~*CIDR*~~	~~Cellular Immunotherapy Data Resource~~
CMV	Cytomegalovirus
COA	Certificate of analysis
DLI	Donor lymphocyte infusion
DNA	Deoxyribonucleic acid
EBMT	Organization formerly known as the European Society for Blood and Marrow Transplantation
ECP	Extracorporeal photopheresis
EFI	European Federation for Immunogenetics
EU	European Union
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	Food and Drug Administration
GMP	Good manufacturing practice
GTP	Good tissue practice
GVHD	Graft versus Host Disease
GxP	Good practice
HCT/P	Human cells, tissues, and cellular and tissue-based products
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPC	Hematopoietic progenitor cell
HTLV	Human T cell lymphotropic virus
IBC	Institutional Biosafety Committee
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICU	Intensive care unit
IEC	Immune Effector Cell
IND	Investigational new drug
IRB	Institutional Review Board
ISCT	International Society for Cell & Gene Therapy
JACIE	Joint Accreditation Committee – ISCT and EBMT
MNC	Mononuclear cell
MSC	Mesenchymal stromal cell or mesenchymal stem cell
NC	Nucleated cell
QM	Quality management
RBC	Red blood cell
Rh	Rhesus system of human red blood cell antigens; used in this document to refer to the Rh(D) antigen only, unless otherwise specified
SOP	Standard operating procedure
~~*U.S.*~~	~~United States~~
WBC	White blood cell

A4 DEFINITIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

Assent: The expression of approval or agreement.

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

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

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

Autologous: Derived from and intended for the same individual.

Calibrate: To set measurement equipment against a known standard.

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

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

Cellular therapy product: Somatic cell-based product (e.g., 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 hematopoietic cell transplantation, chimerism generally refers to the presence of allogeneic donor hematopoietic and/or lymphoid cells in the transplant recipient.

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

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

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

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

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

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

Collection Site: The physical location at which cells are collected for administration, storage, or for further manufacturing.

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

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

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

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

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

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

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

Critical: The quality of any element employed in cellular therapy product manufacturing to potentially change the identity, purity, potency, or safety of the cellular therapy product if altered or omitted. "Element" includes, but is not limited to, materials, equipment, personnel, documents, or facilities.

Cytokine release syndrome: 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 was not feasible or possible.

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

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

DNV: An accreditation program which directly addresses regulatory requirements for hospitals, such as US Government's Centers for Medicare and Medicaid (CMS) or provide guidance and best practices for clinical specialty organizations across healthcare. DNV is now the proper name of the organization formally known as Det Norske Veritas.

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

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

Donor lymphocyte infusion (DLI): A therapy in which lymphocytes from the original cellular therapy product donor are given to a recipient who has received 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 diseases.

Engraftment: The reconstitution of recipient hematopoiesis with blood cells and platelets from a donor. It is recommended that cellular therapy programs use engraftment definitions from CIBMTR, EBMT, or another similar organization.

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

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

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

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

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

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

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

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

Genetically modified cell: A cell that has been modified by replacing a disease-causing gene with a healthy copy of the gene, inactivating a disease-causing gene that is not functioning properly, or introducing a new or modified gene into the body to help treat a disease.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Package insert: A document prepared by the drug manufacturer, approved by the 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, and/or serves as a means by which authority can be delegated.

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

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

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

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

Product code: An eight-character ISBT 128 code that comprises the Product Description Code, a Collection Type Code, and a Division Code. The product code makes each product from a collection unique.

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 hematopoietic sources.

Cellular therapy products are divided into two class name subcategories:

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.

For the current list of definitions, see https://www.isbt128.org/ST-018.

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

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

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

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

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

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

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

NC, DECIDUA: A cell product containing nucleated cells obtained from the decidua.

NC, FLUID: A cell product containing nucleated cells obtained from fluid.

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

NC, MENSTRUAL BLOOD: A cell product containing nucleated cells obtained from menstrual blood.

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

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

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

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

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

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

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

DUAL CELL FUSION: A cell product containing cell fusions formed from two cell populations. The constituent cells are identified in accompanying documentation and may be electronically identified using an ISBT 128 data structure.

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

iPSC, CORD BLOOD: A cell product containing induced pluripotent stem (iPS) cells obtained from cord blood.

iPSC, WHOLE BLOOD: A cell product containing induced pluripotent stem (iPS) cells obtained from whole blood.

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

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

MALIGNANT CELLS, TUMOR: A cell product containing, or derived from, malignant cells obtained from a tumor.

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

MNC, CORD BLOOD: A cell product containing mononuclear cells obtained from cord blood.

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

MNC, WHOLE BLOOD: A cell product containing mononuclear cells obtained from whole blood.

MSC, ADIPOSE TISSUE: A cell product containing mesenchymal stromal cells derived from adipose tissue.

MSC, AMNIOTIC MEMBRANE: A cell product containing mesenchymal stromal cells derived from amniotic membrane.

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

MSC, DECIDUA: A cell product containing mesenchymal stromal cells derived from decidua.

MSC, DENTAL PULP: A cell product containing mesenchymal stromal cells derived from dental pulp.

MSC, FETAL LIVER: A cell product containing mesenchymal stromal cells derived from fetal liver.

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

MSC, PLACENTA: A cell product containing mesenchymal stromal cells derived from placenta.

MSC, UMBILICAL CORD: A cell product containing mesenchymal stromal cells derived from umbilical cord.

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

NC, ADIPOSE TISSUE: A cell product containing nucleated cells obtained from adipose tissue.

NC, PLACENTA: A cell product containing nucleated cells obtained from placenta.

NC, UMBILICAL CORD: A cell product containing nucleated cells obtained from umbilical cord.

NC, UMBILICAL CORD VESSEL: A cell product containing nucleated cells obtained from umbilical vessels.

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

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

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

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

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

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

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

T CELLS, TUMOR: A cell product containing T cells obtained from a tumor.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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.

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

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

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

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

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

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

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

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

Syngeneic: The biologic relationship among genetically identical siblings.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*These definitions are as of the date of publication and use the current terminology as found in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. For the most current list of definitions, see https://www.isbt128.org/ST-018.

PART B: CLINICAL PROGRAM STANDARDS

B1: General

B2: Clinical Unit

B3: Personnel

B4: Quality Management

B5: Policies and Standard Operating Procedures

B6: Allogeneic and Autologous Donor Selection, Evaluation, and Management

B7: Recipient Care

B8: Clinical Research

B9: Data Management

B10: Records

PART B: CLINICAL PROGRAM STANDARDS

B1: GENERAL

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

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

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

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

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

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

B1.4 Clinical Programs responsible for cell collection or processing activities must comply with the Standards in Parts C and D as applicable.

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

B1.6 If the Clinical Program or an intermediary facility receives cellular therapy products directly from a third-party provider, the following responsibilities shall be defined by a written agreement:

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

B1.6.2 Cellular therapy product storage (Sections D9 and D10 apply).

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

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

B1.6.5 Review and verification of certificate of analysis (COA) or product specifications provided by the manufacturer, if applicable.

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

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

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

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

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

B2: CLINICAL UNIT

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

B2.2 There shall be a designated outpatient care area that protects the patient from transmission of infectious agents and allows, as necessary, for appropriate patient isolation; confidential examination and evaluation; and administration of intravenous fluids, medications, blood products, or cellular therapy products.

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

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

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

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

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

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

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

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

B2.9.2 The policy shall define personal protective equipment of the appropriate grade for the risk, to be worn while handling biological specimens.

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

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

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

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

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

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

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

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

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

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

B2.17 Clinical Programs performing allogeneic transplantation or cellular therapy shall use HLA testing laboratories that 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 hematopoietic cellular therapy transplant patients.

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

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

B2.18.1 Lineage specific chimerism should be performed.

B3: PERSONNEL

B3.1 CLINICAL PROGRAM DIRECTOR

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

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

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

B3.1.3 The Clinical Program Director shall be responsible for all elements of the design of the Clinical Program including quality management, the selection and care of recipients and donors, and cell collection and processing, whether internal or contracted services.

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

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

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

B3.2 ATTENDING PHYSICIANS

B3.2.1 Attending physicians shall be appropriately licensed to practice medicine in the jurisdiction of the Clinical Program.

B3.2.1.1 Attending physicians for transplantation shall be specialist certified or trained in one (1) of the following specialties: Hematology, Medical Oncology, Immunology, or Pediatric Hematology/Oncology.

B3.2.1.2 Attending physicians for non-transplant cellular therapies shall be specialist certified or trained in the therapeutic disease area and experienced in cellular therapy.

B3.2.2 Clinical Programs performing adult transplantation shall have at least one (1) attending physician who has achieved specialist certification in Hematology, Medical Oncology, or Immunology.

B3.2.3 Clinical Programs performing pediatric transplantation shall have at least one (1) attending physician who has achieved specialist certification in Pediatric Hematology/Oncology or Pediatric Immunology.

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

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

B3.3 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

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

B3.3.2 Clinical training and competency shall include the management of autologous and allogeneic HPC transplant recipients and patients receiving immune effector cells or other cellular therapies.

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

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

B3.3.4.1 Indications for allogeneic and autologous HPC transplantation.

B3.3.4.2 Selection of suitable recipients and appropriate preparative regimens.

B3.3.4.3 Donor selection, evaluation, and management.

B3.3.4.4 Donor and recipient informed consent.

B3.3.4.5 Selection and administration of preparative regimens.

B3.3.4.6 Selection and administration of growth factors or other agents for HPC mobilization and for post-transplant hematopoietic cell reconstitution.

B3.3.4.7 Administration of cellular therapy products, including HPC, IEC, genetically modified cells, and other cellular therapies.

B3.3.4.8 Management of complications related to the administration of cellular therapy products.

B3.3.4.9 Management of neutropenic fever.

B3.3.4.10 Management of pulmonary complications.

~~B3.3.4.11 Diagnosis and management of fungal disease.~~

B3.3.4.11 Management of sinusoidal obstruction syndrome and other causes of hepatic dysfunction.

B3.3.4.12 Management of thrombocytopenia and bleeding.

B3.3.4.13 Management of hemorrhagic cystitis.

B3.3.4.14 Management of blood transfusion, including the use of CMV-appropriate and irradiated (or equivalent) blood products.

B3.3.4.15 Management of mucositis.

B3.3.4.16 Management of gastrointestinal complications.

B3.3.4.17 Management of pain.

B3.3.4.18 Management of cytokine release syndrome.

B3.3.4.19 Management of neurologic toxicity syndromes, including immune effector cell associated neurotoxicity syndrome (ICANS).

B3.3.4.20 Management of macrophage activation syndrome/ hemophagocytic lymphohistiocytosis.

B3.3.4.21 Management of cardiac dysfunction.

B3.3.4.22 Management of renal dysfunction.

~~B3.3.4.22 Monitoring and management of anaphylaxis.~~

B3.3.4.23 Diagnosis, monitoring, and management of infectious complications.

B3.3.4.24 Management of HPC graft failure.

B3.3.4.25 Management of dermatologic complications.

B3.3.4.26 Evaluation of post-transplant and other cellular therapy outcomes.

B3.3.4.27 Management of tumor lysis syndrome.

B3.3.4.28 Evaluation and management of late effects of cellular therapy.

B3.3.4.29 Documentation and reporting for patients on investigational protocols.

B3.3.4.30 Reporting responsibilities for adverse events according to Applicable Law.

B3.3.4.31 Palliative and end of life care.

B3.3.4.32 Age-specific donor and recipient care.

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

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

B3.3.5.2 Donor eligibility determination.

B3.3.5.3 Methodology and implications of HLA typing.

B3.3.5.4 Methodology and implications of testing for chimerism.

B3.3.5.5 Management of patients receiving ABO incompatible cellular therapy products.

B3.3.5.6 Diagnosis and management of acute and chronic Graft versus Host Disease (GVHD).

B3.3.6 The attending physicians shall be knowledgeable in the following procedures:

B3.3.6.1 Cellular therapy product collection, including apheresis and bone marrow harvest.

~~B3.3.6.1 Bone marrow harvest procedures.~~

B3.3.6.2 Cellular therapy product processing, including washing and diluting.

B3.3.6.3 Genetic modification of cells and impact on patient care.

B3.3.6.4 Cellular therapy product cryopreservation.

~~B3.3.6.5 Cellular therapy product administration procedures.~~

B3.3.6.5 Extracorporeal photopheresis (ECP) for GVHD.

B3.3.6.6 Therapeutic apheresis.

B3.4 PHYSICIANS-IN-TRAINING

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

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

B3.5 ADVANCED PRACTICE PROVIDERS/PROFESSIONALS (APPs)

B3.5.1 APPs shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and license.

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

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

B3.6 NURSES

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

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

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

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

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

B3.6.2.2 Administration of preparative and lymphodepletion regimens.

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

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

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

B3.6.2.6 Care interventions to manage cellular therapy complications.

B3.6.2.7 Palliative and end of life care.

B3.6.3 There shall be an adequate number of nurses experienced in the care of cellular therapy recipients.

B3.6.4 There shall be a nurse/recipient ratio satisfactory to manage the severity of the recipients' clinical status.

B3.7 PHARMACISTS

B3.7.1 Pharmacists shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and licensure.

B3.7.2 Training and knowledge of designated pharmacists shall include:

B3.7.2.1 Hematology/oncology patient care, including the process of cellular therapy.

B3.7.2.2 Recognition and management of adverse events including, but not limited to, cytokine release syndrome, neurological toxicities, Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-like Syndrome (IEC-HS), and the appropriate medications.

B3.7.2.3 Therapeutic drug monitoring, including, but not limited to, anti-infective agents, immunosuppressive and preparative regimen agents, anti-seizure medications, and anticoagulants.

B3.7.2.4 Monitoring for and recognition of drug/drug and drug/food interactions and necessary dose modifications.

B3.7.2.5 Recognition of medications that require adjustment for organ dysfunction.

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

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

B3.8 CONSULTING SPECIALISTS

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

B3.8.1.1 Cardiology.

B3.8.1.2 Dermatology.

B3.8.1.3 Gastroenterology.

B3.8.1.4 Infectious disease.

B3.8.1.5 Intensive care.

B3.8.1.6 Nephrology.

B3.8.1.7 Neurology.

B3.8.1.8 Obstetrics/Gynecology.

B3.8.1.9 Ophthalmology.

B3.8.1.10 Palliative and end of life care.

B3.8.1.11 Pathology.

B3.8.1.12 Psychiatry.

B3.8.1.13 Pulmonary medicine.

B3.8.1.14 Radiation oncology with experience in large-field (i.e., total body, total lymphoid) irradiation treatment protocols, if radiation therapy is administered.

B3.8.1.15 Radiology.

B3.8.1.16 Surgery.

B3.8.1.17 Transfusion medicine.

B3.8.1.18 Primary disease specialty, when applicable.

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

B3.9 QUALITY MANAGER

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

B3.9.2 The Clinical Program Quality Manager shall participate in a minimum of ten (10) hours of continuing education related to cellular therapy and Quality Management annually.

B3.10 DATA MANAGEMENT STAFF

B3.10.1 There shall be data management staff sufficient to comply with B9.

