
COMMON STANDARDS FOR CELLULAR THERAPIES



Draft Third Edition

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NOTICE

The FACT Common Standards for Cellular Therapies (Standards) are designed to provide minimum guidelines for programs, facilities, and individuals performing cellular therapy or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a program, facility, or individual should implement if the standard of practice in the community or applicable governmental laws or regulations establish additional requirements. Each program, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with these Standards is not an exclusive means of complying with the standard of care in the industry or community or with local, national, or international laws or regulations, and may not necessarily fulfill all the FDA requirements for 351 HCT/Ps. These Standards are not sufficient for accreditation for hematopoietic cellular therapy (HCT) programs, which are accredited according to the FACT – JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration.

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

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INTRODUCTION

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

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

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

STANDARDS DEVELOPMENT

All FACT Standards are developed by consensus of experts active in the field, based on the best available scientific and medical evidence. Draft Standards for each edition are initially published for public and professional comment and legal review. Appropriate revisions are incorporated into the final version. For those areas where there are few definitive studies or publications, the Standards Committee weighs the available evidence from preclinical studies and utilizes accepted scientific principles to reach consensus. Minimal standards have always required that there be in place a quality management program and that clinical outcomes be evaluated and reported.

Since 1996, FACT has been a leader in improving the quality of cellular therapy processes in the fields of hematopoietic progenitor cell (HPC) transplantation, immune effector cell therapies, and cord blood banking through its program of professional standards and voluntary accreditation. FACT was founded by clinical and laboratory scientists (members of the American Society for Transplantation and Cellular Therapy and the International Society for Cell and Gene Therapy, respectively) to be the standard setting and accreditation arm of these societies, in the belief that quality medical and laboratory care would be enhanced through comprehensive, peer-developed professional standards and voluntary accreditation. In addition, the founders sought to minimize

unnecessary regulatory burden and to protect and foster an environment of research and development that advances the field.

ACCREDITATION

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

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

TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

PART A

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

PART A: TERMINOLOGY, TENETS, ABBREVIATIONS, AND DEFINITIONS

A1 TERMINOLOGY

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

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

A2 TENETS

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

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

~~A2.2—Applicant organizations are responsible for providing verifiable documentation of evidence of compliance with these Standards.~~

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

A2.3 Standards related to services not provided by the applicant do not apply to the applicant organization. The ~~burden—responsibility~~ to demonstrate that a requirement is not applicable rests with the applicant organization.

A3 ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

| | |
|---------------------|--|
| <i>ABO</i> | Major human blood group including erythrocyte antigens, A, B, O |
| <i>AC</i> | Accompany |
| <i>AF</i> | Affixed |
| <i>Anti-</i> | Antibody to the antigen designated |
| <u><i>APP</i></u> | <u>Advanced Practice Provider/Professional</u> |
| <i>ASHI</i> | American Society for Histocompatibility and Immunogenetics |
| <u><i>ASTCT</i></u> | <u>American Society for Transplantation and Cellular Therapy</u> |
| <i>AT</i> | Attached |
| <u><i>CAP</i></u> | <u>College of American Pathologists</u> |
| <u><i>CAPA</i></u> | <u>Corrective and Preventive Action</u> |
| <u><i>CFR</i></u> | <u>Code of Federal Regulations</u> |
| <i>CIBMTR</i> | Center for International Blood and Marrow Transplant Research |
| <i>DNA</i> | Deoxyribonucleic acid |
| <i>EBMT</i> | European Society for Blood and Marrow Transplantation |

| | |
|-------------------------|---|
| <i>EFI</i> | European Federation for Immunogenetics |
| <i>EU</i> | European Union |
| <i>FACT</i> | Foundation for the Accreditation of Cellular Therapy |
| <i>FDA</i> | U. S. Food and Drug Administration |
| <i>GMP</i> | Current Good Manufacturing Practices |
| <i>HLA</i> | Human leukocyte antigen |
| <i>HPC</i> | Hematopoietic progenitor cell |
| <i>IND</i> | Investigational new drug |
| <i>IRB</i> | Institutional Review Board |
| <i>ISCT</i> | International Society for Cell and Gene Therapy |
| <i>JACIE</i> | Joint Accreditation Committee – ISCT and EBMT |
| <i>MNC</i> | Mononuclear cell |
| <i>MSC</i> | Mesenchymal stromal cell or mesenchymal stem cell |
| <i>QM</i> | Quality management |
| <i>RBC</i> | Red blood cell |
| <i>Rh</i> | Rhesus systems of human red <u>blood</u> cell antigens; used in this document to refer to the Rh (D) antigen only, unless otherwise specified |
| <i>SOP</i> | Standard Operating Procedure |
| <i>US</i> | United States |

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.

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 biologic relationship between genetically distinct individuals of the same species.

And/or: Both or either 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, facility where collection activities are performed, or Processing Facility.

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

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

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

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

Autologous: Derived from and intended for the same individual.

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

Calibrate: To set measurement equipment against a known standard.

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) that is procured from a donor and intended for processing or administration.

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.

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

Chimerism: The coexistence of cells of more than one genotype in a single individual. In cellular therapy, chimerism generally refers to the presence of allogeneic donor cells in the recipient.

Chimerism testing: Assessment of the presence of allogeneic donor cells in a 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 providing cellular therapy services and housed in a defined location that includes a Clinical Program Director and demonstrates common staff training, protocols, Standard Operating Procedures, quality management systems, clinical outcome analysis, and regular interaction among clinical sites.

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

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

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

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

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

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

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

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

Critical document: A document that is directly related to and could impact donor welfare, recipient care, or cellular therapy product integrity.

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 approval as the best course of action when adherence to the established course or accepted practice is not feasible or possible.

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

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

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

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

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, and to create or store information used in critical procedures.

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

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

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

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

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.

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.

General Medical Physician: A physician who has training and experience in the cellular therapy that has not been defined or documented, including specialists in the therapeutic disease areas.

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. do not meet criteria doe regulation solely under section 361 of the Public Health Services Act (see 21 CFR 1271.10(a)), and are controlled under GMP regulations. Similar requirements are delineated by the European Union as EU-GMP, and other countries such as the United Kingdom, Australia, Canada, and Singapore have equally well-developed systems of regulations.

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

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

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

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

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

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 that selectively removes, enriches, expands, or functionally alters the cellular therapy product.

Minimally Manipulated: For cells or non-structural tissues, 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: For cells or non-structural tissues, 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 recoverycollection, 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 mononuclear cells from the bone marrow cavity for hematopoietic reconstitution in the recipient or for further cellular therapy product manufacture. This does not include marrow aspirations intended for diagnostic purposes.

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

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

New patient: An individual receiving cellular therapy for the first time in the Clinical Program, whether or not that patient was previously treated by that Clinical Program.

Occurrence: An incident in which an action or circumstance or event that is out of compliance and may results in errors, accidents, deviations, adverse events, adverse reactions, or complaints.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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 www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology.

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

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

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

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

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

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

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

Standards: The current edition of the *FACT Common Standards for Cellular Therapies*, which may be referred to herein as “Standards” or “FACT 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: Complete or partial manufacturing of a cellular therapy product outsourced to a separate entity.

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.

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.

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

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CLINICAL PROGRAM STANDARDS

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PART B: CLINICAL PROGRAM STANDARDS

B1: GENERAL

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

B1.1.1 These Standards apply to all cellular therapy 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 analysis, and regular interaction among all clinical sites.

B1.2 The Clinical Program shall verify that use cell collection procedures and processing facilities ~~that~~ meet FACT Standards, ~~with respect to their interactions with the Clinical Program.~~

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

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

B1.2.1.2 Cellular therapy product storage and distribution.

B1.2.1.3 Verification of cellular therapy product identity.

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

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

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

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

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

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

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

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

B2: CLINICAL UNIT

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

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

B2.3 The Clinical Program shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operation.

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

- B2.4.1 There shall be provisions for prompt evaluation and treatment by a physician who specializes in the therapeutic disease area available on a 24-hour basis.
- B2.4.2 There shall be a pharmacy providing 24-hour availability of medications needed for the care of cellular therapy patients.
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B2.5 There shall be access to an intensive care unit or emergency services.

- B2.5.1 There shall be written guidelines for communication, patient monitoring, and prompt triage or transfer of patients to an intensive care unit, emergency department, or equivalent when appropriate.
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B2.6 There shall be attending physician oversight if general medical physicians or APPs provide care to cellular therapy patients. The scope of responsibility of general medical physicians or APPs shall be defined.

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

B2.8 [Testing to monitor chimerism](#) ~~Chimerism testing~~ shall be performed in laboratories accredited for the techniques used ~~or using validated techniques~~.

B2.9 The Clinical Program shall be operated in a manner designed to minimize risks to the health and safety of [all individuals](#) ~~employees, patients, caregivers, visitors, and volunteers~~.

B2.10 The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen;

communicable disease; and to chemical, biological, ~~or radiological~~, electrical, or fire hazards.

B2.11 All waste generated by Clinical Program activities shall be disposed of in a manner that minimizes hazard to facility personnel and to the environment in accordance with Applicable Law.

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

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

B3.1.2 The Clinical Program Director shall have a minimum of two (2) years of experience as an attending physician responsible for the direct clinical management of patients in the applicable therapeutic disease areas throughout the continuum of care.~~in the inpatient and outpatient settings.~~

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

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

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

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

B3.1.5.2 The Clinical Program Director ~~or designee~~ shall be responsible for verifying ~~the knowledge and skills competency~~ of members of the Clinical Program ~~annually, once per accreditation cycle, at a minimum.~~

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

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

B3.2 ATTENDING PHYSICIANS

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

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

B3.2.2 Attending physicians shall each have had a minimum ~~total~~ of one year of supervised training in the management of patients in the applicable therapeutic disease area throughout the continuum of care, in both inpatient and outpatient settings.

B3.2.3 Attending physicians shall ~~annually~~ participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy.

B3.2.3.1 Continuing education shall include, but is not limited to, activities related to the specific cellular therapy administered within the Clinical Program.

B3.3 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

B3.3.1 Clinical Program Directors and attending physicians shall have received specific training ~~and maintain competency and assessed annually~~ in each of the following areas as applicable to the Clinical Program's services:

B3.3.1.1 Indications for cellular therapy.

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

B3.3.1.3 Donor selection, evaluation, and management.~~Product characteristics including donor eligibility determination.~~

B3.3.1.4 Informed consent of the ~~patient recipient and, if required, donor~~ consistent with institutional policy and Applicable Law.

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

B3.3.1.6 ~~Cellular therapy product a~~Administration of preparative regimen and patient management.

B3.3.1.7 Adverse events associated with cellular therapy.

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

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

B3.3.1.10 Evaluation of late effects of cellular therapy.

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

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

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

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

B3.3.2.2 Donor eligibility determination.

B3.3.2.3 Methodology and implications of HLA typing.

B3.3.2.4 Methodology and implications of testing for chimerism.

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

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

~~B3.3.3.1 Cellular therapy product c~~Collection.

~~B3.3.3.2 Cellular therapy product p~~Processing.

~~B3.3.3.3 Cellular therapy product c~~Ryopreservation.

B3.3.3.4 Shipping and transportation.

B3.3.3.5 Storage.

B3.4 PHYSICIANS-IN-TRAINING

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

B3.4.2 Physicians-in-training shall receive specific training and develop competence in patient management, and the skills related to the therapeutic disease areas that they routinely practice, included within but not limited to those listed in B3.3.1B3.2.4 and B3.2.5B3.3.2.

B3.5 ADVANCED PRACTICE PROVIDERS/PROFESSIONALS (APPs)

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

B3.5.2 APPs shall have received specific training and maintain competence in patient management, and the skills related to the therapeutic disease areas that they routinely practice, included within but not limited to those listed in B3.3.1B3.2.4 and B3.3.2B3.2.5.

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

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

B3.6 CLINICAL PROGRAM TEAM

B3.6.1 Clinical Programs treating pediatric recipients or donors shall have a team trained in the management of pediatric patients.

B3.6.2 Clinical Programs treating adult recipients or donors shall have a team trained in the management of adult patients.

B3.6.3 The Clinical Program shall utilize personnel who are trained and competent for the collection of the cellular therapy product and who use a collection process that meets these Standards.

B3.7 NURSES

B3.7.1 The Clinical Program shall have nurses formally trained and experienced in the management of patients in the therapeutic disease areas.

B3.7.1.1 Nurses shall be trained in age-specific management of patients receiving cellular therapy.

B3.7.1.2 Clinical Programs treating pediatric recipients or donors shall have nurses formally trained and experienced in the management of pediatric patients.

