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

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

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NOTICE

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

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INTRODUCTION

This Accreditation Manual is intended to accompany the *FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration, 7th Edition, 2018* (the Standards). The purpose of the manual is to provide guidance to applicants for accreditation and to on-site inspectors. Requirements to become accredited are detailed in the FACT-JACIE Standards. This manual is intended to explain the intent and rationale for specific standards, and to provide explanations, examples, and alternative approaches that will be helpful in the accreditation process. This is not an exhaustive list of possible ways to meet the Standards, and the only intent is to provide examples since there are many effective mechanisms by which to achieve compliance with FACT-JACIE Standards and by which to inspect applicant cellular therapy programs.

This manual is organized by the alphanumeric order of the Standards. Each standard is quoted in its entirety, followed by the guidance section, which includes an explanation of the applicable standard(s), potential ways an applicant may document and an inspector may verify compliance, and examples to illustrate how the standard may be applied. Inspectors are not restricted to the methods for verifying compliance as described in this manual; rather, this information is intended to prepare applicants for making such evidence available to the inspector. Updates are made to this manual as needed to clarify the intent of the Standards. In the event that a printed copy of this manual differs from the version posted online at www.factwebsite.org and www.jacie.org, the web version prevails.

The major objective of the Standards is to promote quality medical and laboratory practice in hematopoietic progenitor cell transplantation and other therapies using cellular products. FACT-JACIE Standards are the outgrowth of the merger of laboratory standards, developed by the International Society for Cellular Therapy (ISCT) and the clinical and training guidelines developed by the American Society of Blood and Marrow Transplantation (ASBMT). Standards were developed by consensus from the medical literature and the contributions of experts in the field. The Standards apply to all phases of collection, processing, storage, and administration of hematopoietic cellular therapy products. This includes hematopoietic progenitor cells (HPCs), mononuclear cells (MNCs), and immune effector cells (IECs) derived from marrow, apheresis, or cord blood, and administered by a FACT or JACIE-accredited blood and marrow transplant team, and various manipulations such as removal or enrichment of various cell populations, expansion of hematopoietic cell populations, and cryopreservation. For hematopoietic progenitor cells or therapeutic cells derived from umbilical cord and/or placental blood, these Standards apply only to the administration of the cellular product and the preparation of the product for administration, applying the clinical and/or processing standards as appropriate. These Standards do not apply to the collection, processing, or banking of umbilical cord and placental blood cells. Standards for these processes are found in the current edition of *NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration*.

In the FACT-JACIE Standards, there is a deliberate and specific use of the terms "shall" and "should." For purposes of both the Standards and this manual, "shall" is used to indicate that the standard is a requirement and 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. An applicant is expected to defend its practice when it deviates from a recommended or advised activity. Wherever there is a discrepancy between the language of the Standards and the guidance in this manual, the term used in the Standards shall prevail.

These Standards are designed to provide voluntary minimum guidelines for programs, facilities, and individuals performing cell transplantation and therapy or providing support services for such procedures. These Standards are not intended to establish best practices or include all procedures and practices that a program, facility, or individual should implement if the standard of practice in the community or applicable governmental laws or regulations establish additional requirements. Each program, facility, and individual should analyze its practices and procedures to determine whether additional standards apply. Compliance with these Standards is not an exclusive means of complying with the standard of care in the industry or community or with local, national, or international laws or regulations. The Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee – ISCT and EBMT expressly disclaim any responsibility for setting maximum standards and further expressly disclaim any responsibility, liability or duty to member programs, directors, staff, or program donors or patients for any such liability arising out of injury or loss to any person by the failure of member programs, directors, or staff to adhere to the Standards or related guidance.

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, 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:

A.2.1 Where applicable laws and regulations include more stringent requirements than these Standards, those laws and regulations supersede the Standards. Conversely, when these Standards are more stringent than applicable laws and regulations, the Standards must be followed.

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

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

A3 ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

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

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

A4 DEFINITIONS

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

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

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

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

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

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

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

Ambulatory care: A planned care system in which adults and young people at risk of prolonged neutropenia are based at home or in other specified accommodation. There should be specific safeguards to minimize the risk from potentially life-threatening complications of chemotherapy.

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

And/or: Either or both maybe 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.

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

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

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

Audit: Documented, systematic evaluation to determine whether approved policies or 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.

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

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

Calibrate: To set measurement equipment against a known standard.

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

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

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

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

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

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

Clinical guidelines: A document that describes recommended practices for a clinical situation. A guideline allows for variations in practice that might better suit the clinical situation.