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

B3.11 SUPPORT SERVICES STAFF

B3.11.1 The Clinical Program shall have one (1) or more designated staff with appropriate training and education to assist in the provision of pre-transplant cellular therapy recipient evaluation, treatment, and post-therapy follow-up. Designated staff shall include:

B3.11.1.1 Dietary staff.

B3.11.1.2 Social Services staff.

B3.11.1.3 Psychology services staff.

B3.11.1.4 Physical therapy staff.

B4: QUALITY MANAGEMENT

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

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

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

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

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.

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

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 each position.

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

B4.4.2.1 Initial qualifications.

B4.4.2.2 New employee orientation.

B4.4.2.3 Initial training, competency, and retraining when appropriate for all procedures performed, and in accordance with Applicable Law.

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

B4.4.2.5 Annual training in applicable current GxP appropriate to the processes performed in accordance with Applicable Law.

B4.4.2.6 Continuing education.

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

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, Standard Operating Procedures, Manuals, and Guidelines.

B4.5.1.2 Worksheets.

B4.5.1.3 Forms.

B4.5.1.4 Labels.

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

B4.5.3 The document control system shall include:

B4.5.3.1 A standardized format for controlled documents.

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

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

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

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

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 change as applicable, effective date, and archival date.

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

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

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

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.

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.~~

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

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 safety and efficacy to verify that the procedures in use consistently provide a safe and effective product.

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.

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.

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

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

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

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

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

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

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

B4.7.3.7 Central venous catheter infection.

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

B4.7.5 The Clinical Program should achieve one-year survival outcome within or above the expected range when compared to national or international outcome data.

B4.7.5.1 If expected one-year survival outcome is not met, the Clinical Program shall implement a Corrective Action Plan that meets FACT or JACIE requirements.

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

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

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

B4.8.2 The results of Clinical Program audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions in a timely manner.

B4.8.3 Clinical Program audits shall be performed annually at a minimum, and shall include at least the following:

B4.8.3.1 Audit of the accuracy of the clinical data, including, but not limited to, the data contained in the Transplant Essential Data Forms and the Adoptive Cellular Therapies Initiatives of the Center for International Blood and Marrow Transplant Research (CIBMTR) or the Data Collection Forms of the EBMT.

B4.8.3.2 Donor screening and testing.

B4.8.3.3 Documentation of donor eligibility determination prior to start of the collection procedure.

B4.8.3.4 Management of cellular therapy products with positive microbial culture results.

B4.8.3.5 Safety endpoints and immune effector cellular therapy toxicity management.

B4.8.3.6 Documentation that each external facility performing critical contracted services has met the requirements of the written agreements.

B4.8.3.7 Verification of chemotherapy drug administered against the written order.

B4.8.3.8 Prescription ordering system against the protocol.

B4.8.3.9 Incidence and management of hospital acquired infections.

B4.8.4 Additional audits shall be performed periodically.

B4.8.4.1 Verification of accurate patient/donor identity.

B4.8.4.2 Timely receipt of complete collection prescription and medical information to ensure donor safety.

B4.8.4.3 Environmental monitoring to include temperature, humidity, facility cleaning, and prevention of contamination and cross-contamination.

B4.8.4.4 Staff training and competency.

B4.8.5 Additional audits shall be performed as part of follow-up of occurrences.

B4.8.6 There shall be policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency.

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 that address 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, collection staff, processing staff, and any other facility in receipt of the cellular therapy product and if relevant, the donor and the sponsor.

B4.9.3 Recipient follow-up and outcome analysis.

B4.9.4 Donor follow-up, if relevant.

B4.9.5 Documentation and investigation of cause.

B4.9.6 Reporting to regulatory agencies as required by Applicable Law.

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, incidents, and complaints). The following activities shall be included at a minimum:

B4.10.1 Detection.

B4.10.2 Investigation.

B4.10.2.1 A thorough and timely investigation shall be conducted by the Clinical Program in collaboration with the Collection Facility, Processing Facility, and other entities involved in the manufacture of the cellular therapy product, as appropriate.

B4.10.2.2 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.

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) including the unique identifier for the product involved, as applicable, 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 include written investigation reports containing conclusions, root-cause analysis, follow-up, corrective and preventive actions, and a link to the records of the involved cellular therapy products, donors, and recipients, if applicable.

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 Occurrence Report 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 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, sponsors, Institutional Biosafety Committees (IBCs), Institutional Review Boards (IRBs), or Ethics Committees.

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.

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.

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.

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, drugs, supplies, reagents, facilities, and services.

B4.13.1 Critical equipment, software, supplies, reagents, and facilities used for cellular therapy collection procedures shall be qualified.

B4.13.1.1 Qualification shall be required following any significant changes to these items.

B4.13.1.2 Qualification plans shall include minimum acceptance criteria for performance.

B4.13.1.3 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.

B4.14.1 Critical procedures to be validated shall include at least the following: collection procedures, testing, labeling, storage, distribution, preparation for administration, and infusion.

B4.14.2 Validation studies for a procedure shall be retained at a minimum until the procedure is no longer in use.

B4.14.3 Each validation or verification shall include at a minimum:

B4.14.3.1 An approved plan, including conditions to be assessed.

B4.14.3.2 Acceptance criteria.

B4.14.3.3 Data collection.

B4.14.3.4 Evaluation of data.

B4.14.3.5 Summary of results.

B4.14.3.6 References, if applicable.

B4.14.3.7 Review and approval of the plan, report, and conclusion by the Quality Manager and the Clinical Program Director.

B4.14.4 Significant changes to critical procedures shall be validated and 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 elsewhere in the operation.

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

B4.16 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining and reviewing feedback and taking action when appropriate.

B4.16.1 Feedback shall be obtained from associated Collection and Processing Facilities.

B4.16.2 Feedback shall be obtained from donors and recipients or legally authorized representatives.

B4.17 The Clinical Program Director shall review the quality management activities with representatives in key positions in all elements of the cellular therapy program, at a minimum, quarterly.

B4.17.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

B4.17.2 Performance data and review findings shall be reported to key positions and staff.

B4.17.3 The Clinical Program Director shall not have oversight of their own work if this person also performs other tasks in the Clinical Program.

B4.18 The Clinical Program Director shall annually review the effectiveness of the Quality Management Program.

B4.18.1 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

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:

B5.1.1 Donor and recipient confidentiality.

B5.1.2 Recipient evaluation, selection, and treatment across the continuum of cellular therapy care.

B5.1.3 Donor and recipient informed consent related to treatment and cellular therapy product collection, storage, and disposition.

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

B5.1.5 Management of donors and recipients who require central venous access.

B5.1.6 Administration of the preparative regimen.

B5.1.7 Administration of cytotoxic and immunosuppressive therapy.

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

B5.1.9 Management of ABO-incompatible cellular therapy products including indications for red blood cell or plasma reduction.

B5.1.10 Care of immunocompromised recipients.

B5.1.11 Administration of blood products.

B5.1.12 Management of complications of transplant and other cellular therapy, including cytokine release syndrome, neurologic syndromes, and IEC-HS.

B5.1.13 Monitoring patients following cellular therapy product administration, including recognition of cellular therapy complications and emergencies requiring rapid notification of the responsible clinical team.

B5.1.14 Provision of appropriate long-term follow-up care.

B5.1.15 Duration and conditions of cellular therapy product storage and indications for disposal.

B5.1.16 Data management.

B5.1.17 Hygiene and use of personal protective equipment and attire.

B5.1.18 Handling and disposal of medical and biohazard waste.

B5.1.19 Clinical Programs utilizing genetically modified cellular therapy products shall incorporate or reference institutional or regulatory requirements relating to biosafety practices, including handling and disposal.

B5.1.20 Cellular therapy emergency and disaster plan, including the Clinical Program response.

B5.1.21 Chain of Identity.

B5.1.22 Chain of Custody.

B5.2 The Clinical Program shall maintain a detailed list of all controlled documents, including title and identifier.

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:

B5.3.1 A clearly written description of the objectives.

B5.3.2 A description of equipment and supplies used.

B5.3.3 Acceptable endpoints and the range of expected results.

B5.3.4 A stepwise description of the procedure.

B5.3.5 Reference to other policies or Standard Operating Procedures required to perform the procedure.

B5.3.6 Age and weight-specific issues where relevant.

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

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

B5.3.9 Documented approval of each procedural modification by the Clinical Program Director or designated physician prior to implementation.

B5.3.10 Reference to a current version of orders, worksheets, reports, labels, and forms.

B5.4 Controlled documents relevant to the processes being performed shall be readily available to the facility staff.

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

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

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

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

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

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

B6.1.2 There shall be written criteria for each collection site that define the level of donor acuity and risks that can be safely managed.

B6.1.2.1 Allogeneic and autologous donors shall be collected at a collection site with the appropriate capabilities to manage the level of acuity and risks from comorbidities.

B6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT FOR COLLECTION

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

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 or donor's specimens to protect the health of the donor and the recipient.

B6.2.1.4 The rights of the donor or legally authorized representative to review the results of such tests according to Applicable Law.

B6.2.1.5 Protection of medical information and confidentiality.

B6.2.1.6 Alternative collection methods.

B6.2.2 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.

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.

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

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.

B6.2.6 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.

B6.2.6.1 There should be a process to obtain appropriate assent from minor donors.

B6.2.7 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient or recipient's physician.

B6.2.8 The donor shall be informed of the policy for cellular therapy product storage, discard, or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product.

B6.2.9 Documentation of consent shall be available to the Collection Facility 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.

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.

B6.3.1.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

B6.3.1.3 Autologous donors shall be evaluated and tested as required by Applicable Law.

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

B6.3.2.1 Possible need for central venous access.

B6.3.2.2 Mobilization for collection of HPC, Apheresis.

B6.3.2.3 Anesthesia for collection of HPC, Marrow.

B6.3.3 The donor shall be evaluated for the risk of hemoglobinopathy, and if indicated, tested.

B6.3.3.1 The evaluation shall occur prior to donor selection.

B6.3.3.2 The evaluation shall be verified prior to collection or administration of the mobilization regimen, if used.

B6.3.4 Appropriate mobilization should be used for the disease being treated and for the donor being collected.

B6.3.5 A pregnancy test shall be performed for all donors with childbearing potential within seven (7) days prior to starting the donor mobilization regimen or undergoing anesthesia, and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.

B6.3.5.1 For collections without mobilization, a pregnancy test shall be performed within seven (7) days prior to collection.

B6.3.6 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, certified, or licensed in accordance with Applicable Law.

B6.3.7 The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.

B6.3.8 There shall be a written order from a physician specifying, at a minimum, anticipated date and goals of collection and processing.

B6.3.9 Collection from a donor who does not meet donor suitability criteria shall require documentation of the rationale for donor selection by the donor's physician and approval by the Collection Facility Medical Director.

B6.3.9.1 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff prior to collection.

B6.3.10 There shall be written guidelines for communication between the Clinical Program and the Collection Facility or registry for the management of collection-related complications.

B6.3.11 There shall be policies or Standard Operating Procedures for follow-up of donors that include routine management and the management of collection-associated adverse events.

B6.3.11.1 There shall be a process to track and trend collection-associated adverse events.

B6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

B6.4.1 Written criteria shall include criteria for the selection of allogeneic donors when more than one (1) donor is available and suitable.

B6.4.2 Information regarding the donation process should be provided, including the considerations for donation, to the potential allogeneic donor prior to HLA typing.

B6.4.3 A donor advocate shall be available to represent allogeneic donors who are minors or who do not have capacity to give consent, as those terms are defined by Applicable Law.

B6.4.4 Allogeneic donor infectious disease testing shall be performed using donor screening tests licensed, approved, or cleared by the governmental authority.

B6.4.5 Allogeneic donors and allogeneic recipients shall be tested for ABO group and Rh type using two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

B6.4.6 A red blood cell antibody screen shall be performed on allogeneic recipients.

B6.4.7 Allogeneic donors shall be evaluated for risk factors that might result in disease transmission from the cellular therapy product by medical history, physical examination, examination of relevant medical records, and laboratory testing.

B6.4.8 The medical history for allogeneic donors shall include at least the following:

B6.4.8.1 Vaccination history.

B6.4.8.2 Travel history.

B6.4.8.3 Blood transfusion history.

B6.4.8.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the applicable governmental authority.

B6.4.8.5 Questions to identify persons at risk of transmitting inherited conditions.

B6.4.8.6 Questions to identify persons at risk of transmitting a hematological or immunological disease.

B6.4.8.7 Questions to identify a past history of malignant disease.

B6.4.8.8 Allogeneic donors shall confirm that all the information provided is true to the best of their knowledge.

B6.4.9 Allogeneic donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests required by Applicable Law.

B6.4.9.1 Human immunodeficiency virus, type 1.

B6.4.9.2 Human immunodeficiency virus, type 2.

B6.4.9.3 Hepatitis B virus.

B6.4.9.4 Hepatitis C virus.

B6.4.9.5 *Treponema pallidum* (syphilis).

B6.4.10 If required by Applicable Law, allogeneic donors shall also be tested for evidence of clinically relevant infection by the following disease agents:

B6.4.10.1 Human T cell lymphotropic virus I.

B6.4.10.2 Human T cell lymphotropic virus II.

B6.4.10.3 West Nile Virus.

B6.4.10.4 *Trypanosoma cruzi* (Chagas Disease).

B6.4.11 Blood samples for testing for evidence of clinically relevant infection shall be drawn and tested within timeframes required by Applicable Law.

B6.4.11.1 Blood samples from allogeneic donors of HPC, Apheresis or HPC, Marrow for communicable disease testing shall be obtained within thirty (30) days prior to collection.

B6.4.11.2 For viable lymphocyte-rich cells, including mononuclear cells and other cellular therapy products, blood samples from allogeneic donors shall be obtained within seven (7) days prior to or after collection, or in accordance with Applicable Law.

B6.4.12 Allogeneic donors shall be tested for cytomegalovirus unless previously documented to be positive.

B6.4.13 Additional tests shall be performed as required to assess the possibility of transmission of other infectious and non-infectious diseases.

B6.4.14 Allogeneic donors and recipients shall be tested for HLA alleles by a laboratory accredited by ASHI, EFI, CAP, or other appropriate organization. Typing shall include at a minimum HLA-A, B, and DRB1 type for all allogeneic donors and also HLA-C type for unrelated allogeneic donors and related allogeneic donors other than siblings.

B6.4.14.1 DNA high resolution molecular typing shall be used for HLA typing.

B6.4.14.2 Verification typing shall be performed on the recipient and selected allogeneic donor using independently collected samples. Results shall be confirmed prior to administration of the preparative regimen, mobilization, or cellular therapy product collection, whichever is earliest.

B6.4.14.3 There shall be a policy or Standard Operating Procedure to confirm the identity of cord blood units if verification typing cannot be performed on attached segments.

B6.4.14.4 There shall be a policy or Standard Operating Procedure for anti-HLA antibody testing for mismatched donors and recipients.

B6.4.15 Allogeneic donor eligibility, as defined by Applicable Law, shall be determined by a licensed health care provider after history, exam, medical record review, and testing. The donor eligibility determination shall be documented in the recipient's medical record before the recipient's preparative regimen is initiated and before the allogeneic donor begins the mobilization regimen.