~~B3.6.3 Clinical Programs treating adult recipients or donors shall have nurses formally trained and experienced in the management of adult patients.~~

B3.7.2 Nurses shall have received specific training and maintain competence in the cellular therapy related skills that they ~~routinely~~ practice including:

B3.7.2.1 Administration of preparative medications.

B3.7.2.2 Administration of cellular therapy products.

B3.7.2.3 Care interventions to manage cellular therapy related complications.

B3.7.2.4 Recognition of cellular therapy related complications and emergencies requiring rapid notification of the clinical team.

B3.7.3 There shall be an adequate number of nurses experienced in the care of patients in the applicable therapeutic disease areas.

B3.7.4 There shall be a nurse/recipient ratio satisfactory to manage the severity of the recipients' clinical status.

B3.8 PHARMACISTS

B3.8.1 Pharmacists shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to a scope of practice within the parameters of their training and licensure.

B3.8.2 Training and knowledge of designated pharmacists shall include:

B3.8.2.1 An overview of the process of cellular therapy.

B3.8.2.2 Pharmacological management of expected complications, if applicable.

B3.9 CONSULTING SPECIALISTS

B3.9.1 The Clinical Program shall define and have access to certified or trained consulting specialists or specialist groups from key disciplines who are

capable of assisting in the management of recipients or donors requiring medical care.

B3.9.2 A Clinical Program treating pediatric recipients or donors shall define and have access to consultants qualified to manage pediatric patients.

~~B3.8.3 A Clinical Program treating adult recipients or donors shall define and have access to consultants qualified to manage adult patients.~~

B3.10 QUALITY MANAGER

B3.10.1 There shall be a Clinical Program Quality Manager to establish and maintain systems to review, modify, and approve all policies and Standard Operating Procedures intended to monitor compliance with Applicable Law, these Standards, or the performance of the Clinical Program.

~~B3.9.2 The Clinical Program Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.~~

B3.10.2 The Clinical Program Quality Manager shall ~~annually~~ participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy and quality management.

B3.10.2.1 Continuing education shall include, but is not limited to, activities related to the specific cellular therapy administered within the Clinical Program and Quality Management.

B3.11 SUPPORT SERVICES STAFF

B3.11.1 The Clinical Program shall have one or more designated staff with appropriate training and education to assist in ~~the provision of pre-cellular therapy product administration,~~ recipient evaluation, ~~treatment,~~ and post-cellular therapy product administration, and follow-up ~~and~~ care.

B3.11.1.1 Designated staff shall include data management staff.

B4: QUALITY MANAGEMENT

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

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

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

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

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

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

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

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.
 - B4.4.2.4 Continued competency for each critical function performed, assessed annually at a minimum.
 - B4.4.2.5 Continuing education.
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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, and Standard Operating Procedures.

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 development, approval, implementation, distribution, review, revision, and archival of all critical documents.

B4.5.3 The document control system shall include:

B4.5.3.1 A standardized format for ~~each critical documents, type including, but not limited to, policies, protocols, Standard Operating Procedures, worksheets, forms, and labels.~~

B4.5.3.2 Assignment of a numeric or an alphanumeric identifier and a title to each document and document version regulated within the system.

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 changes as applicable, effective date, and archival date.

B4.5.3.7 Archival of controlled documents including ~~policies and Standard Operating Procedures~~, the inclusive dates of use, and their historical sequence for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

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

~~B4.5.3.8 A system for record creation, assembly, review, storage, archival, and retrieval.~~

B4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for 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 Applicable Law and these Standards.

B4.6.3 Agreements should include the responsibility of the external parties to provide clinically relevant information related to products or services.

B4.6.4 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 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/or~~ recipient type shall be evaluated.
- B4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:
- B4.7.3.1 An endpoint of clinical function as approved by the Clinical Program Director, ~~or designee~~.
- B4.7.3.2 Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration or in accordance with Applicable Law.
- 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.
- B4.8 The Quality Management Plan shall include, or summarize and reference, policies, Standard Operating Procedures for, and a schedule of, audits of the Clinical Program's activities to verify compliance with the Quality Management Program, and operational policies and Standard Operating Procedures, Applicable Law, and these Standards.
- B4.8.1 Audits shall be conducted by an individual with sufficient knowledge of the process and competence in auditing~~expertise~~ to identify problems, but who is not solely responsible for the process being audited.

- B4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow up on the effectiveness of these actions in a timely manner.
- B4.8.3 Audits shall be performed annually at a minimum, and shall include at ~~a minimum least the following~~:
- B4.8.3.1 ~~Periodic audit of the a~~Accuracy of clinical data.
 - B4.8.3.2 ~~Annual audit of donor screening and testing. Documentation of proper donor eligibility and suitability determination.~~
 - B4.8.3.3 ~~Annual audit of m~~Management of cellular therapy products with positive microbial culture results.
 - B4.8.3.4 ~~Annual audit of i~~Infectious disease resulting from cellular therapy product collection or administration.
 - B4.8.3.5 ~~Annual audit of d~~Documentation that external facilities performing critical services met the requirements of the written agreements.
 - B4.8.3.6 ~~Annual audit of~~Chain of identity and chain of custody of cellular therapy products.

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, recipient's physician, collection staff, processing staff, any other facility in receipt of the cellular therapy product, and, if relevant, the donor and the sponsor.
- B4.9.3 Recipient follow-up~~and outcome analysis.~~
- B4.9.4 Follow-up of the donor, if relevant.

- B4.9.5 Documentation and investigation of cause.
- B4.9.6 Reporting to regulatory agencies, as required by Applicable Law.

B4.10 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for ~~Occurrences~~ (errors, accidents, deviations, adverse events, adverse reactions, and complaints)~~(See A4 Definitions)~~. 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 staff and Processing Facility, and other~~ all entities involved in the collection, manufacture, testing, or administration of the cellular therapy product, as appropriate.

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

B4.10.2.3 Occurrences shall be tracked and trended.

B4.10.3 Documentation.

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

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

~~B4.9.3.3 Cumulative files of Occurrences shall be maintained.~~

B4.10.3.3 Cumulative files of occurrences shall be maintained and shall include written investigation reports containing conclusions, follow-up, corrective and preventive actions, and a link to the records s(s) of the involved cellular therapy products s(s), donors s(s), and recipients s(s), 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 made available to the donor's and recipient's physician(s), as applicable, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by Applicable Law.

B4.10.4.2 Occurrences shall be reported as required to other facilities performing cellular therapy product functions on the affected cellular therapy product, ~~and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.~~

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

B4.10.5 Corrective and preventive action.

B4.10.5.1 Corrective and preventive action shall be implemented, 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 action shall be performed in a timeframe as indicated in the investigative report.

B4.11 There shall be a process for the regular review and assessment of activities to identify recurring problems, potential points of failure, or need for process improvement.

B4.12 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for cellular therapy product ~~tracking and tracing 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.

B4.13 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.

B4.14 The Quality Management Plan shall include, or summarize and reference policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services relevant to the cellular therapy product.

~~B4.13.1 Critical equipment, supplies, reagents, and facilities used for the collection procedure shall be qualified.~~

~~B4.14.1 Qualification plans shall include minimum acceptance criteria for performance.~~

~~B4.14.2 Qualification shall be required following any significant changes to these items.~~

B4.14.3 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Clinical Program Director ~~or designee~~.

B4.15 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

B4.15.1 Critical procedures to be validated shall include at least collection procedures, labeling, storage, ~~and~~ distribution, preparation for administration, and infusion.

B4.15.2 Each validation or verification shall include at a minimum:

B4.15.2.1 An approved ~~validation~~ plan, including conditions to be ~~validated~~ assessed.

B4.15.2.2 Acceptance criteria.

B4.15.2.3 Data collection.

B4.15.2.4 Evaluation of data.

B4.15.2.5 Summary of results.

B4.15.2.6 References, if applicable.

B4.15.2.7 Review and approval of the ~~validation~~ plan, results report, and conclusion by the Medical-Clinical Program Director ~~of collection activities or designee~~ and the Quality Manager ~~or designee~~.

B4.15.3 Significant changes to critical procedures shall be validated or verified as appropriate.

B4.16 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the evaluation of risk in changes to a process to assess the effect of the change elsewhere in the operation.

~~B4.16 The Quality Management Plan should include, or summarize and reference, policies and Standard Operating Procedures for obtaining feedback.~~

~~B4.16.1 Feedback should be obtained from associated collection staff and Processing Facilities.~~

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

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

B4.17.1 ~~Key p~~Performance data and review findings shall be reported to key positions and staff.

B4.17.2 The meetings ~~should~~ shall have ~~designated~~ defined attendees, documented minutes, and assigned actions.

B4.17.3 The Clinical Program Director ~~or designee~~ shall not ~~have oversight of~~ approve his/her own work, ~~if this person also performs other tasks in the Clinical Program.~~

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- B4.18 The Clinical Program Director ~~or designee~~ shall annually review the effectiveness of the overall Quality Management Program.
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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 Recipient evaluation, selection, and treatment across the continuum of care related to cellular therapy.
 - B5.1.2 Donor and recipient confidentiality.
 - B5.1.3 Donor and recipient informed consent related to treatment, cellular therapy product collection, and storage.
 - B5.1.4 Donor search and selection, including screening, testing, eligibility determination, ~~selection,~~ and management.
 - B5.1.5 Preparation of the recipient prior to cellular therapy product administration.
 - B5.1.6 Administration of preparative regimens.
 - B5.1.7 Administration of blood products.
 - B5.1.8 Administration of cellular therapy products, including products under exceptional release.
 - B5.1.9 Management of ABO incompatible products, if applicable.
 - B5.1.10 Detection and management of complications that include toxicities related to preparative medications or cellular therapy product administration.

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

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

B5.1.13 Disposal of medical and biohazard waste.

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

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

B5.2 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 end-points and the range of expected results.

B5.3.4 A stepwise description of the procedure.

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

B5.3.6 Age-specific issues where relevant.

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

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

- B5.3.9 Documented approval of each modification to a Standard Operating Procedure~~procedural modification~~ by the Clinical Program Director or designated physician prior to implementation.
- B5.3.10 Reference to current version of orders, worksheets, reports, labels, and forms.

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

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

~~B5.5.1 Staff knowledge shall be documented before implementing a new or revised policy.~~

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

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

- B6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:
 - B6.2.1.1 The risks and benefits of the procedure.
 - B6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.
 - B6.2.1.3 The rights of the donor or legally authorized representative to review the results of such tests according to Applicable Law.
 - B6.2.1.4 Alternative collection methods.
 - B6.2.1.5 Protection of medical information and confidentiality.
- B6.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.
 - B6.2.2.1 Family members and legally authorized representatives ~~should~~ 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 ~~at any time~~.
 - B6.2.4.1 The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal or withdrawal.
- B6.2.5 Donor informed consent for the cellular therapy product donation shall be obtained and documented by a licensed health care professional familiar with the collection procedure.
 - 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.

- B6.2.7 The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician or the recipient.
 - B6.2.8 The donor shall be informed of the policy for cellular therapy product discard, including actions taken when an intended recipient no longer requires the cellular therapy product.
 - B6.2.9 Documentation of consent shall be made available to collection staff prior to the collection procedure.
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B6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

- B6.3.1 There shall be criteria and evaluation policies 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 tested as required by Applicable Law.
- B6.3.2 The risks of donation shall be evaluated and documented.
- B6.3.3 A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to preparation for collection or undergoing anesthesia.
- B6.3.4 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, certified, or licensed in accordance with Applicable Law.
- B6.3.5 The Clinical Program shall inform collection staff and the Processing Facility of donor test results or if any testing was not performed.

- B6.3.6 There shall be a written order from a physician specifying, at a minimum, an anticipated date and goals of collection and processing.
- B6.3.7 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the administering physician.
- B6.3.7.1 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the collection staff prior to collection.
- B6.3.8 There shall be a policy or Standard Operating Procedure for the management of collection-associated adverse events and follow-up of donors that includes routine management.
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B6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

- B6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated as those terms are defined by Applicable Law.
- B6.4.2 Allogeneic donor infectious disease testing shall be performed using donor screening tests that are licensed, approved, or cleared by the governmental authority.
- B6.4.2.1 Hemodilution efin the donor prior to collection of blood samples for infectious disease testing and acceptance criteria shall be assessed and documented.
- B6.4.3 For allogeneic products containing red blood cells sufficient to cause a transfusion reaction, donors and recipients shall be tested for ABO group and Rh type using two (2) independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.
- B6.4.4 When relevant, a red blood cell antibody screen shall be performed on allogeneic recipients.
- B6.4.5 Allogeneic donors shall be evaluated for risk factors that might result in disease transmission from the cellular therapy product by medical history, physical examination, examination of relevant medical records, and laboratory testing.