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

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

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

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

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

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

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

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

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

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

Current Good Manufacturing Practice: The set of current practices followed by entities producing drug and biologic products, including cellular therapy products, to ensure that the products produced meet specific requirements for identity, strength, quality, and purity. In the US, cGMPs are enforced under Section 501(B) of the Federal Food, Drug, and Cosmetic Act (21USC351). Cellular therapy products that are extensively manipulated or that are used for non-homologous purposes are examples of products controlled under cGMP regulations. Similar requirements are delineated by the European Union as EU-GMP, and other countries such as United Kingdom, Australia, Canada, and Singapore have equally well-developed systems of regulations.

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

Designee: An individual with appropriate education, experience, or expertise who is given the authority to assume a specific responsibility. The person appointing the designee retains ultimate responsibility.

Deviation: The action of departing from an established course of action or accepted practice. Also referred to as a variance.

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

Unplanned deviation: Occurred without intent.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Procedure: A treatment or course of action intended to achieve a result in the delivery of healthcare.

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

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

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

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

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

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

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

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

Subcategory 1: The type of cells at collection (HPC, NC, or MNC). If product is collected for infusion without further manipulation, there is no name change. HPCs may be further manipulated, and retain the class name HPC if they are used as a source of hematopoietic progenitor cells; the modification (such as cryopreservation) is added into the product description as an attribute.

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

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

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

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

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

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

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

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

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

CONCURRENT PLASMA, APHERESIS: Plasma collected from the donor as part of an apheresis cell collection procedure, intended for use in further processing of that cellular therapy product.

Subcategory 2: After enumeration or manufacture/processing of a collected product, the product class is identified by the target cell population thought to be present in the product.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Syngeneic: The biologic relationship between identical twins.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Written: Documentation in human readable form.

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

***These definitions are as of the date of publication and use the current terminology as found in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. Available at: www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology.*

CLINICAL PROGRAM STANDARDS

PART B

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PART B: CLINICAL PROGRAM STANDARDS

B1: GENERAL

STANDARD:

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

Explanation:

This standard is the definition of a Clinical Program, an entity that can be inspected and independently accredited. Different clinical sites that make up a single program must be within a defined location(s) that allows for integrated and regular interaction among all members of the medical team. Only those programs that truly function as a single integrated program may apply as one Clinical Program. Electronic medical record (EMR) system access shared among multiple sites, although integrated, does not alone meet the overall intent of this standard.

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

Evidence:

The questions on the inspection application and checklist are designed to elicit the information necessary to determine if a single Clinical Program exists. Different clinical sites ideally should be no more than one hour travelling distance in each direction, and they should exist within a single metropolitan area. Advancement in technology and travel may allow for more geographically dispersed sites, but such programs would be expected to provide unequivocal evidence of integration. An organizational chart depicting the relationship between program sites will facilitate documentation of integration and site locale. No matter the distance between sites, the Clinical Program Director(s) should have a documented physical presence at all sites and be actively involved in daily operations to meet the intent of the standard. Other evidence of an integrated medical team is a common Quality Management (QM) Program and meeting minutes demonstrating collaboration between sites on all aspects of the program at defined and regular intervals.

If the sites are more than one hour in traveling distance, data should show that there is no adverse impact on recipient care or donor safety. If there is a delay during the transfer of a patient or the transfer of a cellular therapy product, a plan needs to be put in place to ensure recipient care and donor safety are met. For example, if there is an accident during a patient transfer to another facility, what steps will the program take to continue providing adequate patient care, how will the patient be stabilized, and is there an alternate location to take the patient?

In the case of sites with more than one hour travelling distance from each other or within different metropolitan areas, programs should contact the FACT or JACIE office to verify eligibility for accreditation as a single program.

STANDARD:

B1.1.1 *The Clinical Program shall demonstrate common staff training, protocols, Standard Operating Procedures, quality management systems, clinical outcome analyses, and regular interaction among all clinical sites.*

Explanation:

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

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

In the event of Co-Directors, it is required that the responsibilities for each Director are clearly defined, and that one will be named as the corresponding director for the accreditation activities and interaction with the accrediting organization.

Evidence:

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

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

Example(s):
Examples of a single integrated Clinical Program may include:

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

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

STANDARD:

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

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

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

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

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

Example(s):
A hematopoietic progenitor cell (HPC) Collection Facility may be accredited independently, or in conjunction with a Clinical Program and a Cell Processing Facility. A Clinical Program and the Collection Facility could be a joint facility, with the cells processed and stored by contract at another facility. A Processing Facility may process and store cells for several Clinical Programs, which may or may not be accredited by FACT or JACIE.

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

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

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

- Evaluation of the autologous or allogeneic donor for suitability (e.g. medical fitness) to undergo the collection procedure.
- Evaluation of the allogeneic donor for donor eligibility (e.g. free of risks of transmission of infectious diseases).
- Collection of the cells at the Clinical Program's Collection Facility.
- Temporary storage of the product in the Processing Facility and distribution to the clinical unit.
- Thawing and other needed manipulations of the product before administration to the recipient.