B6.4.16 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

B6.4.17 The use of an ineligible allogeneic donor, or an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of the rationale for their selection by the transplant physician, urgent medical need, and the informed consent of the donor and the recipient.

B6.4.18 Allogeneic donor eligibility shall be communicated in writing to the Collection and Processing Facilities.

B6.5 There shall be a policy for the creation and retention of allogeneic donor records.

B6.5.1 Allogeneic donor eligibility and suitability determination, including the name of the responsible person who made the determination and the date of the determination.

B6.5.2 Donor identification including at least name and date of birth.

B6.5.3 Age, sex at birth, and medical history, and, for allogeneic donors, behavioral history.

B6.5.4 Consent to donate.

B6.5.5 Results of laboratory testing.

B7: RECIPENT CARE

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

B7.1.1 The informed consent process shall include information regarding the risks and benefits of the proposed cellular therapy.

B7.1.2 For a cellular therapy product collected for a specific recipient, informed consent of the recipient for the therapy shall be obtained before collection of the product.

B7.2 The attending physician shall confirm the availability and suitability of a donor or cellular therapy product prior to initiating the recipient's preparative regimen.

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.

B7.3 Records shall be made concurrently with each step of recipient care in such a way that all steps may be accurately traced.

B7.3.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate, of various steps.

B7.4 There shall be policies addressing safe administration of the preparative regimen.

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.

B7.4.2 Preprinted orders or electronic equivalent shall be used for protocols and standardized regimens. These orders shall be verified and documented by an attending physician.

B7.4.3 The pharmacist verifying or preparing the drug shall check and document the dose against the protocol or standardized regimen listed on the orders.

B7.4.4 Prior to administration of the preparative regimen, one (1) qualified person using a validated process or two (2) qualified persons shall verify and document:

B7.4.4.1 The drug and dose in the bag or pill against the orders and the protocol or standardized regimen.

B7.4.4.2 The identity of the recipient.

B7.5 There shall be policies addressing safe administration of radiation therapy.

B7.5.1 There shall be a consultation with a radiation oncologist prior to initiation of therapy if radiation treatment is used in the preparative regimen.

B7.5.2 The recipient's diagnosis, relevant medical history including pre-existing co-morbid conditions, and proposed preparative regimen shall be made available to the consulting radiation oncologist in writing.

B7.5.3 A documented consultation by a radiation oncologist shall address any prior radiation treatment the recipient may have received, any other factors that may increase the toxicity of the radiation, and include a plan for delivery of radiation therapy.

B7.5.4 Prior to administration of each dose of radiation therapy, the dose shall be verified and documented as per institutional radiation therapy standards.

B7.5.5 A final report of the details of the radiation therapy administered shall be documented in the recipient's medical record.

B7.6 There shall be policies addressing safe administration of cellular therapy products.

B7.6.1 There shall be policies for determining the appropriate volume and the appropriate dose of red blood cells, cryoprotectants, and other additives.

B7.6.2 There shall be policies for the infusion of ABO-mismatched red blood cells in allogeneic cellular therapy products.

B7.6.3 There shall be policies for preparation and administration of cellular therapy products according to manufacturer specifications, including thawing and dosing.

B7.6.4 There shall be consultation with the Processing Facility regarding cord blood preparation for administration.

B7.6.4.1 Cord blood units that have not been red blood cell reduced prior to cryopreservation shall be washed prior to administration.

B7.6.4.2 Cord blood units that have been red blood cell reduced prior to cryopreservation should be diluted or washed prior to administration.

B7.6.5 Two (2) qualified persons shall verify the identity of the recipient and the product and the order for administration prior to the administration of the cellular therapy product.

B7.6.6 When administering cellular therapy products from more than one (1) donor, each cellular therapy product shall be administered safely prior to administration of subsequent cellular therapy products.

B7.6.7 There shall be documentation in the recipient's medical record of the unique identifier of each cellular therapy product and dose administered, initiation and completion times of administration, and any adverse events related to administration.

B7.6.8 A Circular of Information, Investigator's Brochure, or other product-specific information for cellular therapy products shall be available to staff.

B7.7 There shall be policies or Standard Operating Procedures addressing appropriate follow-up of recipients after administration of preparative regimens and cellular therapy products, including, at a minimum:

B7.7.1 Management of nausea, vomiting, pain, and other discomforts.

B7.7.2 Monitoring of blood counts and transfusion of blood products.

B7.7.3 Monitoring of infections and use of antimicrobials.

B7.7.4 Monitoring of organ dysfunction or failure and institution of treatment.

B7.7.5 Monitoring of graft failure, prolonged cytopenia, and institution of treatment.

B7.7.6 Regular assessment for evidence of acute GVHD using an established staging and grading system.

B7.7.7 Regular assessment for evidence of chronic GVHD using an established staging and grading system.

B7.8 There shall be policies and Standard Operating Procedures addressing the administration of immune effector cells and management of complications, including the use of cytokine-blocking agents and corticosteroid administration.

B7.8.1 There shall be a consultation with the referring physician prior to initiation of immune effector cellular therapy to review the goal and plan of the treatment.

B7.8.2 There shall be regular assessment of the recipient to detect complications, including cytokine release syndrome and neurologic dysfunction.

B7.8.3 There shall be a written plan for rapid escalation of care, increased intensity of monitoring, and relevant workup to address complications.

B7.8.3.1 Communication to the clinical staff, intensive care unit, emergency department, and pharmacy shall be timely.

B7.9 There shall be policies or Standard Operating Procedures in place for planned discharges and provision of post-transplant or post-cellular therapy care.

B7.9.1 When a recipient is discharged prior to engraftment or recovery of peripheral blood cell counts, the Clinical Program shall verify that the following elements are available:

B7.9.1.1 A consult between the attending physician and the receiving health care professionals regarding the applicable elements in Standard B7.7.

B7.9.1.2 Facilities that provide appropriate location, adequate space, and protection from airborne or surface microbial contamination.

B7.9.1.3 Appropriate medications, blood products, and additional care required by the recipient.

B7.9.2 The Clinical Program shall provide appropriate instructions to recipients prior to discharge.

B7.9.2.1 There shall be a means to provide transplant and cellular therapy-specific instructions for post-discharge care to the recipient, caregivers, and other health care providers who may provide care.

B7.10 There shall be policies addressing indications for and safe administration of ECP if utilized by the Clinical Program.

B7.10.1 There shall be a consultation with the facility or physician that performs ECP prior to initiation of therapy.

B7.10.2 Before ECP is undertaken, there shall be a written therapy plan from an attending physician specifying the patient's diagnosis and GVHD grade, involved organs, timing of the procedure, and any other factors that may affect the safe administration of ECP.

B7.10.3 A report of the details of ECP administered, including an assessment of the response, shall be documented in the recipient's medical record.

B7.10.4 The facility performing ECP shall be qualified to meet FACT-JACIE requirements.

B7.11 There shall be an infrastructure and policies or Standard Operating Procedures in place for provision of appropriate long-term follow-up, treatment, and plans of care.

B7.11.1 There shall be policies or Standard Operating Procedures in place for post-transplant vaccination schedules and indications.

B7.11.2 There should be policies or Standard Operating Procedures in place for psychosocial follow-up care

B7.11.3 There shall be policies and Standard Operating Procedures for monitoring by appropriate specialists of recipients for post-cellular therapy late effects, including at a minimum:

B7.11.3.1 Endocrine and reproductive function and osteoporosis.

B7.11.3.2 Cardiovascular risk factors.

B7.11.3.3 Respiratory function.

B7.11.3.4 Chronic renal impairment.

B7.11.3.5 Secondary malignancies.

B7.11.3.6 Growth and development of pediatric patients.

B7.11.3.7 Assessment for psychosocial needs.

B7.11.4 There shall be policies or Standard Operating Procedures describing the transition of long-term pediatric recipients to adult care as appropriate.

B8: CLINICAL RESEARCH

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

B8.1.1 Those Clinical Programs utilizing investigational treatment protocols shall have 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 conducted in accordance with institutional policies and Applicable Law.

B8.2.1 The Clinical Program shall maintain:

B8.2.1.1 Documentation of approval by the Institutional Review Board, Ethics Committee, or equivalent.

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

B8.2.1.3 Correspondence with regulatory agencies.

B8.2.1.4 Audits and any adverse events, including their resolution.

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

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

B8.3.2 Informed consent for a research subject shall contain the following elements at a minimum and comply with Applicable Law:

B8.3.2.1 An explanation of the research purposes, a description of the procedures to be followed, and the identification of investigational procedures.

B8.3.2.2 The expected duration of the subject's participation.

B8.3.2.3 A description of the reasonably expected risks, discomforts, benefits to the subject and others, and alternative procedures.

B8.3.2.4 A statement of the extent to which confidentiality will be maintained.

B8.3.2.5 An explanation of the extent of compensation for injury.

B8.3.2.6 A statement whether the participant will receive compensation for participating in the study or if it will cost the participant to be in the study.

B8.3.2.7 A statement stating who is sponsoring the study.

B8.3.2.8 A statement of whether there is a potential conflict of interest.

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.

B9: DATA MANAGEMENT

B9.1 The Clinical Program shall collect and maintain complete and accurate data necessary to complete the Transplant Essential Data Forms of the CIBMTR or the Data Collection Forms of the EBMT.

B9.1.1 Clinical Programs shall submit the data specified in B9.1 for allogeneic and autologous transplants to a national or international database.

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

B9.1.3 Clinical Programs should meet accuracy criteria established by FACT or JACIE, and CIBMTR or EBMT.

B9.1.3.1 If data accuracy criteria are not met, the program shall implement a corrective action plan that meets FACT or JACIE requirements.

B9.2 The Clinical Program should collect and submit all data elements included in the Adoptive Cellular Therapies Initiative forms of the CIBMTR or the Data Collection Forms of the EBMT.

B9.3 The Clinical Program shall define staff responsible for collecting data and, as appropriate, reporting data to institutional repositories and CIBMTR or EBMT.

B10: RECORDS

B10.1 There shall be a records management system for quality and cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

B10.1.1 A records management system shall be established and maintained to facilitate the review of records.

B10.1.2 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor

B101.3 Records shall be maintained to ensure their integrity, preservation, and retrieval.

B10.1.4 Records shall be accurate and legible.

B10.1.5 Written records shall be indelible.

B10.1.6 Safeguards to secure the confidentiality of all records and communications among the collection staff, processing, and clinical facilities, and health care providers and their recipients and donors, shall be established and followed in compliance with Applicable Law.

B10.2 The Clinical Program shall define and follow good documentation practices.

B10.3 RECORDS TO BE MAINTAINED

B10.3.1 Clinical Program records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years, after the creation of the cellular therapy product record, date of the cellular therapy product's distribution, disposition, or expiration, or, whichever is latest or according to Applicable Law.

B10.3.2 Employee records shall be maintained by the Clinical Program in a confidential manner and as long as required by Applicable Law.

B10.3.3 Cleaning and sanitation records shall be retained for at least three (3) years or longer in accordance with Applicable Law or regulations, or by a defined program or institution policy.

B10.3.4 Records to allow tracking and tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, or as required by Applicable Law, whichever is latest. 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.

B10.3.5 Recipient and donor records including, but not limited to, consents and records of care, shall be maintained in a confidential manner as required by Applicable Law for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, whichever date is latest.

B10.3.6 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 date is latest.

B10.4 ELECTRONIC RECORDS

B10.4.1 The Clinical Program shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum, systems that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures. For all critical electronic record systems:

B10.4.1.1 There shall be policies, Standard Operating Procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

B10.4.1.2 There shall be a means by which access is limited to authorized individuals.

B10.4.1.3 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

B10.4.1.4 There shall be written Standard Operating Procedures for record entry, verification, and revision.

B10.4.1.5 A method shall be established, or the system shall provide for review of data before final acceptance.

B10.4.1.6 There shall be documented training of personnel in the system's use.

B10.4.1.7 There shall be a defined process for continued competency of personnel in the system's use.

B10.4.1.8 The utilization of electronic signatures shall be defined.

B10.4.1.9 Critical electronic record systems shall maintain unique identifiers.

B10.4.1.10 There shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

B10.4.1.11 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

B10.4.1.12 All system modifications shall be authorized, documented, and validated prior to implementation.

B10.4.2 For all critical electronic record systems under the control of the Facility, there shall be validated processes for and documentation of:

B10.4.2.1 Prospective validation of systems, including hardware, software, and databases.

B10.4.2.2 Installation of the system.

B10.4.2.3 Numerical designation of system versions, if applicable.

B10.4.2.4 Authorization, documentation, and validation of all system modifications prior to implementation.

B10.4.2.5 Systems development including the verification of calculations and algorithms.

B10.4.2.6 System maintenance and operations.

B10.4.2.7 Monitoring of data integrity.

B10.4.2.8 Back-up of the electronic records system on a regular schedule.

B10.4.3 For each critical electronic record system, there shall be an alternative system to allow for continuous operation of the Clinical Program if the critical electronic record system is not available. The alternative system shall be validated, and clinical personnel shall be trained in its use.

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 to other facilities involved in the collection or processing of the cellular therapy product.

PART C: COLLECTION FACILITY STANDARDS

C1: General

C2: Collection Facility

C3: Personnel

C4: Quality Management

C5: Policies and Standard Operating Procedures

C6: Allogeneic and Autologous Donor Evaluation and Management

C7: Coding and Labeling of Cellular Therapy Products

C8: Equipment, Supplies and Reagents

C9: Process Controls

C10: Cellular Therapy Product Storage

C11: Cellular Therapy Product Transportation and Shipping

C12: Records

~~C12: Direct Distribution to Clinical Program~~

PART C: COLLECTION FACILITY STANDARDS

C1: GENERAL

C1.1 These Standards apply to all collection, storage, and distribution activities performed in the Collection Facility for cellular therapy products.

C1.2 The Collection Facility shall abide by Applicable Law.

C1.2.1 The Collection Facility shall be licensed, registered, or accredited as required by the appropriate governmental authorities for the activities performed.

C1.3 The Collection Facility shall have a Collection Facility Director, a Collection Facility Medical Director, a Quality Manager, and a minimum of one (1) additional designated staff member. The designated team shall have been in place and performing cellular therapy product collections for at least twelve (12) months preceding initial accreditation.

C1.4 The Collection Facility shall use cell processing facilities that meet FACT-JACIE Standards with respect to its interactions with the Collection Facility.

C1.5 There shall be a process to qualify the sites for cellular collections, including at a minimum Chain of Identity.

C1.6 The Collection Facility shall meet the minimum number of cellular therapy collections as defined in Appendix I.

C1.7 There shall be written criteria for each collection site that define the level of donor acuity and risks that can be safely managed.

C2: COLLECTION FACILITY

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

C2.1.1 The designated area for collection shall be in an appropriate location of adequate space and design to minimize the risk of microbial contamination.

C2.1.2 The collection area shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

C2.1.3 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of cellular therapy products.

C2.1.4 There shall be suitable space for confidential donor examination and evaluation.