- B6.4.6 When appropriate for the cellular therapy product, the medical history for allogeneic donors shall include at least the following:
- B6.4.6.1 Vaccination history.
 - B6.4.6.2 Travel history.
 - B6.4.6.3 Blood transfusion history.
 - B6.4.6.4 Questions to identify persons at high risk for transmission of relevant communicable disease agents as defined by the applicable governmental authority.
 - ~~B6.4.6.5 Questions to identify persons at risk of transmitting inherited conditions.~~
 - B6.4.6.5 Questions to identify persons at risk of transmitting a hematologic, ~~al or~~ immunological disease, or genetic conditions.
 - B6.4.6.6 Questions to identify a past history of malignant disease.
 - B6.4.6.7 The allogeneic donor shall confirm that all the information provided is true to the best of his/her knowledge.
- B6.4.7 Allogeneic donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests as required by Applicable Law:
- B6.4.7.1 Human immunodeficiency virus, type 1.
 - B6.4.7.2 Human immunodeficiency virus, type 2.
 - B6.4.7.3 Hepatitis B virus.
 - B6.4.7.4 Hepatitis C virus.
 - B6.4.7.5 *Treponema pallidum* (syphilis).
- B6.4.8 If required by Applicable Law, allogeneic donors shall also be tested for evidence of clinically relevant infection by the following disease agents:
- B6.4.8.1 Human T Cell lymphotropic virus I.

B6.4.8.2 Human T Cell lymphotropic virus II.

B6.4.8.3 West Nile Virus.

B6.4.8.4 *Trypanosoma cruzi* (Chagas Disease).

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

B6.4.9.1 For viable, lymphocyte rich cells, including mononuclear cells and other cellular therapy products, blood samples from allogeneic donors shall be obtained within seven (7) days prior to or after collection in the U.S. or 30 days prior to collection in European Union member states.

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

B6.4.11 Additional tests shall be performed as required to assess the possibility of transmission of other infectious and non-infectious diseases.

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

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

B6.4.12.2 Verification typing shall be performed on the recipient and selected allogeneic donor using an independently collected samples. Results shall be confirmed prior to administration of the preparative regimen, mobilization, or cellular therapy product collection, whichever is earliest.

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

B6.4.13 Allogeneic donor eligibility, as defined by Applicable Law, shall be determined by a licensed health care provider~~physician~~ after history, exam, medical record review, and testing. The donor eligibility

determination shall be documented in the recipient's medical record before the recipient is prepared for administration and before the allogeneic donor begins the mobilization regimen, if applicable.

- B6.4.14 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.
- B6.4.15 The use of an ineligible allogeneic donor, or an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of the rationale for his/her selection by the administering physician, urgent medical need documentation, and the informed consent of the donor and the recipient.
- B6.4.16 Allogeneic donor eligibility and suitability shall be communicated in writing to the Collection personnel and Processing Facilities.
- B6.4.17 There shall be a policy covering the creation, and retention of allogeneic donor records.

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

B6.5 ALLOGENEIC CELLULAR THERAPY PRODUCTS MANUFACTURED FOR MULTIPLE RECIPIENTS

- B6.5.1 At the time of selection for administration, the Clinical Program shall request all technical data from the cellular therapy product manufacturing facility regarding the product after processing prior to cryopreservation, including at a minimum:
 - B6.5.1.1 Total count of relevant cell.
 - B6.5.1.2 Viability and/or potency, if applicable.
 - B6.5.1.3 Microbial cultures from the cellular therapy product after processing prior to cryopreservation.
 - B6.5.1.4 ABO group and Rh type, if applicable.
 - B6.5.1.5 All HLA Class I and II typing results, if applicable.
 - B6.5.1.6 Communicable disease testing results performed on the donor.

- B6.5.1.7 Final donor eligibility determination and risks of communicable and/or genetic diseases disclosed by the donor medical and genetic screening or clinical chart review and the results of any investigation or further testing performed.
 - B6.5.1.8 The method of processing.
 - B6.5.1.9 Any variances in collection, processing, testing, cryopreservation, storage, or transport or shipping procedures that may influence the integrity or quality of the cellular therapy product.
 - B6.5.1.10 Physical characteristics of the cellular therapy product, including at a minimum the number and type of bags or compartments used for storage.
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B7: RECIPIENT CARE

- B7.1 Recipient informed consent for the cellular therapy shall be obtained and documented by a licensed healthcare professional knowledgeable of familiar ~~with~~ the proposed therapy.
 - B7.1.1 The Clinical Program shall provide information regarding the risks and benefits of the proposed cellular therapy.
 - B7.2 The attending physician shall confirm the availability and suitability of a donor or cellular therapy product prior to preparing the recipient for cellular therapy.
 - 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, if appropriate, times.
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- B7.4 There shall be policies or Standard Operating Procedures addressing safe administration of the preparative medication regimen, if applicable.
- 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 equivalents shall be used for protocols and standardized regimens. These orders shall be verified and documented by an attending physician.
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- B7.5 There shall be policies or Standard Operating Procedures addressing safe administration of cellular therapy products.
- B7.5.1 The cellular therapy product shall be administered by a licensed healthcare professional trained in the procedure.
- B7.5.2 Two (2) qualified persons shall verify the identity of the recipient and the product and the order for administration prior to the administration of the cellular therapy product.
- ~~B7.5.2 Cellular therapy products shall be filtered to remove particulate material prior to administration using filters that are non-reactive.~~
- B7.5.3 There shall be documentation in the recipient's medical record of the unique identifier of the administered cellular therapy product unique identifier, initiation and completion times of administration, and any adverse events related to administration.
- B7.5.4 A circular of information or investigator's brochure for cellular therapy products shall be available to staff.
- B7.6 There shall be policies or Standard Operating Procedures addressing appropriate follow-up after administration of cellular therapy products.
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- B7.7 There shall be policies or Standard Operating Procedures in place for the planned discharge and provision of follow-up care.
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- B7.8 There shall be policies or Standard Operating Procedures in place for provision of appropriate long-term follow-up care to recipients.

B8: CLINICAL RESEARCH

- B8.1 Clinical Programs shall have formal review of investigational treatment protocols and patient consent forms by a process that is approved under institutional policies and Applicable Law.
- B8.1.1 Clinical Programs utilizing investigational treatment protocols shall have in place a pharmacy equipped for research activities, including a process for tracking, inventory, and secured storage of investigational drugs.
- B8.1.2 There shall be a process to manage investigational cellular therapy products.
- B8.2 ~~Clinical research protocols shall be performed in accordance with institutional policies and Applicable Law. Documentation for all research protocols performed by the Clinical Program shall be maintained in accordance with institutional policies and Applicable Law, including audits; approvals by the Institutional Review Board, Ethics Committee, or equivalent; correspondence with regulatory agencies; and adverse events including the resolution.~~
- 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 language he or she can

understand, and under circumstances that minimize the possibility of coercion or undue influence.

- B8.3.1 The research subjects or legally authorized representatives, shall be given the opportunity to ask questions and to have his/her questions answered to his/her satisfaction, and to withdraw from the research without prejudice.
- B8.3.2 Informed consent for a research subject shall contain the following elements at a minimum and comply with Applicable Law:
 - B8.3.2.1 An explanation of the research purposes, a description of the procedures to be followed, and the identification of investigational procedures.
 - B8.3.2.2 The expected duration of the subject's participation.
 - B8.3.2.3 A description of the reasonably expected risks, discomforts, benefits to the subject and others, and alternative procedures.
 - B8.3.2.4 A statement of the extent to which confidentiality will be maintained.
 - B8.3.2.5 An explanation of the extent of compensation for injury.
 - B8.3.2.6 Contact information for the person research subjects can contact in case of questions or concerns.

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

- B9.1 The Clinical Program shall collect and maintain complete and accurate all the data necessary to complete the Cellular Immunotherapy Data Resource (CIDR) forms or the Cellular Therapy Med-A forms of the EBMT~~Cellular Therapy Essential Data Forms of the CIBMTR for Regenerative Medicine or the Minimum Essential Data-A forms of the EBMT.~~

- B9.1.1 Clinical Programs shall submit the data specified in B9.1 to a national or international database if required by Applicable Law.
- B9.1.2 Clinical Programs should collect the data specified in B9.1 for all patients for at least one (1) year following administration of the cellular therapy product.
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B9.2 The Clinical Program shall define staff responsible for collecting and reporting data.

- B9.2.1 Defined data management staff should ~~annually~~ participate in continuing education annually.
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B10: RECORDS

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

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

B10.1.2 Cleaning and sanitation records shall be retained for a minimum of three (3) years or longer in accordance with Applicable Law, or by a defined program or institution policy.

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

B10.2 Recipient and donor records including, but not limited to, consents and records of care, shall be maintained in a confidential manner as required by Applicable Law for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration, whichever is latest.

- B10.3 Research records shall be maintained in a confidential manner as required by Applicable Law for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.
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B10.4 ELECTRONIC RECORDS

- B10.4.1 The Clinical Program shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the Clinical Program that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.
- B10.4.2 For all critical electronic record systems, there shall be policies, Standard Operating Procedures, and system elements to maintain the accuracy, integrity, identity, and confidentiality of all records.
- B10.4.3 There shall be a means by which access to electronic records is limited to authorized individuals.
- B10.4.4 The critical electronic record system shall maintain unique identifiers.
- B10.4.5 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.
- B10.4.6 For each critical electronic record system, there shall be an alternative system for all electronic records to allow for continuous operation in the event that a critical electronic record system is not available. The alternative system shall be validated and Clinical Program staff shall be trained in its use.
- B10.4.7 For all critical electronic record systems, there shall be written Standard Operating Procedures for record entry, verification, and revision.
- B10.4.7.1 A method shall be established or the system shall provide for review of data before final acceptance.
- B10.4.7.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

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

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

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

B10.4.9.2 Monitoring of data integrity.

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

B10.4.9.4 System assignment of unique identifiers.

B10.5 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

B10.5.1 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

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

COLLECTION STANDARDS

PART C

- C1 General
- C2 Collection ~~Activities~~ Environment
- 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 Process Controls
- C9 Cellular Therapy Product Storage
- C10 Cellular Therapy Product Transportation and Shipping
- C11 Records

PART C: COLLECTION STANDARDS

C1: GENERAL

C1.1 These Standards apply to all collection, storage, and distribution ~~activities~~ services performed on cellular therapy products ~~obtained from living donors~~.

C1.2 Collected cellular therapy products shall be distributed to ~~cell processing~~ facilities that meet ~~the FACT~~ Standards with respect to their role in ~~the cellular therapy product manufacturing process~~.

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

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

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

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

C2: COLLECTION ~~ACTIVITIES~~ ENVIRONMENT

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

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

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

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

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

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

C2.4 There shall be a written assessment of critical parameters of the facility in which collection is performed that may affect cellular therapy product viability, integrity, contamination, or cross-contamination during collection.

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

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

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

C2.6 There shall be adequate equipment and materials for the procedures performed.

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

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

C2.9 The facility in which collection is performed shall be operated in a manner designed to minimize risks to the health and safety of employees, donors, visitors, caregivers, and volunteers.

C2.10 There shall be a written safety manual that includes instructions for action in case of exposure to communicable disease and to chemical, biological, ~~or~~ radiological, electrical, or fire hazards.

C2.11 All waste generated by collection activities shall be disposed of in a manner that minimizes hazard to facility personnel and to the environment in accordance with Applicable Law.

C2.12 ~~Gloves, p~~Personal protective equipment, including gloves and protective clothing shall be used while handling biological specimens. Such protective ~~clothing equipment~~ shall not be worn outside the work area.

C2.13 When a collection kit is prepared and sent to collection staff, there shall be adequate instructions and materials to collect, label, store, pack, and transport or ship the cellular therapy product and associated samples to the Processing Facility.

C2.13.1 The collection kit shall be transported or shipped under conditions validated to maintain the designated temperature range from the time it leaves the shipping facility until it is received by the collection staff.

C3: PERSONNEL

C3.1 MEDICAL DIRECTOR OF COLLECTION ACTIVITIES SERVICES

C3.1.1 There shall be a Medical Director who is a licensed physician with postgraduate training in the methods required for cellular therapy product collection or the therapeutic disease areas.

C3.1.2 The Medical Director or designee shall be responsible for the following elements:

C3.1.2.1 All technical procedures.