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

STANDARD:

B1.2.1 If cellular therapy products are received directly by the Clinical Program 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 donor eligibility screening and testing in accordance with applicable laws and regulations.

Explanation:
The Standards apply to novel cellular therapy products that are manufactured by a third-party and routed through an accredited blood bank, accredited tissue bank, or a hospital pharmacy rather than a Processing Facility. Communication with manufacturers is critical to the safety, efficacy, and quality of the cellular therapy product, and the Clinical Program is responsible for handling products according to the Standards.

Chain of custody documentation should include dates, times, and responsible parties for distribution and receipt; storage; and release for administration. The distribution conditions should be defined by the Clinical Program with documentation that those conditions were met (e.g., temperatures during transport or shipping). The program (or receiving blood bank, tissue bank, or pharmacy) should have a designated space with suitable equipment for receiving and storing cellular therapy products. To prevent mix-ups, product identity should be confirmed by two professionals. Before administration to a recipient, the product must be compared against the written physician order and patient identity.

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

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

Explanation:
FACT and JACIE are voluntary inspection and accreditation programs sponsored by the American and European Societies for Blood and Marrow Transplantation and the International Society for Cellular Therapy. Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with the Standards does not guarantee compliance with all applicable laws and regulations. Governmental regulations must also be followed. It is the responsibility of the individual Clinical Program to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the program may apply; for example, when a program receives cellular therapy products either to or from outside of its immediate jurisdiction.

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

Evidence:
Current certificates, permits, or licenses will demonstrate which areas of a facility have been authorized by other organizations and governmental authorities. While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with applicable laws and regulations. Evidence of compliance with the Standards will require preinspection information identifying prevailing governmental authorities.

Example(s):
In the U.S., minimally manipulated cellular therapy products from first or second degree related donors are regulated under the 21 CFR 1271 Good Tissue Practices (GTP) regulations and section 361 of the Public Health Service Act. A cellular therapy product that is extensively manipulated, obtained from an unrelated donor, combined with a drug or device, or used for non-homologous use (does not perform the same function in the recipient as in the donor) is regulated as a drug, device, and biologic product under section 351 of the Public Health Service Act and other applicable regulations in title 21 of the Code of Federal Regulations. Minimally manipulated HPC, Marrow is not included under these regulations.

In the Member States of the European Union (EU), HPCs fall under the European Directive 2004/23/EC on all tissues and cells, "Setting standards on quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells" and the implementing directives 2006/17/EC and 2006/86/EC. The 2001/83/EC directive regulates products that are classified as medicinal products (MP). This includes somatic cellular therapy MPs and gene therapy MPs. The ATMP Regulation 1394/2007 entered into force on December 30, 2008 to include tissue engineered products. The consequence of classification as an MP is that a Good Manufacturing Practice (GMP) environment is required for the production of these cells. Furthermore, each Member State in the EU may add regulations to the directives that also must be followed. Member State-specific regulations will not be detailed here but all shall apply.

STANDARD:

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

Explanation:
National or state laws and regulations may require registration or certification with the government or may require accreditation from professional organizations for the activities performed within the program.

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

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

Example(s):
In the U.S., Clinical Programs must have or utilize inpatient units that are located in facilities accredited by the Joint Commission (Joint Commission on Accreditation of Healthcare Organizations or JCAHO), the Healthcare Facilities Accreditation Program (HFAP) of the American Osteopathic Association, or DNV (Det Norske Veritas) Healthcare, Inc. Alternatively, U.S. Clinical Programs may choose to be directly inspected by the Centers for Medicare & Medicaid Services (CMS). In addition, U.S. Clinical Programs must be licensed as required by applicable law. Other countries have their own hospital certification bodies, such as the Haute Autorité de santé (HAS) in France.

STANDARD:

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

Explanation:
A Clinical Program must have sufficient experience as a team in caring for transplant patients. A designated transplant team does not necessarily mean that each of the individuals has no other responsibilities or duties. It is likely that some individuals may perform basic research, clinical research, other non-transplant clinical care, or administrative work during the time they are not actively attending to transplant patients. However, each transplant team member must each meet the training and experience requirements in B3.

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

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

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

If an experienced team relocates and develops a new Clinical Program, that new program must have been in place at least 12 months, and the team must have performed a minimum number of transplants (per Appendix I) at the new location prior to accreditation of the new program. This is true regardless of the experience of the team.