C2.2 The Collection Facility shall provide adequate lighting, ventilation, and access to toilets and sinks for handwashing to prevent the introduction, transmission, or spread of communicable disease.

C2.3 Environmental conditions shall be controlled to protect the safety and comfort of donors and personnel.

C2.4 There shall be a written assessment of critical Collection Facility environmental parameters, including storage areas, that may affect cellular therapy product viability, integrity, contamination, or cross-contamination during collection.

C2.4.1 The written assessment shall include temperature and humidity at a minimum.

C2.4.2 Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.

C2.4.3 If using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled, monitored, and recorded for air quality and surface contaminants.

C2.5 The Collection Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.

C2.6 The Collection Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, caregivers, and volunteers.

C2.7 The Collection Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease and to chemical, biological, radiological, electrical, or fire hazards.

C2.8 All waste generated by the Collection Facility's activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with Applicable Law.

C2.9 There shall be a written policy for personal hygiene and the use of personal protective equipment and attire.

C2.9.1 The policy shall define the protective clothing to be worn upon entering the work area and working within it.

C2.9.2 The policy shall define personal protective equipment of the appropriate grade for the risk, to be worn while handling biological specimens.

C2.9.3 Such personal protective equipment shall not be worn outside the designated work area.

C2.10 There shall be access to an intensive care unit or emergency services.

C3: PERSONNEL

C3.1 COLLECTION FACILITY DIRECTOR

C3.1.1 There shall be a Collection Facility Director with a degree in a relevant science, with a minimum of two (2) years of experience, including relevant operational experience, in management and oversight of the Collection Facility.

C3.1.1.1 The Apheresis Collection Facility Director shall have performed or supervised a minimum of five (5) cellular therapy product apheresis collection procedures in the twelve (12) months preceding initial accreditation and a minimum average of five (5) cellular therapy product apheresis collection procedures per year within each accreditation cycle.

C3.1.1.2 The Marrow Collection Facility Director shall has performed a minimum of 10 (ten) marrow harvests lifetime and a minimum of one in the past 12 (twelve) months.

C3.1.1.3 The Collection Facility Director for Other Tissue shall have performed a tissue collection procedure.

C3.1.2 The Collection Facility Director shall be responsible for all Standard Operating Procedures, technical procedures, performance of the collection procedure(s), supervision of staff, administrative operations, and the Quality Management Program, including compliance with these Standards and Applicable Law.

C3.1.3 The Collection Facility Director shall participate in a minimum of ten (10) hours of educational activities annually.

C3.1.3.1 The Apheresis Collection Facility Director shall participate in educational activities related to the field of HPC transplantation, Quality Management, or cellular therapy.

C3.1.3.2 The Marrow Collection Facility Director shall participate in educational activities related to the field of HPC transplantation, Quality Management, or cellular therapy.

C3.1.3.3 The Collection Facility Director for Other Tissue shall participate in educational activities related to the field of cellular therapy, Quality Management, or relevant therapeutic disease areas.

C3.2 COLLECTION FACILITY MEDICAL DIRECTOR

C3.2.1 There shall be a Collection Facility Medical Director who is a licensed physician with a minimum of two (2) years postgraduate education, with training and practical and relevant experience in cellular therapy product collection, transplantation, and administration.

C3.2.1.1 For Other Tissues, there shall be a Medical Director who is a licensed physician with postgraduate training in the methods required for cellular therapy product collection or diseases treated by cellular therapy products.

C3.2.2 The Collection Facility Medical Director shall be directly responsible for the medical care of donors undergoing collection including:

C3.2.2.1 All technical procedures.

C3.2.2.2 Performance of the collection procedures.

C3.2.2.3 The medical care of donors undergoing product collections.

C3.2.2.4 Pre-collection evaluation of allogeneic and autologous donors at the time of donation.

C3.2.2.5 Evaluation of donors before, during, and after the donation.

C3.2.2.6 Care of any complications resulting from the collection procedure.

C3.2.3 The Collection Facility Medical Director for Apheresis shall have performed or supervised a minimum of five (5) cellular therapy product apheresis collection procedures in the twelve (12) months preceding initial accreditation and a minimum average of five (5) cellular therapy product apheresis collection procedures per year within each accreditation cycle.

C3.2.4 The Collection Facility Medical Director for Bone Marrow shall have performed a minimum of one marrow harvest in the twelve (12) months preceding initial accreditation and a minimum average of one marrow harvest per year within each accreditation cycle.

C3.2.5 The Collection Facility Medical Director shall participate in a minimum of ten (10) hours of educational activities related to the field of HPC transplantation, cell or tissue collection, Quality Management, or cellular therapy annually.

C3.3 QUALITY MANAGER

C3.3.1 There shall be a Collection Facility Quality Manager to establish and maintain systems to review, modify, and approve all policies and Standard Operating Procedures intended to monitor compliance with these Standards or the performance of the Collection Facility.

C3.3.2 The Collection Facility Quality Manager should have a reporting structure independent of cellular therapy product collection.

C3.3.3 The Collection Facility Quality Manager shall participate in a minimum of ten (10) hours of continuing education activities which includes cellular therapy, cell collection, and Quality Management annually.

C3.4 STAFF

C3.4.1 The number of trained and competent collection personnel shall be adequate for the number of procedures performed and shall include a minimum of one (1) designated trained individual with an identified trained and competent backup individual to maintain sufficient coverage.

C3.4.2 For collection activities involving pediatric donors, physicians and collection staff shall have documented training and experience with pediatric donors.

C3.4.3 There shall be attending physician oversight if general medical physicians, physicians-in-training, or APPs provide care to the cellular therapy donors.

C3.4.3.1 The scope of responsibility of general medical physicians, physicians-in-training, or APPs shall be defined.

C4: QUALITY MANAGEMENT

C4.1 There shall be a Quality Management Program that incorporates key performance data.

C4.1.1 The Collection Facility Director shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

C4.1.2 The Collection Facility shall comply with C4 if it operates independently of a Clinical Program.

C4.2 The Collection Facility shall establish and maintain a written Quality Management Plan.

C4.2.1 The Collection Facility Director shall be responsible for the Quality Management Plan.

C4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions, functions, and reporting relationships within the Collection Facility.

C4.3.1 The Quality Management Plan shall include a description of how these key positions interact to implement the quality management activities.

C4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Collection Facility. Personnel requirements shall include at a minimum:

C4.4.1 A current job description for each position.

C4.4.2 A system to document the following for all staff:

C4.4.2.1 Initial qualifications.

C4.4.2.2 New employee orientation.

C4.4.2.3 Initial training, competency, and retraining when appropriate for all procedures performed, and in accordance with Applicable Law.

C4.4.2.4 Continued competency for each critical function performed, assessed annually at a minimum.

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

C4.4.2.6 Continuing education.

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

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, Protocols, Standard Operating Procedures, Manuals, and Guidelines.

C4.5.1.2 Worksheets.

C4.5.1.3 Forms.

C4.5.1.4 Labels.

C4.5.2 There shall be policies or Standard Operating Procedures for the development, approval, implementation, distribution, review, revision, and archival of all controlled documents.

C4.5.3 The document control system shall include:

C4.5.3.1 A standardized format for controlled documents.

C4.5.3.2 Assignment of a numeric or alphanumeric identifier, version, and a title to each controlled document.

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

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

C4.5.3.5 Review of controlled documents every two (2) years at a minimum.

C4.5.3.6 A system for document change control that includes a description of the change, version, the signature of approving individual(s), approval date(s), communication or training on the change as applicable, effective date, and archival date.

C4.5.3.7 A system for archival of controlled documents for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer. The system must include inclusive dates of use and their historical sequence.

C4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

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.

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.

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 accreditation and to comply with these Standards and Applicable Law.

C4.6.3 Agreements shall be established when the Collection Facility provides critical services to external parties.

C4.6.4 Agreements shall be dated and reviewed on a regular basis, at a minimum every two (2) years.

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 safety and efficacy to verify that the procedures in use consistently provide a safe and effective product.

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.

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

C4.7.3 For HPC products intended for hematopoietic reconstitution, time to neutrophil and platelet engraftment following cellular therapy product administration shall be analyzed.

C4.8 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for, and a schedule of, audits of the Collection Facility's activities to verify compliance with elements of the Quality Management Program, policies and Standard Operating Procedures, these Standards, and Applicable Law.

C4.8.1 Collection Facility audits shall be conducted by an individual with sufficient knowledge in the process and competence in auditing to identify problems, but who is not solely responsible for the process being audited.

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

C4.8.3 Audits shall be performed annually at a minimum, and shall include at least the following:

C4.8.3.1 Documentation of interim assessment of donor suitability and eligibility prior to the start of the collection procedure.

C4.8.3.2 Documentation of donor eligibility determination prior to start of the collection procedure.

C4.8.3.3 Management of cellular therapy products with positive microbial culture results.

C4.8.3.4 Documentation that each external facility performing critical contracted services has met the requirements of the written agreement.

C4.8.4 Additional audits shall be performed periodically.

C4.8.4.1 Verification of accurate donor identity.

C4.8.4.2 Timely receipt of complete collection prescription and medical information to ensure donor safety.

C4.8.4.3 Critical supplies inventory control.

C4.8.4.4 Equipment maintenance.

C4.8.4.5 Environmental monitoring to include temperature, humidity, facility cleaning, and prevention of contamination and cross-contamination.

C4.8.4.6 Marrow and Other Tissue collection process.

C4.8.4.7 Staff training and competency.

C4.8.5 Additional audits shall be performed as part of follow-up of occurrences.

C4.8.6 There shall be policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency.

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 that address at a minimum:

C4.9.1 Notification of the recipient's physician and any other facility in receipt of the cellular therapy product.

C4.9.2 Donor follow-up, if relevant.

C4.9.3 Documentation and investigation of cause.

C4.9.4 Reporting to regulatory agencies as required by Applicable Law.

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:

C4.10.1 Detection.

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.

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) including the unique identifier for the product involved, as applicable, 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 Collection Facility Director, Medical Director, and Quality Manager.

C4.10.3.3 Cumulative files of occurrences shall be maintained and include written investigation reports containing conclusions, root-cause analysis, follow-up, corrective and preventive actions, and a link to the records of the involved cellular therapy products, donors, and recipients, if applicable.

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 Occurrence Report 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 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, sponsors, Institutional Biosafety Committees, and Institutional Review Boards (IRBs), or Ethics Committees.

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.

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.

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

C4.13 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures qualification of critical manufacturers, vendors, equipment, software, drugs, supplies, reagents, facilities, and services.

C4.13.1 Critical equipment, software, supplies, reagents, and facilities used for cellular therapy product collection procedures shall be qualified.

C4.13.1.1 Qualification shall be required following any significant changes to these items.

C4.13.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

C4.13.3 Qualification plans shall include minimum acceptance criteria for performance.

C4.13.4 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Collection Facility Director.

C4.14 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

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

C4.14.2 Validation studies for a procedure shall be retained at a minimum until the procedure is no longer in use.

C4.14.3 Each validation or verification shall include at a minimum:

C4.14.3.1 An approved plan, including conditions to be assessed.

C4.14.3.2 Acceptance criteria.

C4.14.3.3 Data collection.

C4.14.3.4 Evaluation of data.

C4.14.3.5 Summary of results.

C4.14.3.6 References, if applicable.

C4.14.3.7 Review and approval of the plan, report, and conclusion by the Collection Facility Director and the Quality Manager.

C4.14.4 Significant changes to critical procedures shall be validated and verified as appropriate.

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(s) elsewhere in the operation.

C4.15.1 Evaluation of risk shall be completed for changes in critical procedures.

C4.16 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining and reviewing feedback and taking action when appropriate.

C4.16.1 Feedback shall be obtained from associated Clinical Programs and Processing Facilities.

C4.16.2 Feedback shall be obtained from donors or legally authorized representatives.

C4.17 The Collection Facility Director shall review the quality management activities with representatives in key positions in all areas of the cellular therapy program, at a minimum, quarterly.

C4.17.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

C4.17.2 Performance data and review findings shall be reported to key positions and staff.

C4.17.3 The Collection Facility Director shall not have oversight of their own work if this person also performs other tasks in the Collection Facility.

C4.18 The Collection Facility Director shall annually review the effectiveness of the Quality Management Program.

C4.18.1 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.

C5: POLICIES AND STANDARD OPERATING PROCEDURES

C5.1 The Collection Facility shall establish and maintain policies or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in C4. These documents shall include all elements required by these Standards and shall address at a minimum:

C5.1.1 Donor and recipient confidentiality.

C5.1.2 Donor informed consent for cellular therapy product collection.

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

C5.1.4 Donor age-specific and weight-specific issues where relevant.

C5.1.5 Management of donors who require central venous access.

C5.1.6 Cellular therapy product collection.

C5.1.7 Administration of blood products.

C5.1.8 Prevention of mix-ups and cross-contamination.

C5.1.9 Labeling including associated forms and samples.

C5.1.10 Cellular therapy product expiration dates.

C5.1.11 Cellular therapy product storage, including alternative storage if the primary storage device fails.

C5.1.12 Release and exceptional release.

C5.1.13 Packaging, transportation, and shipping, including methods and conditions within the Collection Facility and to and from external facilities.

C5.1.13.1 Use of additives to the product for long duration of shipment or transportation.

C5.1.14 Cellular therapy product disposal.

C5.1.15 Critical equipment, reagent, and supply management including recalls and corrective actions in the event of failure.

C5.1.16 Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.

C5.1.17 Cleaning and sanitation procedures, including beds, chairs, and operating rooms as applicable, and the identification of the individuals performing the activities.

C5.1.18 Environmental control, as determined in C2.4.2, including a description of the environmental monitoring plan.

C5.1.19 Hygiene and use of personal protective equipment and attire.

C5.1.20 Handling and disposal of medical and biohazard waste.

C5.1.21 Cellular therapy emergency and disaster plan, including the Collection Facility response and product management.

C5.1.22 Extracorporeal photopheresis, if performed by the Collection Facility.

C5.1.23 Chain of Identity.

C5.1.24 Chain of Custody.

C5.2 The Collection Facility shall maintain a detailed list of all controlled documents, including title and identifier.

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:

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.

C5.3.4 A stepwise description of the procedure.

C5.3.4.1 Age and weight-specific issues where relevant.

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C5.3.5 Reference to other policies or Standard Operating Procedures required to perform the procedure.

C5.3.6 A reference section listing appropriate and current literature.

C5.3.7 Documented approval of each Standard Operating Procedure by the Collection Facility Director or Medical Director, as appropriate, prior to implementation and every two (2) years thereafter.

C5.3.8 Documented approval of each procedural modification by the Collection Facility Director or Medical Director, as appropriate, prior to implementation.

C5.3.9 Reference to a current version of orders, worksheets, reports, labels, and forms.

C5.4 Controlled documents relevant to processes being performed shall be readily available to the facility staff.

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

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

C5.7 Planned deviations shall be pre-approved by the Collection Facility Director or Medical Director and reviewed by the Quality Manager.

C6: ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

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

C6.1.1 The donor shall undergo the collection procedure at a site with the appropriate capabilities to manage the level of acuity and risks.