- C3.1.2.2 Performance of the collection procedures.
 - C3.1.2.3 Supervision of staff.
 - C3.1.2.4 Administrative operations.
 - C3.1.2.5 The medical care of donors undergoing cell collections.
 - C3.1.2.6 Pre-collection evaluation of donors at the time of donation.
 - C3.1.2.7 Care of any complications resulting from the collection procedure.
 - C3.1.2.8 Compliance with the Quality Management Program, these Standards, and Applicable Law.
- C3.1.3 The Medical Director shall have at least one (1) year experience in performing or supervising cellular therapy product collection procedures.
- C3.1.4 The Medical Director shall ~~annually~~ participate in a minimum of ten (10) hours annually of educational activities related to cellular therapy product collection or the therapeutic disease areas.
- C3.1.4.1 Continuing education shall include, but is not limited to, activities related to cellular therapy product collection or the applicable therapeutic disease area.

C3.2 QUALITY MANAGER

- C3.2.1 There shall be a Quality Manager for collection activities to establish and maintain systems to review, modify, and approve all policies and Standard Operating Procedures intended to monitor compliance with Applicable Law, these Standards, or the performance of the collection activities.
- C3.2.2 The Quality Manager of collection activities should have a reporting structure independent of cellular therapy product ~~manufacturing~~collections.

C3.2.3 The Quality Manager shall ~~annually~~ participate in a minimum of ten (10) hours annually of educational activities ~~related to cellular therapy, cell collection, and quality management.~~

C3.2.3.1 Continuing education shall include, but is not limited to, activities related to cellular therapy, cell collection, and Quality Management.

C3.3 STAFF

C3.3.1 The number of trained collection personnel shall be adequate for the number of procedures performed and shall include a minimum of one designated trained individual with an identified trained backup individual to maintain sufficient coverage.

C3.3.2 For collection activities involving pediatric donors, physicians and collection staff shall have documented training and experience with pediatric donors.

C4: QUALITY MANAGEMENT

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

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

C4.2 Collection activities shall be performed in compliance with a written Quality Management Plan.

C4.2.1 The Medical Director ~~or designee~~ shall be responsible for the Quality Management Plan as it pertains to collection activities.

C4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions, ~~and~~ functions, and reporting relationships required for collection.

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

C4.4 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position required for cellular therapy product collection. Personnel requirements shall include at a minimum:

C4.4.1 A current job description for ~~each position~~ all staff.

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

C4.4.2.1 Initial qualifications.

C4.4.2.2 New employee orientation.

C4.4.2.3 Initial training, 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.

C4.4.2.56 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 and Standard Operating Procedures.

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 development, approval, implementation, distribution, review, revision, and archival of all critical documents.

C4.5.3 The document control system shall include:

C4.5.3.1 A standardized format for ~~each critical documents type including, but not limited to, policies, Standard Operating Procedures, worksheets, forms, and labels.~~

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

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, the signature of the approving individual(s), approval date, communication or training on the changes as applicable, effective date, and archival date.

C4.5.3.7 Archival of controlled documents including policies and Standard Operating Procedures, the inclusive dates of use, and their historical sequence for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

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

C4.5.3.9 A system for record creation, assembly, review, storage, archival, and retrieval.

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- C4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for 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 accreditations, and to comply with Applicable Law and these Standards.
- C4.6.3 Agreements shall be established when collections or other critical services are performed for external parties.
- C4.6.4 Agreements shall be dated and reviewed on a regular basis, at a minimum every two (2) years.
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- C4.7 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for documentation and review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.
- 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 or recipient type shall be evaluated.
- C4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:
- C4.7.3.1 An endpoint of clinical function as approved by the Clinical Program Director.
- C4.7.3.2 Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular

therapy product administration or in accordance with Applicable Law.

C4.7.4 Data on outcome analysis and cellular therapy product efficacy, including adverse events related to the recipient, donor, or product, shall be provided in a timely manner to entities involved in the clinical, processing, or distribution of the cellular therapy product.

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

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

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

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

C4.8.3.1 ~~Annual audit of d~~Documentation of proper donor eligibility and suitability determination.

C4.8.3.2 Management of cellular therapy products with positive microbial culture results.

C4.8.3.3 ~~Annual audit of d~~Documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

C4.8.3.4 ~~Annual audit of~~ Chain of identity and chain of custody of cellular therapy products.

C4.8.4 There shall be policies or Standard Operating Procedures for the management of external audits requested by the commercial manufacturer or applicable regulatory agency.

C4.9 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results and responsibility for the following activities at a minimum:

C4.9.1 Notification of the recipient, recipient's physician, collection staff, processing staff, and any other facility in receipt of the cellular therapy product; and if relevant, the donor and the sponsor.

C4.9.2 Recipient follow-up.

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

C4.9.4 Documentation and investigation of cause.

C4.9.5 Reporting to regulatory agencies, as required by Applicable Law.

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~~See A4 Definitions~~). 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 the Processing Facility and Clinical Program, and other 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), when and to whom the occurrence was reported, and the immediate actions taken.

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

~~C4.9.3.3 Cumulative files of Occurrences shall be maintained.~~

C4.10.3.3 Cumulative files of occurrences shall be maintained and shall include written investigation reports containing conclusions, follow-up, corrective and preventive actions, and a link to the records~~s(s)~~ of the involved cellular therapy products~~s(s)~~, donors~~s(s)~~, and recipients~~s(s)~~, 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 made available to the donor's and recipient's physician(s), as applicable, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by Applicable Law.

C4.10.4.2 Occurrences shall be reported as required to other facilities performing cellular therapy product functions on the affected cellular therapy product ~~and to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.~~

C4.10.4.3 Occurrences shall be reported as required to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.

C4.10.5 Corrective and preventive action.

C4.10.5.1 Corrective and preventive action shall be implemented, 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 action shall be performed in a timeframe as indicated in the investigative report.

~~C4.11~~ There shall be a process for the regular review and assessment of activities to identify recurring problems, potential points of failure, or need for process improvement.

C4.1211 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 ~~tracking and tracing~~ that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

C4.1312 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event collection operations are interrupted.

C4.1413 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, equipment, software, supplies, reagents, facilities, and services.

C4.1413.1 Qualification plans shall include minimum acceptance criteria for performance.

C4.1413.2 Qualification shall be required following any significant changes to these items.

C4.1413.3 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Medical Director ~~or~~ designee.

C4.1413.4 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

C4.1514 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

C4.1514.1 Critical procedures to be validated shall include at least collection procedures, testing, labeling, storage, and distribution.

C4.1514.2 Each validation or verification shall include at a minimum:

C4.1514.2.1 An approved validation plan, including conditions to be validated~~assessed~~.

C4.1514.2.2 Acceptance criteria.

C4.1514.2.3 Data collection.

C4.1514.2.4 Evaluation of data.

C4.1514.2.5 Summary of results.

C4.1514.2.6 References, if applicable.

C4.1514.2.7 Review and approval of the validation plan, results report, and conclusion by the Medical Director or designee and the Quality Manager or designee.

C4.1514.3 Significant changes to critical procedures shall be validated or verified as appropriate.

C4.1615 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the evaluation of risk in changes to a process to assess the effect of the change elsewhere in the operation.

C4.1615.1 Evaluation of risk shall be completed for changes in critical procedures.

~~C4.16 The Quality Management Plan should include, or summarize and reference, policies and Standard Operating Procedures for obtaining feedback.~~

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

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

C4.1716 The Medical Director ~~or designee~~ shall review the quality management activities with representatives in key positions in all ~~elements~~ areas of the cellular therapy program, at a minimum, quarterly.

C4.1716.1 ~~Meetings shall have defined attendees, documented minutes, and assigned actions. Key p~~Performance data and review findings shall be reported to key positions and staff.

C4.1716.2 ~~The meetings should shall have designated defined attendees, documented minutes, and assigned actions. Performance data and review findings shall be reported to key positions and staff.~~

C4.1716.3 The Medical Director ~~or designee~~ shall not ~~have oversight of~~approve his/her own work ~~if this person also performs other tasks related to cellular therapy product collection.~~

C4.1817 The Medical Director ~~or designee~~ shall annually review the effectiveness of the Quality Management Program.

C5: POLICIES AND STANDARD OPERATING PROCEDURES

C5.1 Policies or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in C4 shall be established and maintained. These documents shall include all elements required by these Standards and shall address at a minimum:

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 Management of donors who require central venous access.

C5.1.5 Cellular therapy product collection.

- C5.1.6 Prevention of mix-ups and cross-contamination.
- C5.1.7 Labeling (including associated forms and samples).
- C5.1.8 Cellular therapy product expiration dates.
- C5.1.9 Cellular therapy product storage.
- C5.1.10 Release and exceptional release.
- C5.1.11 Packaging, Transportation and shipping, including
 - C5.1.11.1 Methods and conditions to be used for distribution to external facilities.
 - C5.1.11.2 Use of additives for long duration of shipment.
- C5.1.12 Critical equipment, reagent and supply management, including recalls and corrective actions in the event of failure.
- C5.1.13 Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.
- ~~C5.1.13 — Recalls of equipment, supplies, and reagents.~~
- C5.1.14 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.
- C5.1.15 Hygiene and use of personal protective equipment and attire.
- C5.1.16 Disposal of medical and biohazard waste.
- C5.1.17 Cellular therapy emergency and disaster plan, including the collection staff response.

C5.2 A detailed list of all controlled documents, including title and identifier, shall be maintained for collection activities.

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 end-points and the range of expected results.
- C5.3.4 A stepwise description of the procedure.
- C5.3.5 Donor Age-specific issues where relevant.
- C5.3.6 Reference to other Standard Operating Procedures or policies required to perform the procedure.
- C5.3.7 A reference section listing appropriate and current literature.
- ~~C5.3.8~~ Reference to the current version of orders, worksheets, reports, labels, and forms.
- C5.3.9 Documented approval of each procedure by the Medical Director prior to implementation and every two (2) years thereafter.
- C5.3.10 Documented approval of each modification to a Standard Operating Procedure ~~procedural modification~~ by the Medical Director or designee prior to implementation.

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

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

~~C5.5.1 — Staff knowledge shall be documented before implementing a new or revised policy.~~

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

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

C6.2.1.1 The risks and benefits of the procedure.

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

C6.2.1.3 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

C6.2.1.4 The rights of the donor ~~and-or~~ legally authorized representative ~~of the donor who is a minor~~ to review the results of such tests according to Applicable Law.

C6.2.1.5 Protection of medical information and confidentiality.

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

C6.2.3.1 Family members and legally authorized representatives ~~should~~ 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 at any time.

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 or withdrawal after the recipient has begun the preparative regimen.

C6.2.5 Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional knowledgeable in familiar with the collection procedure.

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

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's physician or the recipient.

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 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 prospective donor with documentation in the donor record of recommendations made for follow-up care.

- C6.3.1.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.
- C6.3.1.3 Autologous donors shall be evaluated and tested as required by Applicable Law.
- C6.3.2 The risks of the cellular therapy product collection procedure shall be evaluated and documented.
- C6.3.3 A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to cellular therapy product collection, undergoing anesthesia, and, as applicable, within seven (7) days prior to the preparation of the recipient for administration.
- C6.3.3.1 For collection with mobilization, a pregnancy test shall be performed within seven (7) days prior to the initiation of the mobilization regimen.
- C6.3.4 Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, certified, or licensed in accordance with Applicable Law.
- C6.3.5 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the administering physician and approval by the Medical Director. ~~Collection staff shall document review of these donor safety issues.~~
- C6.3.5.1 ~~There shall be written documentation of i~~ssues of donor health that pertain to the safety of the collection procedure shall be available to the collection staff. Collection staff shall document review of these issues prior to collection.
- C6.3.6 There shall be a policy or Standard Operating Procedure for the management of collection-associated adverse events and follow-up of donors that includes routine management.