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

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

C6.2.1.1 The risks and benefits of the procedure.

C6.2.1.2 Intent of the collection for treatment or research.

C6.2.1.3 Tests and procedures performed on the donor or donor's specimens to protect the health of the donor and the recipient.

C6.2.1.4 The rights of the donor or legally authorized representative to review the results of such tests according to Applicable Law.

C6.2.1.5 Protection of medical information and confidentiality.

C6.2.1.6 Alternative collection methods.

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

C6.2.2.1 Family members and legally authorized representatives shall not serve as interpreters or translators.

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.

C6.2.5 Donor informed consent for the cellular therapy product collection, including use, storage, and discard, shall be obtained and documented by a licensed health care professional knowledgeable in the collection procedure and the intended use of the product.

C6.2.5.1 Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

C6.2.6 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.

C6.2.7 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient or recipient's physician.

C6.2.8 The donor shall be informed of the policy for cellular therapy product storage, discard, or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product.

C6.2.9 Documentation of consent shall be verified by the Collection Facility staff prior to the collection procedure.

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.

C6.3.1.1 The collection staff shall confirm that clinically significant findings are reported to the donor with documentation in the donor record of recommendations made for follow-up care.

C6.3.1.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

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

C6.3.2 The risks of collection shall be evaluated and documented, including:

C6.3.2.1 Possible need for central venous access.

C6.3.2.2 Mobilization for collection of HPC, Apheresis.

C6.3.2.3 Anesthesia for collection of HPC, Marrow.

C6.3.2.4 Other donor specific risks

C6.3.3 The donor shall be evaluated for the risk of hemoglobinopathy, and if indicated, tested.

C6.3.3.1 The evaluation shall be verified prior to collection or administration of the mobilization regimen, if used.

C6.3.4 For all donors with childbearing potential, a pregnancy test shall be performed within seven (7) days prior to starting the donor mobilization regimen or undergoing anesthesia, and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.

C6.3.4.1 For collections without mobilization, a pregnancy test shall be performed within seven (7) days prior to cellular therapy collection.

C6.3.5 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, certified, or licensed in accordance with Applicable Law.

~~C6.3.6 The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.~~

C6.3.6 The Collection Facility shall verify that appropriate donor suitability has been determined.

C6.3.7 Collection from a donor who does not meet collection suitability criteria shall require documentation of the rationale for selection by the donor's physician and approval by the Collection Facility Medical Director. Collection staff shall document review of these donor safety issues.

C6.3.8 If central venous access is required, the rationale shall be documented in the donor's records.

C6.3.9 Adequacy of central line placement shall be verified and documented by the Collection Facility staff prior to initiating each collection procedure.

C6.3.10 There shall be policies or Standard Operating Procedures for the management of collection-associated adverse events and follow-up of donors.

C6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

C6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who do not have capacity to consent, as those terms are defined by Applicable Law.

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 shall be assessed and acceptance criteria shall be defined.

C6.4.3 Collection staff shall comply with B6.4.8 ~~through B6.4.8.8~~ when primarily responsible for donor screening for transmissible disease.

C6.4.4 Collection staff shall comply with B6.4.9 through B6.4.13 when primarily responsible for infectious and non-infectious disease testing of donors.

C6.4.5 Collection staff shall comply with B6.4.4, B6.4.5~~, B6.4.6~~, and B6.4.14 through B6.4.14.4 when primarily responsible for testing for the selection of allogeneic donors.

C6.4.6 Collection staff shall confirm that allogeneic donor eligibility determination was performed prior to collection, starting the donor mobilization regimen, or initiation of the recipient's preparative regimen.

C6.4.7 Collection of a cellular therapy product from an ineligible allogeneic donor, or from an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of urgent medical need that includes the rationale for the selection and documentation of the informed consent of the donor and the recipient.

C6.4.8 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

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

C6.4.10 Allogeneic blood products administered to the donor during apheresis collection or used during priming procedures shall be CMV-appropriate and irradiated or equivalent prior to transfusion.

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

C6.5.1 Allogeneic donor eligibility and suitability determination, including the name of the responsible person who made the determination and the date of the determination.

C6.5.2 Donor identification including at least name and date of birth.

C6.5.3 Age, sex at birth, and medical history, and, for allogeneic donors, behavioral history.

C6.5.4 Consent to donate.

C6.5.5 Results of laboratory testing.

C7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

C7.1 ISBT 128 AND EUROCODE CODING AND LABELING

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

C7.1.2 Coding and labeling technologies shall be implemented using ISBT 128 or Eurocode.

C7.1.3 Cellular therapy collections for further manufacturing should be labeled with the ISBT Hybrid Label in accordance with ISBT 128 Standard ST-018.

C7.2 LABELING OPERATIONS

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

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

C7.2.1.2 Obsolete labels shall be restricted from use.

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

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.

C7.2.4 Label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Collection Facility Director.

C7.2.5 A system for label version control shall be employed.

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.

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.

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.

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.

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.

C7.2.9 All data fields on labels shall be completed.

C7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

C7.2.11 Labels affixed directly to a cellular therapy product bag or container shall be applied using appropriate materials as defined by the applicable regulatory authority.

C7.2.12 The label shall be validated as reliable for storage under the conditions in use.

C7.3 PRODUCT IDENTIFICATION

C7.3.1 Each cellular therapy product collection shall be assigned a unique numeric or alphanumeric donation identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.

C7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected donor samples shall be labeled with the same identifier.

C7.3.1.2 If a single cellular therapy product is stored in more than one (1) container, there shall be a system to identify each container.

C7.3.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.

C7.3.2 An ISBT 128 Chain of Identity identifier should be assigned before or at the time of collection to each product or donation intended for further manufacturing.

C7.3.2.1 If more than one donation is needed to deliver a given therapy, the Chain of Identity identifier shall link all donations.

C7.3.3 Supplementary identifiers shall not obscure the original identifier.

C7.3.4 The facility associated with each identifier shall be named in the documents to accompany the cellular therapy product.

C7.3.5 If the original donation identifier is replaced, documentation shall link the new identifier to the original.

C7.4 LABEL CONTENT

C7.4.1 The cellular therapy product shall be labeled with the proper name of the product and the unique numeric or alphanumeric identifier, at a minimum.

C7.4.1.1 For Apheresis collections, the proper name of the product and the unique numeric or alphanumeric identifier shall be applied to the collection container prior to the collection procedure.

C7.4.2 Labeling at the end of collection shall occur before the cellular therapy product is removed from the proximity of or disconnected from the donor.

C7.4.2.1 The content of the label shall be verified prior to removing the cellular therapy product from the proximity of the donor.

C7.4.3 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix II.

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."

C7.4.4.1 For cellular therapy products not collected, processed, or administered in the U.S., the appropriate Biohazard and Warning Labels shall follow Applicable Law, or C7.4.4 if no Applicable Law exists.

C7.4.5 A cellular therapy product collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documentation table in Appendix IV at the time it leaves the control of the Collection Facility.

C7.4.6 Any container bearing a partial label at the time of distribution shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix II. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.

C7.4.7 For allogeneic cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after distribution of the cellular therapy product and that the physician using the product shall be informed of the results of that determination.

C7.4.8 Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "For Nonclinical Use Only."

C8: EQUIPMENT, SUPPLIES, AND REAGENTS

C8.1 Equipment, supplies, and reagents used to collect cellular therapy products shall be qualified and used in a manner that maintains product function and integrity and minimizes risks of product mix-ups, contamination, and cross-contamination.

C8.2 There shall be adequate equipment and materials for the procedures performed.

C8.3 There shall be a process for inventory control that encompasses equipment, containers for transport and shipping, supplies, reagents, and labels.

C8.3.1 There shall be a system to uniquely identify and track and trace all critical equipment, supplies, reagents, and labels used in the collection of cellular therapy products.

C8.3.2 Each supply and reagent used to collect cellular therapy products shall be visually examined for damage or evidence of contamination and acceptance criteria defined at receipt and prior to use.

C8.~~2~~3.2.1 Supplies and reagents shall be quarantined prior to use until verified to have met acceptance criteria.

C8.3.3 Records of receipt shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.

C8.3.4 Materials shall be stored under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix up or unintended use.

C8.3.5 Supplies and reagents coming into contact with cellular therapy products during collection shall be qualified, sterile, and meet predetermined specifications for the intended use.

C8.3.6 Non-disposable supplies or instruments shall be cleaned and sterilized using a procedure verified to remove infectious agents and other contaminants.

C8.3.7 Supplies and reagents shall be used in a manner consistent with manufacturer instructions.

C8.3.8 There shall be a process to prevent the use of expired reagents and supplies.

C8.4 There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration.

C8.4.1 Equipment used in the collection of cellular therapy products shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.

C8.4.1.1 Maintenance, calibration, and cleaning shall be performed according to established schedules and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.4.1.2 The equipment shall be inspected for cleanliness and verified to be in compliance with the maintenance schedule prior to use.

C8.4.2 The equipment shall be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.4.2.1 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.

C8.4.2.2 Calibration shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.4.2.3 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products collected since the last calibration.

C8.4.2.4 There shall be a Standard Operating Procedure that addresses the actions to take in the event of equipment malfunction or failure.

C8.5 Lot numbers, expiration dates, manufacturers of critical reagents and supplies, and key equipment used in each procedure shall be documented.

C8.6 An inventory control system shall be used to document the availability and identity of critical equipment, supplies and reagents. This shall include at a minimum:

C8.6.1 A system to uniquely identify, track, and trace all critical reagents and supplies used to manufacture cellular therapy products.

C8.6.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.

C8.6.3 A system to maintain adequate stocks of reagents and supplies for the procedures to be performed.

C8.6.4 Equipment, supplies, and reagents for the collection procedure shall conform to Applicable Law.

C9: PROCESS CONTROLS

C9.1 Collection of cellular therapy products shall be performed according to written Standard Operating Procedures.

C9.2 CMV-appropriate and irradiated or equivalent, or autologous blood components shall be available during the collection procedure for all donors.

C9.3 There shall be a written order from a physician specifying, at a minimum, the anticipated date and goals of collection.

C9.4 There shall be peripheral blood count criteria to proceed with collection including the timing of sample collection.

C9.4.1 The peripheral blood count criteria shall be met and documented prior to each collection.

C9.4.1.1 A complete blood count, including platelet count, shall be performed within 24 hours prior to each subsequent cellular therapy product collection.

C9.5 There shall be written documentation of a daily assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

C9.6 General or regional anesthesia, if required, shall be performed or supervised by a health care provider licensed and credentialed to administer anesthesia.

C9.7 Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.

C9.7.1 Appropriate mobilization should be used for the disease being treated and for the donor being collected.

C9.8 Collection procedures shall include a validated process for assessing the quality of cellular therapy products to assure product safety, viability, and integrity, and to document that products meet predetermined release specifications. Results of all such assessments and procedures shall become part of the permanent record of the product collected.

C9.8.1 Methods for collection shall employ procedures that minimize the risk of microbial contamination and are validated to result in acceptable cell viability and collection yield.

C9.9 There shall be a process to verify the donor identity and collection procedure prior to initiating the collection procedure.

C9.10 Collection methods shall employ appropriate age and weight adjustments to the procedures.

C9.11 Cellular therapy products shall be collected in sterile containers appropriate for the product.

C9.11.1 Containers shall be securely closed to prevent leakage or contamination prior to distribution.

C9.12 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.

C9.12.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.

C9.13 There shall be policies addressing safe treatment with ECP, if applicable.

C9.13.1 Before ECP is undertaken, there shall be a written therapy plan from a physician specifying the patient's diagnosis and GVHD grade, involved organs, indication, timing of the procedure, proposed regimen, and any other factors that may affect the safe treatment with ECP.

C9.13.2 A final report of the ECP treatment, including procedure details, shall be documented in the patient's medical record.

C9.14 Where cellular therapy products are distributed directly from the Collection Facility to the Clinical Program for administration, the Standards related to labeling, documentation, distribution, transportation, and record keeping in Sections D7, D8.4.5, D10, D11, D13, and the Appendices apply.

C9.15 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

C9.15.1 The Collection Facility shall provide to the Clinical Facility, Processing Facility, or manufacturer a summary of all cellular therapy product records relating to the collection procedure and storage procedures performed.

C9.16 ADDITIONAL REQUIREMENTS FOR APHERESIS COLLECTION

C9.16.1 There shall be a process to assess the extracorporeal blood volume and the need for blood priming.

C9.16.2 There shall be a process to ensure compliance with additional requirements of applicable registries.

C9.17 ADDITIONAL REQUIREMENTS FOR BONE MARROW COLLECTION

C9.17.1 There shall be a process to determine that the red cell volume and marrow volume to be collected is appropriate for the donor.

C9.17.2 There shall be a process to ensure compliance with additional requirements of applicable registries.

C9.17.3 HPC, Marrow products shall be filtered to remove particulate material prior to final packaging, distribution, or administration using filters that are non-reactive with blood.

C9.18 ADDITIONAL REQUIREMENTS FOR OTHER TISSUE COLLECTION

C9.18.1 When a collection kit is received by the collection staff, the staff shall review for adequate instructions and materials for collection, labeling, storage, packing, and transporting or shipping the cellular therapy collection and associated samples to the Processing Facility.

C9.18.1.1 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.

C9.18.2 Surgically collected cellular material shall be collected at a site accredited by the Joint Commission, DNV, ACHC, or other appropriate accrediting body as required by Applicable Law or licensed by the appropriate regulatory agency.

C10: CELLULAR THERAPY PRODUCT STORAGE

C10.1 Collection Facilities shall control and secure storage areas in a manner to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of cellular therapy products.

C10.2 STORAGE DURATION

C10.2.1 The Collection Facility shall have policies or Standard Operating Procedures that define the duration and conditions of short-term storage prior to distribution.

C10.2.1.1 Conditions and duration of storage, including temperature of all cellular therapy products shall be validated.

C10.2.1.2 Facilities collecting, storing, or releasing cellular therapy products for administration, processing, or further manufacturing shall assign an expiration date and time.

C10.3 STORAGE TEMPERATURE

C10.3.1 Storage temperatures shall be defined in Standard Operating Procedures.

C10.3.2 Cellular therapy products shall be maintained within a specific temperature range to maintain viability and function, to inhibit infectious agents for a period of time not to exceed that specified in Standard Operating Procedures.

C10.4 STORAGE MONITORING

C10.4.1 Storage devices shall have a system to monitor the temperature continuously and to record the temperature at least every four (4) hours.

C11: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

C11.1 Standard Operating Procedures for transportation and shipping of cellular therapy products shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area.

C11.2 The primary cellular therapy product container shall be placed in a secondary container and is sealed to prevent leakage.

C11.3 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

C11.4 Cellular therapy products transported internally shall be packaged in a closed and rigid outer container.

C11.4.1 The outer container for internal transport shall be labeled as defined in Appendix III B.

C11.5 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.

C11.5.1 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.

C11.5.2 The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transport or shipping.

C11.5.3 The outer container shall be secured.

C11.5.4 The outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix III A.

C11.5.5 There shall be a document inside the outer container that includes all the information required on the outer container, in conformity with the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix III A.