C6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

- C6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated, as those terms are defined by Applicable Law.
- C6.4.2 Allogeneic donor infectious disease testing shall be performed using donor screening tests ~~that are~~ licensed, approved, or cleared by the governmental authority.
- C6.4.2.1 Hemodilution in the donor prior to collection of blood samples for infectious disease testing and acceptance criteria shall be assessed.
- C6.4.3 Collection staff shall comply with B6.4.6 through B6.4.6.8 when primarily responsible for donor screening for transmissible disease.
- C6.4.4 Collection staff shall comply with B6.4.7 through B6.4.11 when primarily responsible for infectious and non-infectious disease testing of donors.
- C6.4.5 Collection staff shall comply with B6.4.3, B6.4.4, and B6.4.12 through B6.4.12.3 when primarily responsible for testing for the selection of allogeneic donors.
- C6.4.6 Collection staff shall confirm that allogeneic donor eligibility, as defined by Applicable Law, is determined by a ~~physician-licensed health care provider~~ after history, exam, medical record review, and testing before the donor begins the mobilization regimen, if mobilization is utilized within seven (7) days of collection.
- C6.4.7 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.
- C6.4.8 Collection of a cellular therapy product from an ineligible allogeneic donor, or from an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of urgent medical need that includes the rationale for the selection and documentation of the informed consent of the donor and the recipient.
- C6.4.9 Allogeneic donor eligibility shall be communicated in writing to the Processing Facility.
- C6.5 There shall be policies covering the creation and retention of donor records including at a minimum:

- C6.5.1 Allogeneic donor eligibility determination, including the name of the responsible person who made the determination and the date of the determination.
 - C6.5.2 Donor identification including name and date of birth.
 - C6.5.3 Age, gender, medical history, and, for allogeneic donors, behavioral history.
 - C6.5.4 Consent to donate.
 - C6.5.5 Results of laboratory testing.
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C7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

C7.1 ISBT 128 CODING AND LABELING

- C7.1.1 Cellular therapy products shall be identified by name according to ISBT 128 standard terminology.
 - C7.1.2 Coding and labeling technologies shall be implemented using ISBT 128.
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C7.2 LABELING OPERATIONS

- C7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products, product samples, and associated records.
- C7.2.2 Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Medical Director to confirm accuracy regarding identity, content, and conformity.
 - C7.2.2.1 Stocks of unused labels representing different products shall be stored in a controlled manner to prevent errors.
- 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.

- C7.2.3 ~~Print-on-demand~~ Label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Medical Director ~~or designee~~.
- C7.2.4 A system for label version control shall be employed.
- C7.2.4.1 Obsolete labels shall be restricted from use.
- C7.2.4.2 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.
- C7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.
- C7.2.5.1 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process or two (2) qualified staff members prior to distribution of the cellular therapy product.
- C7.2.5.2 A controlled labeling procedure consistent with Applicable Law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.
- C7.2.5.3 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.
- C7.2.6 When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.
- C7.2.7 Labeling elements required by Applicable Law shall be present.
- C7.2.8 All data fields on labels shall be completed.
- C7.2.9 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

- C7.2.10 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.
- C7.2.11 The label shall be validated as reliable for storage under the conditions in use.
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C7.3 PRODUCT IDENTIFICATION

- C7.3.1 Each cellular therapy product collection shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, all accompanying records, and its recipient or final disposition, ~~and all records~~.
- C7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.
- C7.3.1.2 If a single cellular therapy product is stored in more than one (1) container, there shall be a system to identify each container.
- C7.3.1.3 If cellular therapy products from the same donor are pooled, the identifier on the pooled product shall allow tracing to the original products.
- C7.3.1.4 Supplementary identifiers shall not obscure the original identifier.
- C7.3.1.5 The facility associated with each identifier shall be named in the documents to accompany the cellular therapy product.
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C7.4 LABEL CONTENT

- C7.4.1 At all stages of collection, the cellular therapy product label shall minimally contain the proper name of the product and the unique numeric or alphanumeric identifier.
- C7.4.2 Labeling at the end of collection shall occur before the cellular therapy product is removed from the proximity of the donor.
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- C7.4.3 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.
- C7.4.4 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States" or other appropriate labels as required by Applicable Law.
- C7.4.5 Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix III at the time of distribution.
- C7.4.6 Any container bearing a partial label at the time of distribution shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix I. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.
- 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 ~~the use of the product~~ distribution of the cellular therapy product and that the physician using the product was informed of the results of that determination.
- C7.4.8 Cellular therapy products for third-party manufacturers shall be labeled with product labels that conform to FACT requirements or Applicable Law.
- C7.4.9 Cellular therapy products distributed for nonclinical purposes shall be designated and labeled as not for clinical use.

C8: PROCESS CONTROLS

- C8.1 Collection of cellular therapy products shall be performed according to written Standard Operating Procedures.

C8.2 There shall be a process for inventory control that encompasses equipment, containers for transport and shipping, supplies, reagents, and labels.

C8.2.1 There shall be a system to uniquely identify and track and trace all critical equipment, supplies, reagents, and labels used in the collection of cellular therapy products.

C8.2.2 Each supply and reagent used to collect cellular therapy products shall be visually examined at receipt and prior to use for damage or evidence of contamination.

C8.2.2.1 Supplies and reagents shall be quarantined prior to use until verified to have met acceptance criteria.

C8.2.3 Supplies and reagents coming into contact with cellular therapy products during collection shall be sterile and of the appropriate grade for the intended use.

~~C8.2.4 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination.~~

~~C8.3 Equipment shall be inspected for cleanliness and verified to be in compliance with the maintenance schedule prior to each use.~~

C8.3 There shall be a process for equipment management that encompasses maintenance, cleaning, and calibration.

C8.3.1 Equipment shall be maintained in a clean and orderly manner.

C8.3.1.1 Cleaning shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.3.1.2 Equipment shall be inspected for cleanliness and documented to be clean prior to use.

C8.3.2 ~~Maintenance~~Equipment shall be performed according to established schedules standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.3.2.1 The equipment shall be verified and documented to be in compliance with the maintenance schedule prior to use.

C8.4 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.

C8.4.1 Calibration shall be performed according to established schedules as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.4.2 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products collected since the last calibration.

C8.5 Equipment, supplies and reagents for the collection procedure shall conform to Applicable Law.

C8.6 There shall be written documentation of an assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

C8.7 Administration of appropriate mobilization agents if required shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.

C8.8 There shall be a written order from a physician specifying, at a minimum, an anticipated date and goals of collection.

C8.7~~9~~ Collection procedures shall include a process for assessing the quality of cellular therapy products to confirm product safety and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.

~~C8.7.1 Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to confirm products meet predetermined release specifications.~~

C8.9.1 Methods for collection shall employ procedures that minimize the risk of microbial contamination and are validated to result in acceptable cell viability and yield ~~and, if applicable, recovery~~.

~~C8.8 Collection methods shall employ aseptic technique so that cellular therapy products do not become contaminated during collection.~~

C8.10 Collection methods ~~for pediatric donors~~ shall employ appropriate age and size adjustments to the procedures when required.

C8.11 Marrow products shall be filtered to remove particulate material prior to final packaging, distribution, or administration using filters that are non-reactive with blood.

C8.12 Cellular therapy products shall be packaged in closed sterile containers appropriate for the product collected.

C8.13 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

C8.13.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.

C9: CELLULAR THERAPY PRODUCT STORAGE

C9.1 Storage areas shall be secure and controlled in a manner to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of cellular therapy products.

C9.2 Collection policies or Standard Operating Procedures shall include the duration and conditions of short-term storage prior to distribution to a Processing Facility or Clinical Program.

C9.2.1 Conditions and duration of storage for all cellular therapy products shall be validated.

C9.2.2 When collecting, storing, or releasing cellular therapy products for administration or further manufacturing, an expiration date and time shall be assigned.

C10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

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

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

C10.3 ~~The cellular therapy product shall be transported or shipped to the Processing Facility in a validated container within a temperature range defined in a Standard Operating Procedure or written agreement. Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.~~

C10.3.1 Cellular therapy products ~~that require a temperature-controlled environment and~~ that are transported or shipped from the collection site to a processing facility shall be in an outer container made of material adequate to withstand leakage of contents, impact shocks, pressure changes, temperature changes, puncture, and other conditions incident to ordinary handling.~~over an extended period of time shall be transported or shipped in a container validated to maintain the appropriate temperature range.~~

~~C10.5 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.~~

C10.3.2 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.

C10.4 The outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II A.

C10.4.1 There shall be a document inside the outer container that includes all the information required on the outer container, in conformity with the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II A.

C10.4.2 The cellular therapy product shall be transported or shipped with required accompanying records as defined in the transportation and shipping Standard Operating Procedures and in compliance with C7.4.5 and C7.4.7.

C10.4.3 The outer container shall be labeled in accordance with Applicable Law regarding the cryogenic material used and the transport or shipment of biological materials.

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

C10.6 The transit time shall be within time limits determined by the distributing facility in consultation with the receiving facility to maintain cellular therapy product safety.

C10.7 There shall be contingency plans for alternative means of transport or shipping in an emergency.

C10.8 The cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.

C10.8.1 There should be a mechanism in place to notify the shipping facility if the shipping container was opened.

C11: RECORDS

C11.1 GENERAL REQUIREMENTS

C11.1.1 A records management system shall be established and maintained to facilitate the review of records.~~There shall be a records management~~

~~system for quality and cellular therapy product record creation, assembly, review, storage, archival, and retrieval.~~

~~C11.1.1.1 The records management system shall facilitate the review of records pertaining to a particular cellular therapy product prior to distribution and for follow-up evaluation or investigation.~~

C11.1.1.1 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

C11.1.1.2 For cellular therapy products that are to be distributed for use at another institution, the collection staff shall inform the receiving institution ~~shall be informed~~ of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

C11.1.2 Good documentation practices shall be defined and used.

C11.1.2.1 Records shall be accurate and legible.

C11.1.2.2 Written records shall be indelible.

C11.1.3 Records shall be maintained in such a way as to secure their integrity, preservation, and retrieval.

C11.1.4 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.

C11.2 Collection records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years or longer in accordance with Applicable Law.

C11.2.1 Employee records shall be maintained in a confidential manner, as required by Applicable Law.

C11.2.2 Cleaning and sanitation records shall be retained for a minimum of three (3) years or longer in accordance with Applicable Law.

C11.2.3 Validation studies for a collection procedure shall be retained for the duration of the use of the procedure.

C11.3 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, whichever is latest. These records shall include: product ~~identity~~code, unique numeric or alphanumeric identifier, and collection date and time; and donor and recipient identification as far as known.

C11.4 ~~Recipient and Donor~~ records including, but not limited to, consents and records of care shall be maintained in a confidential manner as required by Applicable Law for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration of the product, whichever is latest.

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

C11.6 ELECTRONIC RECORDS

C11.6.1 There shall be a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the cellular therapy program that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.

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

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

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

- C11.6.5 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.
- C11.6.6 For each critical electronic record system, there shall be an alternative system for all electronic records to allow for continuous operation in the event that critical electronic record system is not available. The alternative system shall be validated and collection staff shall be trained in its use.
- C11.6.7 For all critical electronic record systems, there shall be written Standard Operating Procedures for record entry, verification, and revision.
 - C11.6.7.1 A method shall be established or the system shall provide for review of data before final acceptance.
 - C11.6.7.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.
- C11.6.8 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.
- C11.6.9 For all critical electronic record systems, there shall be validated procedures for and documentation of:
 - C11.6.9.1 Systems development.
 - C11.6.9.2 Numerical designation of system versions, if applicable.
 - C11.6.9.3 Prospective validation of systems, including hardware, software, and databases.
 - C11.6.9.4 Installation of the system.
 - C11.6.9.5 Training and continued competency of personnel in systems use.
 - C11.6.9.6 Monitoring of data integrity.
 - C11.6.9.7 Back-up of the electronic records system on a regular schedule.
 - C11.6.9.8 System maintenance and operations.

C11.6.9.9 System assignment of unique identifiers.

C11.6.10 All system modifications shall be authorized, documented, and validated prior to implementation.

C11.7 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

C11.7.1 ~~The collection staff shall furnish to the facility of final disposition a~~ copy of all cellular therapy product records relating to the collection procedure shall be furnished to the facility of final disposition.s ~~performed related to the safety, purity, or potency of the cellular therapy product involved.~~

C11.7.2 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

PROCESSING FACILITY STANDARDS

PART D

- 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 ~~and Receipt~~
- 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, ~~obtained from living donors.~~

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. This team shall have been in place and performing cellular therapy product processing for ~~a minimum of at least~~ twelve (12) months preceding initial accreditation.

D2: PROCESSING FACILITY

D2.1 There shall be secured and controlled access to designated areas for the processing procedure and for storage of equipment, supplies, and reagents.

D2.1.1. The ~~designated area for P~~processing Facility shall be in an appropriate location of adequate space, and design to minimize the risk of airborne microbial contamination, ~~and location for the intended procedures.~~

D2.1.2 The Processing Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy or genetically modified products.

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 sinks for hand washing and to toilets to prevent the introduction, transmission, or spread of communicable disease.

D2.2.1 Oxygen sensors shall be appropriately placed and utilized in areas where liquid nitrogen is present.

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

D2.3 Processing Facility parameters and 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 parameters that may affect cellular therapy product viability, integrity, or contamination or cross contamination during processing, storage, or distribution ~~of the cellular therapy product.~~

D2.4.1 The written assessment shall include temperature, humidity, air quality, and surface contaminants at a minimum.

D2.4.2 Critical facility Pparameters 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, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, ~~or~~ radiological, electrical or fire hazards.

D2.8 There shall be a biosafety plan consistent with the institutional biosafety committee requirements that addresses genetically modified products in compliance with Applicable Law.

D2.9 All waste generated by Processing Facility activities shall be disposed of in a manner that minimizes hazard to facility personnel and to the environment in accordance with Applicable Law.

D2.10 Personal protective equipment, including Ggloves, personal protective equipment, including and protective clothing shall be used while handling biological specimens. Such protective clothing equipment shall not be worn outside the work area.

D2.11 When a collection kit is prepared and sent to collection staff, there shall be adequate instructions and materials to collect, label, store, pack, and transport or ship the cellular therapy product and associated samples to the Processing Facility.

D2.11.1 The collection kit shall be transported or shipped under conditions validated to maintain the designated temperature range from the time it leaves the Processing Facility until it is received by the collection staff.

D2.11.2 Identity of the supplies and reagents including manufacturer, lot number, and expiration date shall be documented for each collection.

D2.11.3 Supplies and reagents shipped to the collection staff from the Processing Facility shall be in an outer container validated to maintain the designated temperature range.

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, qualified by a minimum of two (2) years training and experience for the scope of activities carried out in the Processing Facility.

D3.1.2 The Processing Facility Director shall be responsible for all Standard Operating Procedures, administrative operations, and compliance with the Quality Management Program of the Processing Facility, including compliance with these Standards and Applicable Law.

D3.1.3 The Processing Facility Director shall ~~annually~~ participate in a minimum of ten (10) hours of educational activities ~~annually related to cellular therapy~~.

D3.1.3.1 Continuing education shall include, but is not limited to, activities related to cellular therapy product processing or the applicable therapeutic disease area.

D3.2 PROCESSING FACILITY MEDICAL DIRECTOR

D3.2.1 There shall be a Processing Facility Medical Director who is a licensed physician with a minimum of two (2) years postgraduate training and practical and relevant experience for the scope of activities carried out in the preparation and clinical use of cellular therapy products.

D3.2.2 The Processing Facility Medical Director ~~or designee~~ shall be directly responsible for all medical aspects related to the Processing Facility.

D3.2.3 The Processing Facility Medical Director shall ~~annually~~ participate in a minimum of ten (10) hours of educational activities ~~annually related to cellular therapy~~.

D3.2.3.1 Continuing education shall include, but is not limited to, activities related to cellular therapy product processing or the applicable therapeutic disease area.

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 Applicable Law, 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 ~~annually~~ participate in a minimum of ten (10) hours annually of educational activities ~~related to cellular therapy and quality management~~.

D3.3.3.1 Continuing education shall include, but is not limited to, activities related to cellular therapy, cell processing, and Quality Management.

D3.4 STAFF

D3.4.1 The number of trained processing personnel shall be adequate for the number of procedures performed and shall include a minimum of one (1) designated trained individual with an identified trained backup individual to maintain sufficient coverage.

D4: QUALITY MANAGEMENT

D4.1 There shall be a Quality Management Program that incorporates key performance data.

D4.1.1 The Processing Facility Director ~~or designee~~ shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

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

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

D4.3 The Quality Management Plan shall include, or summarize and reference, an organizational chart of key positions, ~~and~~ 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 and Standard Operating Procedures.

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 development, approval, implementation, distribution, review, revision, and archival of all critical documents.

D4.5.3 The document control system shall include:

D4.5.3.1 A standardized format for ~~each critical documents. type including, but not limited to, policies, Standard Operating Procedures, worksheets, forms, and labels.~~

D4.5.3.2 Assignment of a numeric or an alphanumeric identifier and a title to each document and document version regulated within the system.

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 changes as applicable, effective date, and archival date.

D4.5.3.7 Archival of controlled documents including policies and Standard Operating Procedures, the inclusive dates of use, and their historical sequence for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

D4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

~~D4.5.3.8 A system for record creation, assembly, review, storage, archival, and retrieval.~~

D4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for 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 health and safety of the donor or recipient.
- D4.6.2 Agreements shall include the responsibility of the external party performing any step in processing, testing, storage, distribution, or administration to maintain required accreditations, and to comply with Applicable Law and these Standards.
- 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.

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- D4.7 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.
- 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 or recipient type shall be evaluated.
- D4.7.3 Review of outcome analysis and/or product efficacy shall include at a minimum:
- D4.7.3.1 An endpoint of clinical function as approved by the Clinical Program Director.
- D4.7.3.2 Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration or in accordance with Applicable Law.
- D4.7.4 Data on outcome analysis and cellular therapy product efficacy, including adverse events related to the recipient, donor, or product,

shall be collected and made available in a timely manner to clinical, collection, or distribution personnel as applicable.

D4.8 The Quality Management Plan shall include, or summarize and reference, policies, Standard Operating Procedures for, and a schedule of, audits of the Processing Facility's activities to verify compliance with the Quality Management Program, and operational policies and Standard Operating Procedures, Applicable Law, and these Standards.

D4.8.1 Audits shall be conducted by an individual with sufficient knowledge of the process and competence in auditing ~~expertise~~ to identify problems, but who is not solely responsible for the process being audited.

D4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions in a timely manner.

D4.8.3 Audits shall be performed annually at a minimum, and shall include at least the following:

D4.8.3.1 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

D4.8.3.2 Management of cellular therapy products with positive microbial culture results.

D4.8.3.3 Infectious disease resulting from cellular therapy product collection or administration.

D4.8.3.4 Chain of identity and ~~Chain of custody~~ of cellular therapy products ~~shall be audited annually.~~

D4.9 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results and responsibility for the following activities at a minimum:

D4.9.1 Documentation and product labeling.

D4.9.2 Product quarantine.

- D4.9.3 Criteria for product release.
- D4.9.4 Identification of individuals authorized to approve release, including the ~~Processing Facility Director and~~ Processing Facility Medical Director at a minimum.
- D4.9.5 Notification of the recipient, recipient's physician, collection staff, and any other facility in receipt of the cellular therapy product; and if relevant, the donor and the sponsor.
- D4.9.6 Documentation and investigation of cause.
- D4.9.7 Reporting to regulatory agencies, as required by Applicable Law.
- D4.9.8 Recipient follow-up.
- D4.9.9 Follow-up of the donor, if relevant.

D4.10 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for ~~Occurrences~~ (errors, accidents, deviations, adverse events, adverse reactions, and complaints)~~See A4 Definitions~~). 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 Facility in collaboration with ~~the collection staff and Clinical Program, and other~~ all entities involved in the collection, manufacture, testing, or administration of the cellular therapy product, as appropriate.
 - D4.10.2.2 Investigations shall identify the root cause and a plan for short- and long-term corrective and preventive 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), 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, ~~or designee~~ and ~~the~~ Quality Manager.

~~D4.9.3.3 Cumulative files of Occurrences shall be maintained.~~

D4.10.3.4 Cumulative files shall be maintained and include written investigation reports containing conclusions, follow-up, corrective and preventive actions, and a link to the records~~s(s)~~ of the involved cellular therapy products~~s(s)~~, donors~~s(s)~~, and recipients~~s(s)~~, 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 made available to the donor's and recipient's physician(s), as applicable, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by Applicable Law.

D4.10.4.2 Occurrences shall be reported as required to other facilities performing cellular therapy product functions on the affected cellular therapy product. ~~and~~

D4.10.4.3 Occurrences shall be reported as required to the appropriate regulatory and accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees.

D4.10.5 Corrective and preventive action.

D4.10.5.1 ~~Corrective and preventive~~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 action 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 ~~tracking and tracing~~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, supplies, reagents, facilities, and services.

D4.13.1 Qualification plans, results, reports, and conclusions shall be reviewed and approved by the Quality Manager and Processing Facility Director ~~or designee~~.

D4.13.2 Qualification plans shall include minimum acceptance criteria for performance.

D4.13.3 Qualification shall be required following any significant changes to these items.

D4.13.4 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

D4.14 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

D4.14.1 Critical procedures to be validated shall include at least the following: processing techniques, cryopreservation procedures, testing, labeling, storage, ~~and~~ distribution, and preparation for administration.

- D4.14.2 Each validation or verification shall include at a minimum:
- D4.14.2.1 An approved ~~validation~~ plan, including conditions to be assessed-validated.
 - D4.14.2.2 Acceptance criteria.
 - D4.14.2.3 Data collection.
 - D4.14.2.4 Evaluation of data.
 - D4.14.2.5 Summary of results.
 - D4.14.2.6 References, if applicable.
 - D4.14.2.7 Review and approval of the ~~validation~~ plan, report results, and conclusion by the Processing Facility Director ~~or designee~~ and the Quality Manager ~~or designee~~.
- D4.14.3 Significant changes to critical procedures shall be validated or verified as appropriate.

D4.15 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the evaluation of risk in changes to a process to confirm that the changes do not create an adverse impact or inherent risk ~~assess the effect of the change~~ elsewhere in the operation.

D4.15.1 Evaluation of risk shall be completed for changes in critical procedures.

~~D4.16 The Quality Management Plan should include, or summarize and reference, policies and Standard Operating Procedures for obtaining feedback.~~

~~D4.16.1 Feedback should be obtained from associated Clinical Programs and collection staff.~~

D4.16 The Processing Facility Director ~~or designee~~ shall review the quality management activities with representatives in key positions in all ~~elements~~ areas of the cellular therapy program, at a minimum, quarterly.

D4.16.1 Meetings shall have defined attendees, documented minutes, and assigned actions.

D4.16.2 ~~Key p~~Performance data and review findings shall be reported to key personnel positions and staff.

D4.16.3 The Processing Facility Director ~~or designee~~ shall not ~~have oversight of~~ approve his/her own work ~~if this person also performs other tasks in the Processing Facility.~~

D4.17 The Processing Facility Director ~~or designee~~ shall annually review the effectiveness of the Quality Management 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 to include a description of the indication for and processing methods to be used for plasma and red blood cell reduction.

D5.1.5 Prevention of mix-ups and cross-contamination.

D5.1.6 Labeling (including associated forms and samples).

D5.1.7 Cryopreservation and thawing.

- D5.1.8 Cellular therapy product expiration dates.
- D5.1.9 Cellular therapy product storage to include alternative storage if the primary storage device fails.
- D5.1.10 Release and exceptional release.
- D5.1.11 Packaging, Transportation and shipping, including methods and conditions within the Processing Facility and to and from external facilities.
- D5.1.12 Cellular therapy product recall, to include a description of responsibilities and actions to be taken, and notification of appropriate regulatory agencies.
- D5.1.13 Cellular therapy product disposal.
- D5.1.14 Critical equipment, reagent, and supply management, including recalls and corrective actions in the event of failure.
- D5.1.15 Equipment operation, maintenance, and monitoring, including corrective actions in the event of failure.
- ~~D5.1.16 — Recalls of equipment, supplies, and reagents.~~
- D5.1.16 Cleaning and sanitation procedures including identification of the individuals responsible for the activities.
- D5.1.17 Environmental control to include a description of environmental monitoring plan.
- D5.1.18 Hygiene and use of personal protective equipment and attire.
- D5.1.19 Disposal of medical and biohazard waste.
 - D5.1.19.1 Processing Facilities utilizing genetically modified cellular therapy products shall incorporate or reference institutional or regulatory requirements related to the disposal of genetic material.
- D5.1.20 Cellular therapy emergency and disaster plan, including the Processing Facility response.

D5.2 The Processing Facility shall maintain a detailed list of all controlled documents, including title and identifier.

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 and supplies used.

D5.3.3 Acceptable end-points and the range of expected results.

D5.3.4 A stepwise description of the procedure.

D5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

D5.3.6 A reference section listing appropriate and current literature.

D5.3.7 Documented approval of each procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation and every two (2) years thereafter.

D5.3.8 Documented approval of each modification to a Standard Operating Procedure by the Processing Facility Director or Medical Director, as appropriate, prior to implementation.~~Documented approval of each Standard Operating Procedure procedural modification by the Processing Facility Director or Medical Director, as appropriate, prior to implementation.~~

D5.3.9 Reference to the current version of orders, worksheets, reports, labels, and forms.