C11.6 Cellular therapy products transported or shipped over an extended period of time shall be transported or shipped in a container within a temperature range defined in a Standard Operating Procedure or written agreement and according to manufacturer instructions.

C11.6.1 Additives to the cellular therapy product should be used for shipping over a prolonged duration of time.

C11.7 There shall be a risk assessment to evaluate the need for continuous temperature monitoring during transportation or shipment of cellular therapy products.

C11.8 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.

C11.9 The transit time shall be within time limits determined by the distributing facility in consultation with the receiving facility to maintain cellular therapy product safety.

C11.10 There shall be contingency plans for alternative means of transport or shipping in an emergency.

C11.11 The cellular therapy product shall be transported or shipped with required accompanying records as defined in the transportation and shipping Standard Operating Procedures and in compliance with C7.4.5 and C7.4.7.

C11.12 There shall be a record of the date and time of cellular therapy product distribution.

C11.13 Cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.

C12: RECORDS

C12.1 There shall be a records management system for quality and cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

C12.1.1 A records management system shall be established and maintained to facilitate the review of records.

C12.1.2 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

C12.1.3 For cellular therapy products that are to be distributed for use at another institution, the Collection Facility shall inform the receiving institution of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

C12.1.4 Records shall be maintained to ensure their integrity, preservation, and retrieval.

C12.1.5 Records shall be accurate and legible.

C12.1.6 Written records shall be indelible.

C12.1.7 Safeguards to secure the confidentiality of all records and communications among the collection staff, processing, and clinical facilities, and health care providers and their recipients and donors, shall be established and followed in compliance with Applicable Law.

C12.2 The Collection Facility shall define and follow good documentation practices.

C12.3 RECORDS TO BE MAINTAINED

C12.3.1 Collection Facility records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years, after the creation of the cellular therapy product record, date of the cellular therapy product's distribution, disposition, or expiration, or, whichever is latest or according to Applicable Law. These records shall include collection facility identity, unique numeric or alphanumeric identifier, collection date and time, product code, and donor and recipient information as found on the original container.

C12.3.2 Employee records shall be maintained by the Collection Facility in a confidential manner, as required by Applicable Law.

C12.3.3 Cleaning and sanitation records shall be retained for a minimum of three (3) years, or longer in accordance with Applicable Law or regulations or by a defined program or institution policy.

C12.4 Records to allow tracking and tracing of cellular therapy products shall be maintained in a confidential manner for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, or as required by Applicable Law, whichever is latest. These records shall include collection facility identity, unique numeric or alphanumeric identifier, collection date and time, product code, and donor and recipient identification as found on the original container.

C12.5 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.

C12.6 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.

C12.7 ELECTRONIC RECORDS

C12.7.1 The Collection Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum, systems that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures. For all critical electronic record systems:

C12.7.1.1 There shall be policies, Standard Operating Procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

C12.7.1.2 There shall be a means by which access is limited to authorized individuals.

C12.7.1.3 A method shall be established, or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

C12.7.1.4 There shall be written Standard Operating Procedures for record entry, verification, and revision.

C12.7.1.5 A method shall be established, or the system shall provide for review of data before final acceptance.

C12.7.1.6 There shall be documented training of personnel in the system's use.

C12.7.1.7 There shall be a defined process for continued competency of personnel in the system's use.

C12.7.1.8 The utilization of electronic signatures shall be defined.

C12.7.1.9 Critical electronic record systems shall maintain unique identifiers.

C12.7.1.10 There shall be the ability to generate true copies of records in both human readable and electronic format suitable for inspection and review.

C12.7.1.11 There shall be protection of records to enable their accurate and ready retrieval throughout the period of record retention.

C12.7.1.12 All system modifications shall be authorized, documented, and validated prior to implementation.

C12.7.2 For all critical electronic record systems under the control of the Facility, there shall be validated processes for and documentation of:

C12.7.2.1 Prospective validation of systems, including hardware, software, and databases.

C12.7.2.2 Installation of the system.

C12.7.2.3 Numerical designation of system versions, if applicable.

C12.7.2.4 Authorization, documentation, and validation of all system modifications prior to implementation.

C12.7.2.5 Systems development including the verification of calculations and algorithms.

C12.7.2.6 System maintenance and operations.

C12.7.2.7 Monitoring of data integrity.

C12.7.2.8 Back-up of the electronic records system on a regular schedule.

C12.7.3 For each critical electronic record system, there shall be an alternative system to allow for continuous operation of the collection facility if the critical electronic record system is not available. The alternative system shall be validated, and collection staff shall be trained in its use.

PART D: PROCESSING FACILITY STANDARDS

D1: General

D2: Processing Facility

D3: Personnel

D4: Quality Management

D5: Policies and Standard Operating Procedures

D6: Equipment, Supplies and Reagents

D7: Coding and Labeling of Cellular Therapy Products

D8: Process Controls

D9: Cellular Therapy Product Storage

D10: Cellular Therapy Product Transportation and Shipping

D11: Receipt and Distribution

D12: Disposal

D13: Records

PART D: PROCESSING FACILITY STANDARDS

D1: GENERAL

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

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.

D1.3 The Processing Facility shall have a Processing Facility Director, a Processing Facility Medical Director, a Quality Manager, and a minimum of one (1) additional designated staff member. The designated team shall have been in place and actively performing cellular therapy product processing for at least twelve (12) months preceding initial accreditation.

D2: PROCESSING FACILITY

D2.1 There shall be secured and controlled access to designated areas appropriate for the processing procedure(s) and for storage of equipment, supplies, reagents, cellular therapy products, and records.

D2.1.1 The designated area for processing shall be in an appropriate location of adequate space and design to minimize the risk of airborne or surface microbial contamination.

D2.1.2 The Processing Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.

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

D2.2 The Processing Facility shall provide adequate lighting, ventilation, and access to toilets and sinks for handwashing to prevent the introduction, transmission, or spread of communicable disease.

D2.3 Environmental conditions shall be controlled to protect the safety and comfort of personnel.

D2.4 There shall be a written assessment of critical Processing Facility environmental parameters that may affect cellular therapy product viability, integrity, or contamination or cross-contamination during processing, storage, or distribution.

D2.4.1 The written assessment shall include temperature, humidity, air quality, and surface contaminants at a minimum.

D2.4.2 Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.

D2.4.3 The Processing Facility shall qualify environmental control systems and validate cleaning and sanitation procedures appropriate for the environmental classification and degree of manipulation performed.

D2.5 The Processing Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.

D2.6 The Processing Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, visitors, and volunteers.

D2.7 The Processing Facility shall have a written safety manual that includes instructions for action in case of exposure to liquid nitrogen; communicable disease; and to chemical, biological, radiological, electrical, or fire hazards.

D2.8 All waste generated by the Processing Facility's activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with Applicable Law.

D2.9 There shall be a written policy for personal hygiene and the use of personal protective equipment and attire.

D2.9.1 The policy shall define the protective clothing to be worn upon entering the work area and working within it.

D2.9.2 The policy shall define personal protective equipment of the appropriate grade for the risk, to be worn while handling biological specimens.

D2.9.3 Such personal protective equipment shall not be worn outside the designated work area.

D2.10 There shall be a biosafety plan consistent with the Institutional Biosafety Committee requirements that addresses genetically modified cellular therapy products in accordance with Applicable Law.

D2.11 Oxygen sensors shall be appropriately placed and utilized in areas where liquid nitrogen is present.

D2.11.1 Oxygen sensors shall have visible and audible alarms with appropriate settings to ensure safety of personnel.

D3: PERSONNEL

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, with a minimum of two (2) years of experience in management and oversight for the scope of activities carried out in the Processing Facility.

D3.1.2 The Processing Facility Director shall be responsible for all Standard Operating Procedures, technical procedures, performance of the processing procedures(s), supervision of staff, administrative operations, and the Quality Management Program, including compliance with these Standards and Applicable Law.

D3.1.3 The Processing Facility Director shall have performed or supervised a minimum of five (5) cellular therapy product processing procedures in the twelve (12) months preceding initial accreditation and a minimum average of five (5) cellular therapy product processing procedures per year within each accreditation cycle.

D3.1.4 The Processing Facility Director shall participate in a minimum of ten (10) hours of educational activities related to HPC transplantation or cellular therapy annually.

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 education, including training and practical and relevant experience in cellular therapy product processing, collection, and administration.

D3.2.2 The Processing Facility Medical Director shall be directly responsible for all medical aspects related to the Processing Facility.

D3.2.3 The Processing Facility Medical Director shall have performed, supervised, or reviewed a minimum of five (5) cellular therapy product processing procedures in the twelve (12) months preceding initial accreditation and a minimum average of five (5) cellular therapy product processing procedures per year within each accreditation cycle.

D3.2.4 The Processing Facility Medical Director shall participate in a minimum of ten (10) hours of educational activities related to HPC transplantation or other cellular therapies annually.

D3.3 QUALITY MANAGER

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

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

D3.3.3 The Processing Facility Quality Manager shall participate in a minimum of ten (10) hours of continuing education activities related to cellular therapy, cell processing, and Quality Management annually.

D3.4 STAFF

D3.4.1 The number of trained and competent processing personnel shall be adequate for the number of procedures performed and shall include a minimum of one (1) designated trained individual with an identified trained and competent backup individual to maintain sufficient coverage.

D4: QUALITY MANAGEMENT

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.

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

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

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.

D4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Processing Facility. Personnel requirements shall include at a minimum:

D4.4.1 A current job description for each position.

D4.4.2 A system to document the following for all staff:

D4.4.2.1 Initial qualifications.

D4.4.2.2 New employee orientation.

D4.4.2.3 Initial training, competency, and retraining when appropriate for all procedures performed, and in accordance with Applicable Law.

D4.4.2.4 Continued competency for each critical function performed, assessed annually at a minimum.

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

D4.4.2.6 Continuing education.

D4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control.

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, Protocols, Standard Operating Procedures, Manuals, and Guidelines.

D4.5.1.2 Worksheets.

D4.5.1.3 Forms.

D4.5.1.4 Labels.

D4.5.2 There shall be policies or Standard Operating Procedures for the development, approval, implementation, distribution, review, revision, and archival of all controlled documents.

D4.5.3 The document control system shall include:

D4.5.3.1 A standardized format for controlled documents.

D4.5.3.2 Assignment of a numeric or alphanumeric identifier, version, and a title to each controlled document.

D4.5.3.3 A system for document approval, including the approval date, signature of approving individual(s), and the effective date.

D4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.

D4.5.3.5 Review of controlled documents every two (2) years at a minimum.

D4.5.3.6 A system for document change control that includes a description of the change, version, the signature of approving individual(s), approval date(s), communication or training on the change as applicable, effective date, and archival date.

D4.5.3.7 A system for archival of controlled documents for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer. The system must include the inclusive dates of use and their historical sequence.

D4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

D4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the establishment and maintenance of written agreements.

D4.6.1 Agreements shall be established with external parties providing critical services that could affect the quality and safety of the cellular therapy product or the health and safety of the donor or recipient.

D4.6.2 Agreements shall include the responsibility of the external party performing any step in collection, processing, testing, storage, distribution, or administration, to maintain required accreditations and to comply with these Standards and Applicable Law.

D4.6.3 Agreements shall be established when the Processing Facility provides critical services to external parties.

D4.6.4 Agreements shall be dated and reviewed on a regular basis, at a minimum every two (2) years.

D4.7 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 safety and efficacy to verify that the procedures in use consistently provide a safe and effective product.

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.

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

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

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 elements of the Quality Management Program policies and Standard Operating Procedures, these Standards, and Applicable Law.

D4.8.1 Processing Facility audits shall be conducted by an individual with sufficient knowledge in the process and competence in auditing to identify problems, but who is not solely responsible for the process being audited.

D4.8.2 The results of Processing Facility audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions in a timely manner.

D4.8.3 Processing Facility audits shall be performed annually at a minimum, and shall include at least the following:

D4.8.3.1 Documentation that each external facility performing critical contracted services has met the requirements of the written agreement.

D4.8.3.2 Audit of management of cellular therapy products with positive microbial culture results.

D4.8.4 Additional audits shall be performed periodically.

D4.8.4.1 Critical supplies inventory control.

D4.8.4.2 Equipment maintenance.

D4.8.4.3 Environmental monitoring to include temperature, humidity, facility cleaning, prevention of contamination and cross-contamination, and air pressure differentials appropriate for the degree of manipulation.

D4.8.4.4 Staff training and competency.

D4.8.5 Additional audits shall be performed as part of follow-up of occurrences.

D4.8.6 There shall be policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency.

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 that address at a minimum:

D4.9.1 Notification of the recipient's physician, Collection Facility, and any other facility in receipt of the cellular therapy product.

D4.9.2 Documentation and product labeling.

D4.9.3 Product quarantine.

D4.9.4 Criteria for the release of cellular therapy products with positive microbial culture results.

D4.9.5 Identification of individuals authorized to approve release, including at a minimum the Processing Facility Medical Director.

D4.9.6 Documentation and investigation of cause.

D4.9.7 Reporting to regulatory agencies as required by Applicable Law.

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, incidents, and complaints). The following activities shall be included at a minimum:

D4.10.1 Detection.

D4.10.2 Investigation.

D4.10.2.1 A thorough and timely investigation shall be conducted by the processing staff in collaboration with the Collection Facility, the Clinical Program, and other entities involved in the manufacture of the cellular therapy product, as appropriate.

D4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective and preventive actions as warranted.

D4.10.2.3 Occurrences shall be tracked and trended.

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) including the unique identifier for the product involved, as applicable, 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 of occurrences shall be maintained and include written investigation reports containing conclusions, root-cause analysis, follow-up, corrective and preventive actions, and a link to the records of the involved cellular therapy products, donors, and recipients, if applicable.

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 Occurrence Report 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 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, sponsors, Institutional Biosafety Committees, and Institutional Review Boards (IRBs) or Ethics Committees.

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.

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.

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.

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, drugs, supplies, reagents, facilities, and services.

D4.13.1 Critical equipment, software, supplies, reagents, and facilities used for cellular therapy product manufacturing procedures shall be qualified.

D4.13.1.1 Qualification shall be required following any significant changes to these items.

D4.13.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

D4.13.3 Qualification plans shall include minimum acceptance criteria for performance.

D4.13.4 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Processing Facility Director.

D4.14 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures in both minimally and more than minimally manipulated products.

D4.14.1 Critical procedures to be validated shall include at least the following: processing procedures, cryopreservation procedures, testing, labeling, storage, distribution, and preparation for administration.

D4.14.2 Validation studies for a procedure shall be retained at a minimum until the procedure is no longer in use.

D4.14.3 Each validation or verification shall include at a minimum:

D4.14.3.1 An approved plan, including conditions to be assessed.

D4.14.3.2 Acceptance criteria.

D4.14.3.3 Data collection.

D4.14.3.4 Evaluation of data.

D4.14.3.5 Summary of results.

D4.14.3.6 References, if applicable.

Commented [EO2]: New to Part D, very similar to D13.3.4. Do we want to keep both?

Commented [MS3R2]: They are similar but one is referencing required SOPs the other records to be maintained. I think both are needed.

D4.14.3.7 Review and approval of the plan, report, and conclusion by the Quality Manager and the Processing Facility Director.

D4.14.4 Significant changes to critical procedures shall be validated and 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 of the Processing Facility, Clinical Program, or Collection Facility.

D4.15.1 Evaluation of risk shall be completed for changes in critical procedures.

D4.16 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining and reviewing feedback and taking action when appropriate.

D4.16.1 Feedback shall be obtained from associated Clinical Programs and Collection Facilities.

D4.17 The Processing Facility Director shall review the quality management activities with representatives in key positions in all elements of the cellular therapy program, at a minimum, quarterly.

D4.17.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

D4.17.2 Performance data and review findings shall be reported to key positions and staff.

D4.17.3 The Processing Facility Director shall not have oversight of their own work if this person also performs other tasks in the Processing Facility.

D4.18 The Processing Facility Director shall annually review the effectiveness of the Quality Management Program.

D4.18.1 The annual report and documentation of the review findings shall be made available to key personnel, the Clinical Program Director, the Collection Facility Director, and staff of the program.

D5: POLICIES AND STANDARD OPERATING PROCEDURES

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:

D5.1.1 Donor and recipient confidentiality.

D5.1.2 Cellular therapy product receipt.

D5.1.3 Processing and process control.

D5.1.3.1 Appropriate processing procedures for specific products, including cryopreservation and thawing.

D5.1.4 Processing of ABO-incompatible cellular therapy products, including a description of the indication for and processing methods to be used for red blood cell and plasma reduction.

D5.1.5 Prevention of mix-ups and cross-contamination.

D5.1.6 Labeling, including associated forms and samples.

D5.1.7 Cellular therapy product expiration dates.

D5.1.8 Cellular therapy product storage, including alternative storage 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.

D5.1.10.1 Use of additives to the product for long duration of shipment or transportation.

D5.1.11 Cellular therapy product recall, including a description of responsibilities and actions to be taken, and notification of appropriate regulatory agencies.

D5.1.12 Cellular therapy product disposal.

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

D5.1.14 Equipment operation, maintenance, and monitoring, including corrective actions in the event of failure.

D5.1.15 Cleaning and sanitation procedures, including identification of the individuals responsible for the activities.

D5.1.16 Environmental control, including a description of the environmental monitoring plan.

D5.1.17 Hygiene and use of personal protective equipment and attire.

D5.1.18 Handling and disposal of medical and biohazard waste.

D5.1.19 Processing Facilities utilizing genetically modified cellular therapy products shall incorporate or reference institutional or regulatory requirements relating to biosafety practices, including handling and disposal.

D5.1.20 Cellular therapy emergency and disaster plan, including the Processing Facility response.

D5.1.21 Chain of Identity.

D5.1.22 Chain of Custody.

D5.2 A detailed list of all controlled documents, including title and identifier, shall be maintained.

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:

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.

D5.3.4 A stepwise description of the procedure.

D5.3.5 Reference to other policies or 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 Standard Operating Procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation and every two (2) years thereafter.

D5.3.8 Documented approval of each procedural modification by the Processing Facility Director or Medical Director, as appropriate, prior to implementation.

D5.3.9 Reference to a current version of orders, worksheets, reports, labels, and forms.

D5.4 Controlled documents relevant to processes being performed shall be readily available to the facility staff.

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

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

D5.7 Planned deviations shall be pre-approved by the Processing Facility Director or Medical Director and reviewed by the Quality Manager.

D6: EQUIPMENT, SUPPLIES, AND REAGENTS

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.

D6.3 There shall be a process for inventory control that encompasses equipment, containers for transport and shipping, supplies, reagents, and labels.

D6.3.1 There shall be a system to uniquely identify, track, and trace all critical equipment used in the processing of cellular therapy products. The system shall identify each cellular therapy product for which the equipment was used.

Commented [EO4]: In my opinion, this made more sense where we had it in HCT 8 (D6.4). Here it precedes all of the Standards about supplies and reagents.

Commented [MS5R4]: We will keep this comment for public comment. Phyllis rearranged this so I will keep it for now and have the committee re-think it during the review.

D6.3.2 Each supply and reagent used to manufacture cellular therapy products shall be visually examined for damage or evidence of contamination and acceptance criteria defined at receipt and prior to use.

D6.3.2.1 Supplies and reagents shall be quarantined prior to use until verified to have met acceptance criteria

D6.3.3 Records of receipt shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.

D6.3.4 Materials shall be stored under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix up or unintended use.

D6.3.5 Supplies and reagents coming into contact with cellular therapy products during processing, storage, or administration shall be qualified, sterile, and meet predetermined specifications for the intended use.

D6.3.4.1 Reagents shall undergo initial qualification for the intended use and meet predetermined specifications.

D6.3.4.2 Reagents shall undergo risk assessment as part of their initial qualification to ensure product integrity and safety.

D6.3.4.3 Reagents shall undergo lot-to-lot verification to ensure that the new lot meets specifications.

D6.3.6 Non-disposable supplies or instruments shall be cleaned and sterilized using a procedure verified to remove infectious agents and other contaminants.

D6.3.7 Supplies and reagents shall be used in a manner consistent with manufacturer instructions.

D6.3.8 There shall be a process to prevent the use of expired reagents and supplies.

D6.4 There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration.

D6.4.1 Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.

Commented [EO6]: These had some pretty major changes from HCT 8. Please double check that these look OK and that we don't need to show any of the deletions. I'm a little concerned that it's going to look like the redline isn't accounting for the previous Standards.

Commented [MS7R6]: I note your concern. I think it is ok. Most people don't simply use this redline in isolation. They use it with the previous edition to understand what has changed. I think it presents ok. Thanks.

D6.4.1.1 Maintenance, calibration, and cleaning shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.4.1.2 The equipment shall be inspected for cleanliness and verified to be in compliance with the maintenance schedule prior to use.

D6.4.2 The equipment shall be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.4.2.1 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.

D6.4.2.2 Calibration shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.4.2.3 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products manufactured since the last calibration.

D6.4.3 There shall be a Standard Operating Procedure that addresses the actions to take in the event of equipment malfunction or failure.

D6.5 Lot numbers, expiration dates, manufacturers of critical reagents and supplies, and key equipment used in each procedure shall be documented.

D6.6 An inventory control system shall be used to document the availability and identity of critical equipment, supplies and reagents. This shall include at a minimum:

D6.6.1 A system to uniquely identify, track, and trace all critical reagents and supplies used to manufacture cellular therapy products.

D6.6.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.

D6.6.3 A system to maintain adequate stocks of reagents and supplies for the procedures to be performed.

D6.6.4 Equipment, supplies, and reagents for processing shall conform to Applicable Law.

D7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

D7.1 ISBT 128 AND EUROCODE CODING AND LABELING

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

D7.1.2 Coding and labeling technologies shall be implemented using ISBT 128 or Eurocode.

D7.1.3 Cellular therapy collections for further manufacturing should be labeled with the ISBT Hybrid Label in accordance with ISBT 128 Standard ST-018.

D7.2 LABELING OPERATIONS

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

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

D7.2.1.2 Obsolete labels shall be restricted from use.

D7.2.2 Pre-printed labels from the manufacturer shall be quarantined 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.

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.

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.

D7.2.5 A system for label version control shall be employed.

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.

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.

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.

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.

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.

D7.2.8 Labeling elements required by Applicable Law shall be present.

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

D7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

D7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

D7.2.12 The label shall be validated as reliable for storage under the conditions in use.

D7.3 PRODUCT IDENTIFICATION

D7.3.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.

D7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected donor samples shall be labeled with the same identifier.

D7.3.1.2 If a single cellular therapy product is stored in more than one (1) container, there shall be a system to identify each container.

D7.3.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.

D7.3.1.4 Supplementary identifiers shall not obscure the original identifier.

D7.3.1.5 The facility associated with each identifier shall be named in the documents to accompany the cellular therapy product.

D7.3.1.6 If the original donation identifier is replaced, documentation shall link the new identifier to the original.

D7.3.2 An ISBT 128 Chain of Identity identifier should be assigned before or at the time of collection to each collection intended for further manufacturing.

D7.3.2.1 If more than one donation is needed to deliver a given therapy, the Chain of Identity identifier shall link all donations.

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.

D7.4.3 At the completion of processing and at distribution for administration, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix II.

D7.4.4 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."

D7.4.4.1 For cellular therapy products not collected, processed, or administered in the U.S., the appropriate Biohazard and Warning Labels shall follow Applicable Law, or D7.4.4 if no Applicable Law exists.

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 Documentation table in Appendix IV at the time it leaves the control of the Processing Facility.

D7.4.6 Any container bearing a partial label at the time of distribution shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix II. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.

D7.4.7 For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after distribution of the cellular therapy product and that the physician using the product was informed of the results.

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

D7.4.9 Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "For Nonclinical Use Only."

D8: PROCESS CONTROLS

D8.1 There shall be a process for controlling and monitoring the manufacturing of cellular therapy products so that products meet predetermined release specifications.

D8.1.1 The Processing Facility Director shall define tests and procedures for measuring and assaying cellular therapy products to assure their safety, viability, and integrity, and to document that products meet predetermined release specifications. Results of all such tests and procedures shall become part of the permanent record of the product processed.

D8.1.2 There shall be a documented system for the identification and handling of test samples so that they are accurately related to the corresponding cellular therapy product, donor, or recipient.

D8.1.2.1 There shall be a mechanism to identify the individual obtaining the sample, the sample source, the date, and the time, if appropriate.

D8.1.2.2 Samples obtained for testing shall be representative of the cellular therapy product to be evaluated.

D8.1.3 There shall be the establishment of appropriate and validated assays and test procedures for the evaluation of cellular therapy products, including as applicable:

D8.1.3.1 ABO group and Rh typing.

D8.1.3.2 Microbial testing after processing.

D8.1.3.3 Cell count including total nucleated cells and viability.

D8.1.3.4 CD34 numeration and viability assays.

D8.1.3.5 Assay of target cell population for products that have been enriched, expanded, or depleted.

D8.1.4 The following assays test procedures for the evaluation of cellular therapy products shall be performed:

D8.1.4.1 For all cellular therapy products, a total nucleated cell count and viability measurement shall be performed.

D8.1.4.2 For HPC products intended for restoration of hematopoiesis, an assay measuring viable CD34 shall be performed.

D8.1.4.3 For cellular therapy products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, shall be employed for evaluation of the viable target cell population before and after the processing procedures.

D8.1.5 For tests required by these Standards performed within the Processing Facility:

D8.1.45.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

D8.1.5.2 New reagent lots shall be verified to provide comparable results to current lots or to give results in agreement with suitable reference material before or concurrently with being placed into service.

D8.1.5.3 Where available, controls shall be used each day of testing and shown to give results within the defined range established for that material.

D8.1.45.4 Function checks shall be performed for testing instruments prior to testing donor, recipient, or cellular therapy product samples.

D8.1.5.5 There shall be documentation of ongoing proficiency testing as designated by the Processing Facility Director. The results shall be reviewed by the Processing Facility Director and outcomes reviewed with the staff.

D8.1.6 Tests required by these Standards, not performed by the Processing Facility, shall be performed by a laboratory that is certified, licensed, or accredited by the appropriate laboratory regulatory agency.

D8.1.7 Infectious disease testing required by these Standards shall be performed using screening tests licensed, approved, or cleared by the governmental authority for cellular therapy product donors.

D8.1.8 Cellular therapy products that do not meet allogeneic donor eligibility requirements, or for which allogeneic donor eligibility determination is not yet complete, shall be distributed only if there is documented urgent medical need for the product. Documentation shall include, at a minimum, the approval of the recipient's physician and the Processing Facility Medical Director.

D8.1.9 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.

D8.3 For allogeneic cellular therapy products, information required by the Processing Facility prior to distribution of the product shall include:

D8.3.1 A statement of donor eligibility.

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

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

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

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

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

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

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

D8.4.5 Preparation for administration of cellular therapy products manufactured by third parties shall follow the instructions provided by the manufacturer.

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

D8.4.5.2 If relabeling of prepared third-party products is required, the label shall follow Applicable Law.

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

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.

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.

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~~can be accurately traced.

D8.9.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.

D8.9.2 Records shall include the test results and where appropriate, the interpretation.

D8.10 The Processing Facility Director shall review the processing record for each cellular therapy product prior to release or distribution.

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.

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 GMP appropriate for the degree of cellular therapy product manipulation.

D8.13 For allogeneic cellular therapy products containing red blood cells at the time of administration:

D8.13.1 Results for ABO group and Rh type testing shall be available from two (2) independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

D8.13.2 Results for a red blood cell antibody screen on the recipient shall be available.

D8.14 There shall be a Standard Operating Procedure to confirm the identity of cord blood units if verification typing cannot be performed on attached segments.

D8.15 One or more samples representing the cryopreserved cellular therapy product shall be stored under conditions that achieve a valid representation of the clinical product and in accordance with Standard Operating Procedures.

D9: CELLULAR THERAPY PRODUCT STORAGE

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

D9.2 STORAGE DURATION

D9.2.1 Processing Facilities shall have policies or Standard Operating Procedures that define the duration and conditions of short-term storage prior to distribution.

D9.2.2 Conditions and duration of storage of all cellular therapy products shall be validated.

D9.2.3 Processing Facilities processing, storing, or releasing cellular therapy products for administration or further manufacturing shall assign an expiration date and time for non-cryopreserved products and for products thawed after cryopreservation.

D9.2.4 There shall be a written stability program that annually evaluates the viability and potency of cryopreserved cellular therapy products.

D9.2.4.1 Samples should include those representative of all processing methods and those representative of maximum storage duration.

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.

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.

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.

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.

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.

D9.5.2 There shall be a mechanism to confirm that levels of liquid nitrogen in liquid nitrogen freezers are consistently maintained to ensure that cellular therapy products remain within the specified temperature range.

D9.6 ALARM SYSTEMS

D9.6.1 Storage devices for cellular therapy products or reagents for cellular therapy product processing shall have alarm systems that are continuously active.

D9.6.2 Alarm systems shall have audible and visible signals.

D9.6.2.1 In areas where liquid nitrogen is present, oxygen sensors shall be placed to alert staff working in the area to evacuate, and to notify any staff responding to the alarm not to enter the area.

D9.6.2.2 Instructions for staff responding to the alarm shall be posted at the entrances of areas where liquid nitrogen is present.

D9.6.3 Alarm systems shall be checked for function according to the manufacturer's recommendation or annually at a minimum.

D9.6.4 If trained personnel are not always present in the immediate area of the storage device, a system shall be in place that alerts responsible personnel of alarm conditions on a 24-hour basis.

D9.6.5 Alarms shall be set to activate at a temperature or level of liquid nitrogen that will allow time to salvage products.

D9.6.6 Storage devices of appropriate temperature shall be available for cellular therapy product storage if the primary storage device fails.

D9.7 Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.

D9.7.1 Instructions shall include a procedure for notifying processing personnel.

D9.8 Storage devices shall be located in a secure area and accessible only to personnel authorized by the Processing Facility Director.