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 Standard Operating Procedure. Staff training and, if appropriate, competency shall be documented before performing a new or revised Standard Operating Procedure.~~
D5.5.1 ~~Staff knowledge shall be documented before implementing a new or revised policy.~~
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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 appropriate Processing Facility Director and/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 Supplies and reagents used in processing, testing, cryopreservation, and storage shall be controlled by a materials management system that includes requirements for the following, at a minimum:

D6.3.1 Visual examination of each supply and reagent used to manufacture cellular therapy products for damage or evidence of contamination upon receipt and acceptance into inventory.

D6.3.2 Records of receipt that shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.

- D6.3.3 Storage of materials under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix up or unintended use.
- D6.3.4 Use of supplies and reagents coming into contact with cellular therapy products during processing, storage, or administration that are sterile and of the appropriate grade for the intended use.
 - D6.3.4.1 Reagents shall undergo initial qualification for the intended use.
 - D6.3.4.2 Where there are no suitable clinical or pharmaceutical grade reagents available, reagents shall undergo lot-to-lot functional verification.
 - D6.3.4.3 Lot-to-lot functional verification shall include acceptance criteria to confirm that new lots perform as expected compared to the previous lots.
- D6.3.5 Cleaning and sterilizing of non-disposable supplies or instruments using a procedure verified to remove infectious agents and other contaminants.
- D6.3.6 Use of supplies and reagents in a manner consistent with manufacturer instructions.
- D6.3.7 Process to prevent the use of expired reagents and supplies.

D6.4 There shall be a system to uniquely identify and track all critical equipment used in the processing of cellular therapy products. The system shall identify each cellular therapy product for which the equipment was used.

D6.5 Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.

D6.6 Equipment shall be inspected for cleanliness and verified to be in compliance with the maintenance schedule prior to each use.

D6.7 Equipment shall be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.7.1 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.

D6.7.2 When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products manufactured since the last calibration.

D6.8 There shall be a Standard Operating Procedure that addresses the actions to take in the event of equipment malfunction or failure.

D6.9 Equipment shall conform to Applicable Law.

D6.10 ~~Critical reagent~~ Lot numbers, expiration dates, manufacturers, and key equipment identifiers used in each procedure shall be documented.

D6.11 The Processing Facility shall use an inventory control system to document the availability and identity of critical reagents and supplies. This shall include at a minimum:

D6.11.1 A system to uniquely identify and track all critical reagents and supplies used to manufacture cellular therapy products.

D6.11.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.

D6.11.3 A system to maintain adequate stocks of reagents and supplies for the procedures to be performed.

D7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

D7.1 ISBT 128 CODING AND LABELING LABELING OPERATIONS

D7.1.1 Cellular therapy products shall be identified by name according to ISBT 128 sStandard tTerminology.

D7.1.2 Coding and labeling technologies shall be implemented using ISBT 128.

D7.2 LABELING OPERATIONS

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

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

D7.2.1.2 Obsolete labels shall be restricted from use.

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

D7.2.3 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 ~~Print-on-demand~~ Label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Processing Facility Director ~~or designee~~.

D7.2.5 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 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.
- D7.2.6.2 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.
- D7.2.7 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 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process or two (2) qualified staff members prior to distribution of the cellular therapy product.
- D7.2.9 Labeling elements required by Applicable Law shall be present.
- D7.2.10 All data fields on labels shall be completed.
- D7.2.11 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.
- D7.1.12 The label shall be validated as reliable for storage under the conditions in use.
- D7.1.13 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

D7.3 PRODUCT IDENTIFICATION

- D7.3.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, all accompanying records, and its recipient or final disposition, ~~and all records~~.
- D7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.

D7.3.1.2 If a single cellular therapy product is stored in more than one (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 identifier is replaced, documentation shall link the new identifier to the original.

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 I.

D7.4.4 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States," or other appropriate labels as required by Applicable Law.

D7.4.5 A ~~C~~cellular therapy products collected in or designated for use in the U.S. shall have the elements in the Accompanying Documents at Distribution table in Appendix III accompany the cellular therapy product when it leaves the Processing Facility.

- D7.4.6 Any container bearing a partial label shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix I. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.
- D7.4.7 For allogeneic cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after distribution of the cellular therapy product and that the physician using the product was informed of the results of that determination.
- D7.4.8 Cellular therapy products from third-party manufacturers shall be labeled with product labels that conform to FACT requirements or Applicable Law.
- D7.4.9 Cellular therapy products distributed for nonclinical purposes shall be designated and labeled as "not for clinical use."

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 established~~ed,ment of appropriate, and validated assays and test procedures for the evaluation of cellular therapy products.
- D8.1.3.1 For all cellular therapy products, cell enumeration and viability assays shall be performed for clinically relevant cell populations.
- D8.1.3.2 For cellular therapy products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, shall be employed for evaluation of the viable target cell population before and after the processing procedures.
- D8.1.4 For tests required by these Standards performed within the Processing Facility:
- D8.1.4.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.
- D8.1.4.2 New reagent lots shall be verified to provide comparable results to current lots or to give results in agreement with suitable reference material before or concurrently with being placed into service.
- D8.1.4.3 Where available, controls shall be used each day of testing and shown to give results within the defined range established for that material.
- D8.1.4.4 Function checks shall be performed for testing instruments prior to testing donor, recipient, or cellular therapy product samples.
- D8.1.4.5 There shall be documentation of ongoing proficiency testing as designated by the Processing Facility Director. The results shall be reviewed by the Processing Facility Director ~~or designee~~ and outcomes reviewed with the staff.
- D8.1.5 Tests required by these Standards, and not performed by the Processing Facility, shall be performed by a laboratory that is certified, licensed, or accredited by the appropriate laboratory regulatory agency.

- D8.1.6 Infectious disease testing required by these Standards shall be performed using screening tests that are licensed, approved, or cleared by the governmental authority for cellular therapy product donors.
- D8.1.7 Cellular therapy products that do not meet allogeneic donor eligibility requirements, or for which allogeneic donor eligibility determination is not yet complete, shall be distributed only if there is documented urgent medical need for the product. Documentation shall include, at a minimum, the approval of the recipient's physician and the Processing Facility Medical Director ~~or other designated physician~~.
- D8.1.8 Notification of the recipient's physician of nonconforming cellular therapy products and approval for their release shall be documented.

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, ~~there shall be a written request from the recipient's physician specifying the cellular therapy product type, recipient and donor identifiers, the type of processing that is to be performed, and the anticipated date of processing.~~

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- D8.3 For allogeneic cellular therapy products, information required by the Processing Facility prior to distribution of the product shall include:
- D8.3.1 A statement of donor eligibility.
- D8.3.2 For ineligible donors, the reason(s) for their ineligibility.
- D8.3.3 For ineligible donors or donors for whom eligibility determination is incomplete, documentation of urgent medical need and physician approval for use.
- 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 Preparation for administration of cellular therapy products manufactured by third parties shall follow the instructions provided by the manufacturer.~~

~~D8.4.3 If the Processing Facility lacks experience with the type of cellular therapy product requested for a recipient, personnel shall obtain the manufacturer's instructions and follow these instructions to the extent possible.~~

D8.4.3.1 The Processing Facility should verify the processing-preparation procedures utilizing practice ~~products-materials~~ similar to the cellular therapy product intended for administration when feasible.

~~D8.4.3.2 If relabeling of prepared third-party products is required, the label shall follow Applicable Law.~~

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 ~~or designee~~ in a timely manner.
- D8.8.2 The recipient's physician shall be notified in a timely manner of any positive microbial cultures.
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- D8.9 Records shall be made concurrently with each step of the processing, testing, cryopreservation, storage, and administration or disposal/disposition/distribution of each cellular therapy product in such a way that all steps may be accurately traced.
- D8.9.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.
- D8.9.2 Records shall show the test results and the interpretation of each result, where appropriate.
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- D8.10 The Processing Facility Director ~~or designee~~ shall review the processing record for each cellular therapy product prior to release or distribution.
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- D8.11 There shall be documented notification to the recipient's physician and the Processing Facility Medical Director of clinically relevant processing end-points not met and remedial actions taken.
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- D8.12 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, with Institutional Review Board or Ethics Committee approval, with the written informed consent of the donor, if applicable, and the recipient of the cellular therapy product, and in compliance with Applicable Law.

- 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 regulations appropriate for the degree of cellular therapy product manipulation.
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D8.13 For allogeneic cellular therapy products containing red blood cells at the time of administration sufficient to cause a transfusion reaction:

D8.13.1 Results for donor and recipient ABO group and Rh type testing shall be available from two (2) independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

D8.13.2 When relevant, results for a red blood cell antibody screen on the recipient shall be available.

D8.14 One or more retention samples representing the cryopreserved cellular therapy product shall be stored under conditions that achieve a valid representation of the clinical product and in accordance with institutional Standard Operating Procedures.

~~D8.13.1 Sample(s) from cryopreserved cellular therapy products shall be stored under conditions that achieve a valid representation of the clinical product.~~

~~D8.13.2 Cryopreserved samples shall be retained according to institutional Standard Operating Procedures.~~

D9: CELLULAR THERAPY PRODUCT STORAGE

D9.1 Processing and storage facilities shall be secured and controlled ~~storage areas~~ to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products.

D9.2 STORAGE DURATION

D9.2.1 Conditions and duration of storage of all cellular therapy products shall be validated.

D9.2.2 Processing Facilities processing, storing, ~~and~~ or releasing cellular therapy products for administration shall assign an expiration date and time for non-cryopreserved products and for products thawed after cryopreservation.

- D9.2.3 There shall be a written stability program that annually evaluates the viability and potency of cryopreserved cellular therapy products, ~~annually at a minimum.~~

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~~defined~~ in ~~the~~ 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. Disposition shall be documented.
 - D9.4.3.3 Processing Facilities storing cellular therapy products shall quarantine each product until completion of the donor eligibility determination as required by Applicable Law.
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D9.5 STORAGE MONITORING

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

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

D9.6.6 Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.

D9.6.6.1 Instructions shall include a procedure for notifying processing personnel.

D9.6.7 Storage devices of appropriate temperature shall be available for cellular therapy product storage if the primary storage device fails.

D9.7 The storage device shall be located in a secure area and accessible only to personnel authorized by the Processing Facility Director ~~or designee~~.

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

D9.8.1 Cellular therapy product unique identifier.

D9.8.2 Recipient name or unique identifier.

D9.8.3 Storage device identifier.

D9.8.4 Location within the storage device.

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

D10.3 Cellular therapy products that require a temperature-controlled environment and that are transported or shipped over an extended period of time shall be

transported or shipped in a container validated to maintain the appropriate temperature range.

D10.4 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

D10.5 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.

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 II A.

D10.5.5 There shall be a document inside the outer container that includes all the information required on the outer container, in conformity with the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II A.

D10.5.6 The outer container shall be labeled in accordance with Applicable Law regarding the cryogenic material used and the transport or shipment of biological materials.

D10.6 Cellular therapy products transported internally shall be packaged in a qualified, closed, and protective outer container.

D10.6.1 The outer container for internal transport shall be labeled as defined in Appendix II B.

D10.7 The transit time shall be within time limits determined by the distributing facility in consultation with the receiving facility to maintain cellular therapy product safety.

D10.8 There shall be plans for alternative means of transport or shipping in an emergency.

D10.9 The cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.

D11: RECEIPT AND DISTRIBUTION AND RECEIPT

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.

D11.1.34 There shall be Standard Operating Procedures to verify that the cellular therapy product was appropriately transported or shipped.

D11.1.~~34~~.1 The receiving facility shall document the temperature inside the container upon arrival if shipped or transported on public roads.

D11.1.~~34~~.2 For cryopreserved cellular therapy products, receiving facility records shall include documentation of the container temperature during shipping.

D11.1.~~45~~ The receiving facility shall review and verify cellular therapy product specifications provided by the manufacturer, if applicable.

D11.1.~~56~~ 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.~~67~~ If the temperature of the cellular therapy product has been compromised, the Processing Facility Director or designee shall give specific authorization to return the product to inventory.

D11.1.~~78~~ The receiving facility shall have readily available access to a summary of documents used to determine allogeneic donor eligibility.

D11.1.~~78~~.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.~~89~~ 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.~~89~~.1 The Processing Facility Director ~~or designee~~ shall consult with the recipient's physician regarding reissue or disposal of the returned cellular therapy product.

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 or designee for compliance with Standard Operating Procedures and Applicable Law prior to product release ~~or~~ and 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 ~~or designee~~ 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 ~~or designee~~ 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 ~~or designee~~ and the recipient's physician to use any non-conforming cellular therapy product shall be retained in the processing record if such release is allowed by policies, Standard Operating Procedures, or package inserts of licensed products.
- D11.2.3 Each cellular therapy product issued for administration shall be visually inspected by two (2) trained personnel immediately before release to verify the integrity of the product container and identity as indicated by appropriate labeling.
- D11.2.3.1 A cellular therapy product shall not be released when the container is compromised and/or recipient, ~~or~~ donor, or product information is not verified unless the Processing Facility Director ~~or designee~~ 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.
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D11.3 DISTRIBUTION RECORDS

- D11.3.1 The cellular therapy product distribution records shall permit tracking and tracing of the cellular therapy product, and shall contain the following information at a minimum:
 - D11.3.1.1 The proper product name and identifier.
 - D11.3.1.2 Unique identifier of the intended recipient.
 - D11.3.1.3 Documentation of donor eligibility determination, as appropriate.
 - D11.3.1.4 Identification of the facilities that requested and distributed the product.
 - D11.3.1.5 Identity of the receiving facility.
 - D11.3.1.6 Date and time cellular therapy product was distributed.
 - D11.3.1.7 Date and time cellular therapy product was received.
 - D11.3.1.8 Identity of the transporting or shipping facility.
 - D11.3.1.9 Identity of personnel responsible for cellular therapy product transportation or shipping and of personnel responsible for receiving the product.
 - D11.3.1.10 Identity of the courier.

D11.3.1.11 Documentation of any delay or problems incurred during transportation or shipping.

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 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.
 - D12.1.4 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 and/or medical waste.
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- D12.2 Processing Facilities, in consultation with the Clinical Program, shall establish policies for the duration and conditions of storage and indications for disposal.
- ~~D12.1.6.1 Recipients, donors, and associated Clinical Programs should be informed about policies for directed cellular therapy products as part of the informed consent process and before the cellular therapy product collection.~~
- D12.2.1 If there is no pre-existing agreement describing conditions for cellular therapy product storage and/or discard or if the intended recipient is lost to follow-up, the storage facility shall make a documented effort to notify the donor, cellular therapy product manufacturer, or designated recipient's physician and facility about product disposition, including disposal or transfer.
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- D12.3 The records for discarded or transferred cellular therapy products shall indicate the identity of the product, ~~was discarded or transferred~~, date of discard or transfer, disposition, and method of disposal or transfer.

D13: RECORDS

~~D13.1~~ GENERAL REQUIREMENTS

- D13.1 There shall be a records management system for quality and cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

D13.1.1 The records management system shall facilitate the review of records pertaining to a particular cellular therapy product prior to its distribution and for follow-up evaluation or investigation.

D13.1.2 The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

D13.1.3 For cellular therapy products that are to be distributed for use at another institution, the Processing Facility shall inform the receiving institution of the tracking system and requirement for tracking the product in writing at or before the time of product distribution.

D13.1.4 Records shall be accurate and, legible, ~~and indelible~~.

~~D13.1.35~~ Records shall be indelible.

D13.1.6 Records shall be maintained in such a way as to secure their integrity, preservation, and retrieval.

D13.1.7 Safeguards to secure the confidentiality of all records and communications among the collection staff, processing facilities, ~~and~~ clinical facilities, and health care providers and their recipients and donors, shall be established and followed in compliance with Applicable Law.

D13.2 The Processing Facility shall define and follow good documentation practices.

D13.3 ELECTRONIC RECORDS

- D13.3.1 The Processing Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the Processing Facility that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.
- D13.3.2 For all critical electronic record systems, there shall be policies, Standard Operating Procedures, and system ~~elements~~ controls to maintain the accuracy, integrity, identity, and confidentiality of all records.
- D13.3.3 There shall be a means by which access to electronic records is limited to authorized individuals.
- D13.3.4 The critical electronic record system shall maintain unique identifiers.
- D13.3.5 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.
- D13.3.6 For each critical electronic record system, there shall be an alternative system for all electronic records to allow for continuous operation of the Processing Facility in the event that a critical electronic record system is not available. The alternative system shall be validated and Processing Facility staff shall be trained in its use.
- D13.3.7 For all critical electronic record systems, there shall be written Standard Operating Procedures for record entry, verification, and revision.
 - D13.3.7.1 A method shall be established or the system shall provide for review of data before final acceptance.
 - D13.3.7.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.
- D13.3.8 For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.

- D13.3.9 For all critical electronic record systems, there shall be validated procedures for and documentation of:
- D13.3.9.1 Systems development.
 - D13.3.9.2 Numerical designation of system versions, if applicable.
 - D13.3.9.3 Prospective validation of systems, including hardware, software, and databases.
 - D13.3.9.4 Installation of the system.
 - D13.3.9.5 Training and continued competency of personnel in systems use.
 - D13.3.9.6 Monitoring of data integrity.
 - D13.3.9.7 Back-up of the electronic records system on a regular schedule.
 - D13.3.9.8 System maintenance and operations.
 - D13.3.9.9 System assignment of unique identifiers.
- D13.3.10 All system modifications shall be authorized, documented, and validated prior to implementation.
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D13.4 RECORDS TO BE MAINTAINED

- D13.4.1 Processing Facility records related to quality control, investigational protocols, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years after the creation of the cellular therapy product record or date of the cellular therapy product's distribution, disposition, or expiration, whichever is latest, or according to by the Processing Facility, or longer in accordance with Applicable Law.
- D13.4.1.1 Employee records shall be maintained in a confidential manner, and as required by Applicable Law.

D13.4.1.2 Facility maintenance records pertaining to facility cleaning and sanitation records shall be retained for a minimum of at least three (3) years or longer in accordance with Applicable Law.

D13.4.1.3 Validation study records for a processing procedure shall be retained for a minimum of ten (10) years after distribution of the final products manufactured using that procedure.

D13.4.2 Records to allow tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after administration, distribution, disposition, or expiration of the cellular therapy product~~after final distribution of the product~~, or as required by Applicable Law. These records shall include collection and processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product identity code, and donor and recipient information as known.

D13.4.3 All records pertaining to the processing, testing, storage, or distribution of cellular therapy products shall be maintained for a minimum of ten (10) years after the date of administration, or if the date of administration is not known, then a minimum of ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, or the creation of the cellular therapy product record, whichever is most recent, or according to Applicable Law or institutional policy, whichever is latest.

D13.4.4 Research records shall be maintained in a confidential manner as required by Applicable Law or for a minimum of ten (10) years after the administration, distribution, disposition, or expiration of the cellular therapy product, whichever is latest.

D13.5 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

D13.5.1 The Processing Facility shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a cellular therapy product.

- D13.5.2 The Processing Facility shall ~~furnish~~provide to the facility of final disposition ~~a copy~~a summary of all records relating to the collection, processing, and storage procedures performed and related to the records concerning the safety, purity, or potency of the cellular therapy product involved.
- D13.5.3 If two (2) or more facilities participate in the collection, processing, or distribution of the cellular therapy product, the records of the Processing Facility shall show ~~plainly~~ the extent of its responsibility.

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APPENDIX I

CELLULAR THERAPY PRODUCT LABELING

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

| Element ² | Label at completion of collection | Label at completion of processing | Partial label at distribution for administration ⁴ | Label at distribution for administration ³ |
|--|-----------------------------------|-----------------------------------|---|---|
| Unique numeric or alphanumeric identifier⁴-identifier³ | AF | AF | <u>AF</u> | AF |
| Proper name of product ^{5,6} | AF | AF | <u>AF</u> | AF |
| Product code⁵ | <u>AF</u> | <u>AF</u> | <u>AF</u> | <u>AF</u> |
| Product attributes ⁵ | <u>AC</u> | AC | <u>AC</u> | <u>AFG</u> |
| Recipient name and/or identifier | AT | AT | <u>AC</u> | AT |
| Identity and address of collection facility or donor registry | AT | AC | <u>AC</u> | AC |
| Date, time collection ends, and (if applicable) time zone | AT | <u>AG</u> | - | <u>AG-</u> |
| Approximate volume | <u>AF+</u> | <u>AF+</u> | <u>AF</u> | <u>AF+</u> |
| Name and quantity of anticoagulant and other additives | <u>AFG</u> | <u>AFG</u> | <u>AF</u> | <u>AFG</u> |
| Recommended storage temperature range | <u>AF</u> | <u>AF</u> | <u>AF</u> | <u>AT</u> |
| Donor identifier and (if applicable) name | AT | AT | <u>AC</u> | <u>AC+</u> |
| Recommended storage temperature range | <u>AT</u> | <u>AT</u> | <u>AT</u> | |
| Biohazard and/or Warning Labels (as applicable, see C7.3.2, D7.3.2). | AT | AT | <u>AC</u> | <u>AC+</u> |
| If As applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" | AT | AT | <u>AC</u> | AT |
| Statement "WARNING: Advise Patient of Communicable Disease Risks" | AT | AT | <u>AC</u> | AT |
| Statement "WARNING: Reactive Test Results for [name of disease agent or disease]" | AT | AT | <u>AC</u> | AT |
| Identity and address of processing and distribution facility(ies) | - | AC | <u>AC</u> | AC |
| Statement "Do Not Irradiate" | - | AT | <u>AC</u> | <u>AF+</u> |
| Expiration Date (if applicable) | - | AC | <u>AC</u> | <u>AFG</u> |
| Expiration Time (if applicable) | - | AC | <u>AC</u> | <u>AC+</u> |
| ABO and Rh of donor (if applicable) | - | AC | <u>AC</u> | <u>ACG</u> |
| RBC compatibility determination (if applicable) | - | - | <u>AC</u> | AC |
| Statement indicating that leukoreduction filters shall not be used. | - | - | <u>AC</u> | <u>AF+</u> |
| Statement "FOR AUTOLOGOUS USE ONLY" (if applicable) | AT | AT | <u>AC</u> | <u>AF+</u> |
| Date of distribution | - | - | <u>AC</u> | AC |

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

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

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

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~~Products thawed at the bedside do not require a new label.~~

⁴~~Overlay-³Overlay 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~~

⁵Product 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, Medical Products of Human Origin~~. Available at: www.icbba.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 II

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 tables:

A: CELLULAR THERAPY PRODUCT LABELS FOR SHIPPING AND TRANSPORT ON PUBLIC ROADS

| Element | Inner container document | Outer container label |
|---|--------------------------|-----------------------|
| Date of distribution, if appropriate | AC | AC |
| Time ¹ of distribution, if appropriate | AC | AC |
| Statement "Do Not X-Ray" and /or "Do Not Irradiate", if applicable | AC | AF |
| Statements "Human Cells for Administration" or equivalent and "Handle with Care" | AC | AF |
| Shipper handling instructions | AC | AF |
| Shipping facility name, street address, contact person, and phone number | AC | AF |
| Receiving facility name, street address, contact person, and phone number | AC | AF |
| Biohazard and/or Warning Labels (as applicable, see C7.3.2, D7.3.2). | AC | = |
| If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" | AC | |
| Statement "WARNING: Advise Patient of Communicable Disease Risks" | AC | = |
| Statement "WARNING: Reactive Test Results for [name of disease agent or disease]" | AC | |

AC= Accompany, AF=Affix

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

B: CELLULAR THERAPY PRODUCT LABELS FOR INTERNAL TRANSPORT

| <u>Element</u> | <u>Internal transport label</u> |
|---|---------------------------------|
| <u>Statements "Human Cells for Administration" or equivalent and "Handle with Care"</u> | <u>AF</u> |
| <u>Emergency contact person name and phone number</u> | <u>AF</u> |

AF=Affix

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APPENDIX III

ACCOMPANYING DOCUMENTS AT DISTRIBUTION

Products collected in or designated for use in the U.S. shall be accompanied upon leaving the Collection or Processing Facility with at least the elements detailed in the following table¹:

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

¹For autologous cellular therapy products, instructions for product use to prevent the introduction, transmission, or spread of communicable diseases and for reporting serious adverse reactions or events to the distributing facility are always required for autologous products. Furthermore, a donor eligibility determination is not required by FDA, but there are specific requirements for labeling under 21 CFR 1271.90 for such products. Appropriate biohazard and warning statements as specified in the Circular of Information Biohazard and Warning Label Table available at: <http://www.factwebsite.org/uploadedFiles/COI-CT-2009.pdf>. Additionally, for products from allogeneic donors that are made available for distribution before the donor eligibility (DE) determination has been completed when there is a documented urgent medical need, there are specific labeling requirements under 21 CFR 1271.60. However, if any donor screening or testing is performed and risk factors or reactive test results are identified, accompanying documentation shall be provided.

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

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

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

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

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