D9.9 The Processing Facility shall use an inventory control system to identify the location of each cellular therapy product and associated samples. The inventory control system records shall include:

D9.9.1 Cellular therapy product unique identifier.

D9.9.2 Recipient name or unique identifier.

D9.9.3 Storage device identifier.

D9.9.4 Location within the storage device.

D10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

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.

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

D10.3 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

D10.4 Cellular therapy products transported internally shall be packaged in a closed and rigid outer container.

D10.4.1 The outer container for internal transport shall be labeled as defined in Appendix III B.

D10.5 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.

D10.5.1 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.

D10.5.2 The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transport or shipping.

D10.5.2.1 The temperature of the shipping container shall be continuously monitored during shipment of cellular therapy products.

D10.5.2.2 The shipping facility shall maintain a record of the temperature over the period of travel.

D10.5.3 The outer container shall be secured.

D10.5.4 The outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix III 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 III A.

D10.5.6 The outer container shall be labeled in accordance with Applicable Law regarding the cryogenic material used and the transport or shipment of biological materials.

D10.6 Cellular therapy products transported or shipped over an extended period of time shall be transported or shipped in a container within a temperature range defined in a Standard Operating Procedure or written agreement and according to manufacturer instructions.

D10.6.1 Additives to the cellular therapy product should be used for shipping over a prolonged duration of time.

D10.7 There shall be a risk assessment to evaluate the need for continuous temperature monitoring during transportation or shipment of cellular therapy products.

D10.8 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.

D10.9 The transit time shall be within time limits determined by the distributing facility in consultation with the receiving facility to maintain cellular therapy product safety.

D10.10 There shall be contingency plans for alternative means of transport or shipping in an emergency.

D10.11 The cellular therapy product shall be transported or shipped with required accompanying records as defined in the transportation and shipping Standard Operating Procedures and in compliance with D7.4.5 and D7.4.7.

D10.12 There shall be a record of the date and time of cellular therapy product distribution.

D10.13 Cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.

D11: RECEIPT AND DISTRIBUTION

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.

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.

D11.1.3 There shall be Standard Operating Procedures to verify that the cellular therapy product was appropriately transported or shipped.

D11.1.3.1 The receiving facility shall document the temperature inside the container upon arrival if shipped or transported on public roads.

D11.1.3.2 For cryopreserved cellular therapy products, the receiving facility records shall include documentation of the container temperature during shipping.

D11.1.4 The receiving facility shall review and verify cellular therapy product specifications provided by the manufacturer, if applicable.

~~D11.1.5 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.~~

D11.1.5 The receiving facility shall have readily available access to a summary of documents used to determine allogeneic donor eligibility.

D11.1.5.1 For cellular therapy products received from an external facility, there shall be documented evidence of donor eligibility screening and testing in accordance with Applicable Law.

D11.1.6 When cellular therapy products are returned to the Processing Facility after distribution for administration, there shall be documentation in the Processing Facility records of the events requiring return, the temporary storage temperature when at the clinical facility, the results of inspection upon return, and subsequent action taken to protect product safety and viability.

D11.1.6.1 The Processing Facility Director shall consult with the recipient's physician regarding reissue or disposal of the returned cellular therapy product.

D11.1.6.2 If the temperature of the cellular therapy product has been compromised, the Processing Facility Director shall give specific authorization to return the product to inventory.

D11.2 DISTRIBUTION CRITERIA

D11.2.1 The processing, collection, and transport or shipping records for each cellular therapy product shall be reviewed by the Processing Facility Director for compliance with Standard Operating Procedures and Applicable Law prior to product release or distribution.

D11.2.1.1 Records shall demonstrate traceability from the donor to the recipient and from the recipient to the donor.

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 product shall be retained in the processing record if such release is allowed by policies, Standard Operating Procedures, or package inserts of licensed products.

D11.2.3 Each cellular therapy product issued for administration shall be visually inspected by two (2) trained personnel immediately before release to verify the integrity of the product container and appropriate labeling.

D11.2.3.1 A cellular therapy product shall not be released when the container is compromised or recipient or donor information is not verified unless the Processing Facility Director gives specific authorization for the product's release.

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.

D11.3 DISTRIBUTION RECORDS

D11.3.1 The cellular therapy product distribution records shall permit tracking and tracing of the cellular therapy product, and shall contain the following information at a minimum:

D11.3.1.1 The proper product name and identifier.

D11.3.1.2 Unique identifier of the intended recipient.

D11.3.1.3 Documentation of allogeneic donor eligibility determination, as appropriate.

D11.3.1.4 Identification of the facilities that requested and distributed the product.

D11.3.1.5 Identity of the receiving facility.

D11.3.1.6 Date and time the cellular therapy product was distributed.

D11.3.1.7 Date and time the cellular therapy product was received.

D11.3.1.8 Identity of the transporting or shipping facility.

D11.3.1.9 Identity of personnel responsible for cellular therapy product transportation or shipping and of personnel responsible for receiving the product.

D11.3.1.10 Identity of the courier.

D11.3.1.11 Documentation of any delay or problems incurred during transportation or shipping.

D12: DISPOSAL

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

D12.1.1 A pre-collection written agreement between the storage facility and the designated recipient or the donor defining the length of storage and the circumstances for disposal of cellular therapy products.

D12.1.2 The option, if in accordance with Applicable Law, to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.

D12.1.3 Documentation of no further need for the cellular therapy product before any product is discarded.

D12.1.3.1 For HPC products, this shall include documentation of the designated recipient's death, if applicable.

D12.1.4 Approval by the Processing Facility Medical Director in consultation with the recipient's physician for cellular therapy product discard or other disposition, and method of disposal.

D12.1.5 A method of disposal and decontamination that meets Applicable Law for disposal of biohazardous materials or medical waste.

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 Recipients, donors, and associated Clinical Programs should be informed about policies for directed cellular therapy products as part of the informed consent process and before the cellular therapy product collection.~~

D12.2.2 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.

D12.3 The records for discarded or transferred cellular therapy products shall indicate the product was discarded or transferred, date of discard or transfer, disposition, and method of disposal or transfer.

D13: RECORDS

D13.1 There shall be a records management system for quality and cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

D13.1.1 A records management system shall be established and maintained to facilitate the review of records.

D13.1.2 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

D13.1.3 For cellular therapy products that are to be distributed for use at another institution, the Processing Facility shall inform the receiving institution of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

D13.1.4 Records shall be maintained to ensure their integrity, preservation, and retrieval.

D13.1.5 Records shall be accurate and legible.

D13.1.6 Written records shall be indelible.

D13.1.7 Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities, and health care providers and their recipients and donors, shall be established and followed in compliance with Applicable Law.

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

D13.3 RECORDS TO BE MAINTAINED

D13.3.1 Processing Facility records related to quality control, investigational protocols, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years after the creation of the cellular therapy product record, date of the cellular therapy product's distribution, disposition, or expiration, or, whichever is latest, or according to Applicable Law.

D13.3.2 Employee records shall be maintained in a confidential manner, as required by Applicable Law.

D13.3.3 Cleaning and sanitation records shall be retained for at least three (3) years, or longer in accordance with Applicable Law or regulations, or by a defined program or institution policy.

D13.3.4 Validation studies for a processing procedure shall be retained at a minimum until no cellular therapy products manufactured using that procedure remain in inventory.

D13.3.5 Records to allow tracking and tracing of cellular therapy products shall be maintained in a confidential manner for a minimum of ten (10) years after administration, distribution, disposition, or expiration of the cellular therapy product, or as required by Applicable Law, whichever is latest. These records shall include collection and processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product code, and donor and recipient identification as found on the original container.

D13.3.6 All records pertaining to the processing, testing, storage, or distribution of cellular therapy products shall be maintained for a minimum of ten (10) years after the date of administration, or if the date of administration is not known, ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, or the creation of the cellular therapy product record, whichever is most recent, or according to Applicable Law or institutional policy, whichever is latest.

D13.3.7 Research records shall be maintained in a confidential manner as required by Applicable Law or for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

D13.4 ELECTRONIC RECORDS

D13.4.1 The Processing Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum, systems that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures. For all critical electronic record systems:

D13.4.1.1 There shall be policies, Standard Operating Procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.

D13.4.1.2 There shall be a means by which access is limited to authorized individuals.

D13.4.1.3 A method shall be established, or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

D13.4.1.4 There shall be written Standard Operating Procedures for record entry, verification, and revision.

D13.4.1.5 A method shall be established, or the system shall provide for review of data before final acceptance.

D13.4.1.6 There shall be documented training of personnel in the system's use.

D13.4.1.7 There shall be a defined process for continued competency of personnel in the system's use.

D13.4.1.8 The utilization of electronic signatures shall be defined.

D13.4.1.9 Critical electronic record systems shall maintain unique identifiers.

D13.4.1.10 There shall be the ability to generate true copies of records in both human readable and electronic format suitable for inspection and review.

D13.4.1.11 There shall be protection of records to enable their accurate and ready retrieval throughout the period of record retention.

D13.4.1.12 All system modifications shall be authorized, documented, and validated prior to implementation.

D13.4.2 For all critical electronic record systems under the control of the Facility, there shall be validated processes for and documentation of:

D13.4.2.1 Prospective validation of systems, including hardware, software, and databases.

D13.4.2.2 Installation of the system.

D13.4.2.3 Numerical designation of system versions, if applicable.

D13.4.2.4 Authorization, documentation, and validation of all system modifications prior to implementation.

D13.4.2.5 Systems development including the verification of calculations and algorithms.

D13.4.2.6 System maintenance and operations.

D13.4.2.7 Monitoring of data integrity.

D13.4.2.8 Back-up of the electronic records system on a regular schedule.

D13.4.3 For each critical electronic record system, there shall be an alternative system to allow for continuous operation of the processing facility if the critical electronic record system is not available. The alternative system shall be validated, and processing staff shall be trained in its use.

D13.5 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

D13.5.1 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

D13.5.2 The Processing Facility shall furnish to the facility of final disposition a summary of records relating to the collection, processing, and storage procedures performed related to the safety, purity, or potency of the cellular therapy product involved.

D13.5.3 The Processing Facility shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a cellular therapy product.

APPENDIX I

MINIMUM NUMBER OF NEW PATIENTS FOR ACCREDITATION

Clinical Programs shall transplant at least the following number of new patients[1] before initial accreditation and annually thereafter:

Transplant Population	Clinical Site(s)	Type of Transplant	Twelve (12) Months Prior to Initial Accreditation	Average Per Year Within Accreditation Cycle
Adult OR Pediatric (only one of these two)	Single Clinical Site	Autologous only	5 autologous	5 autologous
		Allogeneic and Autologous	10 allogeneic recipients	10 allogeneic recipients
		IEC	Within a transplant program: 3	Within a transplant program: 3
	Multiple Clinical Sites	Autologous only	5 autologous recipients at each site	5 autologous recipients at each site
		Allogeneic and Autologous	• 10 allogeneic recipients at each applicable site[2] • 5 autologous at each applicable site[2]	• 10 allogeneic recipients at each applicable site[2] • 5 autologous at applicable each applicable site[2]
		IEC	• Within a transplant program: 3 at each applicable site	• Within a transplant program: 3 at each applicable site
Combined Adult AND Pediatric	Single Clinical Site	Autologous only	• 5 adult autologous • 5 pediatric autologous recipients	• 5 adult autologous • 5 pediatric autologous recipients
		Allogeneic and Autologous	• 5 adult allogeneic recipients • 5 pediatric allogeneic recipients	• 5 adult allogeneic recipients • 5 pediatric allogeneic recipients
		IEC	• Within a transplant program: 6 patients total; at least one in each applicable population	• Within a transplant program: 3 pediatric and 3 adults
	Multiple Clinical Sites	Autologous only	• 5 adult autologous at each applicable site • 5 pediatric autologous recipients at each applicable site	• 5 adult autologous recipients at each applicable site • 5 pediatric autologous recipients at each applicable site
		Allogeneic and Autologous	• ~~5~~ 5 adult allogeneic ~~recipients at each applicable site~~ • and 5 pediatric allogeneic ~~recipients at each applicable site~~ • 5 adult autologous at	• 5 adult allogeneic recipients at each site • 5 pediatric allogeneic recipients at each site • 5 adult autologous at each applicable site[2] • 5 pediatric autologous at each applicable site[2]

			each applicable site[2] • 5 pediatric autologous at each applicable site[2]	
		IEC	• Within a transplant program: 3 pediatric and 3 adults at each applicable clinical site	• Within a transplant program: 3 pediatric and 3 adults at each applicable clinical site
Stand Alone IEC			• 5 in each applicable population[3]	• 5 in each applicable population[3]

[1]The term "new allogeneic patient" or "new autologous patient" includes only a patient who received their first transplant of that type during the period of time in question.

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

[3]Applicable population refers to pediatric or adults with these populations being locally defined.

APPENDIX II

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

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

[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 21of the Code of Federal Regulations (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/or 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 of 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.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology. This includes all potential attributes, in addition to the core attribute referenced in this table (Anticoagulant, Volume, Storage Temperature): Intended Use, Manipulation, Cryoprotectant, Blood Component from Third-Party Donor, Preparation, Genetically Modified, Irradiation, Modification, Mobilization, Pooled Single, Cultured, Enrichment, and Reduction.

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

APPENDIX III

A: CELLULAR THERAPY PRODUCT LABELS FOR SHIPPING AND TRANSPORT ON PUBLIC ROADS

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

Element	Inner container document	Outer container label
Date of distribution	AC	AC
Time[1] of distribution, if appropriate	AC	AC
Statement "Do Not X-Ray" and /or "Do Not Irradiate", if applicable	AC	AF
Statements "Human Cells for Administration" or equivalent and "Handle with Care"	AC	AF
Shipper handling instructions	AC	AF
Shipping facility name, street address, contact person, and phone number	AC	AF
Receiving facility name, street address, contact person, and phone number	AC	AF
Biohazard and/or Warning Labels (as applicable, see C7.4, D7.4)	AC	-
If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" 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

APPENDIX IV

ACCOMPANYING DOCUMENTATION

Products collected in or designated for use in the U.S. shall be accompanied upon leaving the control of the Collection or Processing Facility with at least the elements detailed in the following 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 administered until completion of the donor eligibility determination, except under condition of urgent medical need	-	-	X
Listing of any required screening or testing that has not yet been completed	-	-	X
Results of donor screening that has been performed	-	-	X
Documentation that the physician using the cellular therapy product was notified of incomplete testing or screening	-	-	X
Instructions for product use to prevent the introduction, transmission, or spread of communicable diseases[1]	X	X	X
Instructions for reporting serious adverse reactions or events to the distributing facility[1, 5]	X	X	X

[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. Autologous donor eligibility determination is not required by the 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 (CLIA) of 1988 or those laboratories that have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services~~,~~ (CMS), or those that have met equivalent non-U.S. requirements. If communicable disease testing is not performed by a laboratory that meets regulatory requirements, the donor is ineligible. If a donor is ineligible for other reasons, but the testing was performed in a compliant laboratory, this statement must be included in the documentation.

[5]Access to the Clinical Program SOPs and forms could suffice when the distributing and clinical facilities are within the same institution.