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

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

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

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

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

B2: CLINICAL UNIT

STANDARD:
B2.1 *There shall be a designated inpatient unit of appropriate location and adequate space and design that minimizes airborne microbial contamination.*

Explanation:
Clinical unit facilities may vary among centers. Variability may be based on a number of factors, including the number and type (autologous or allogeneic) of transplants performed, the patient case mix, the cell source, epidemiological factors influencing the prevalence of opportunistic infections, and economic considerations.

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

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

Signs posted around the clinical unit and the behavior of the staff consistent with expectations for the type of infection control described in the policies and procedures demonstrate compliance with this standard. If there are renovation or construction projects underway, the appropriate environmental controls must be present. The risk of spread of communicable disease agents must be minimized in any setting where patients could reasonably be expected (including dialysis or intensive care units). Care should be taken that the ventilation from other isolation rooms (where infected patients may reside) does not pass through the rooms used for recipients. Evidence of compliance with this standard will require preinspection documentation of infection control policies, specifications of air handling, and floor plans.

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

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

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

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

STANDARD:

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

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

Explanation:

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

Evidence:

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

Example(s):

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

STANDARD:

B2.4 *The Clinical Program shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.*

Evidence:
The inspector will observe the facility and look for signs of cleanliness, sanitary practices, and orderly arrangement.

STANDARD:

B2.5 *There shall be adequate equipment and materials for the procedures performed.*

B2.6 *There shall be provisions for prompt evaluation and treatment by an attending physician available on a 24-hour basis.*

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

Evidence:
An on-call schedule should be available for inspector review. Inspectors may choose to test attending physician availability by activating the on-call schedule during the period of the on-site inspection.

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

STANDARD:

B2.7 *There shall be written guidelines for communication, patient monitoring, and prompt transfer or triage of patients to an intensive care unit, emergency department, or equivalent when appropriate.*

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

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

Example(s):
Depending on the recipient's status, acute needs may arise while on an inpatient unit, at an outpatient clinic, or after discharge. The ICU and emergency teams need to be aware of the types of patients served at the Clinical Program and how to adequately care for them. Examples include protecting immunocompromised patients from infection and quickly treating central nervous system disease or cytokine release syndrome (common in CAR-T cell recipients).

STANDARD:

B2.8 *There shall be written guidelines for communication between the Clinical Program and the Collection Facility for the management of collection-related complications.*

B2.9 *There shall be an intensive care unit or equivalent coverage available.*

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

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

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

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

STANDARD:

B2.10 *There shall be attending physician oversight if general medical physicians, physicians in training, or APPs provide care to transplant patients. The scope of responsibility of general medical physicians or APPs shall be defined.*

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

Evidence:
There must be guidelines that describe outpatient and afterhours care, including when and under what conditions the attending physician must be contacted by general medicine physicians. The scope of responsibilities of general medicine physicians and APPs to the transplant program must be defined in policies and SOPs, position descriptions, or similar documents.

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

STANDARD:

B2.11 *There shall be a pharmacy providing 24-hour availability of medications needed for the care of transplant patients.*

B2.11.1 *Pharmacies shall have access to medications adequate to treat expected complications of immune effector cell administration, including cytokine release syndrome.*

Explanation:
Cellular therapy patients often require a highly specialized set of medications that may require special authorization or may not be routinely available. In addition to having medications available, there must always be a pharmacist available on-site or on-call. The pharmacy must have mechanisms to prevent dosing errors.

Example(s):
Institutional limitations on select medications, such as expensive drugs, may need consideration. Tocilizumab is commonly needed to treat cytokine release syndrome, but is not routinely available in 24-hour pharmacies. Clinical Programs may need to consult with their pharmacies to develop a plan for accessing this drug on a 24-hour basis and ultimately dispensing it within 30 minutes of a request. One method is to keep a minimum number of doses on the clinical unit.

STANDARD:

B2.12 *There shall be access to renal support under the direction of nephrologists and trained personnel.*

Evidence:

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

Example(s):

The need for dialysis may be fulfilled by provision of dialysis under the direction of nephrologists and trained staff on the transplant unit, in an intensive care unit, and/or in an outpatient setting as appropriate. Services may be provided through a dialysis unit within the institution or through a written agreement with an outside vendor.

STANDARD:

B2.13 *There shall be 24-hour availability of CMV-appropriate and irradiated blood products needed for the care of transplant recipients.*

Explanation:

This Standard is applicable to autologous and allogeneic recipients.

Those blood components suitable for CMV-negative recipients must be defined by the Clinical Program in an SOP(s). There must be a procedure in place for procurement of irradiated blood products as needed.

Example(s):

If leukocyte-reduction is used to meet this standard, there must be a validated method in place (in the Transfusion Service) to adequately and consistently reduce the leukocytes in the blood components.

STANDARD:

B2.14 *Clinical Programs performing allogeneic transplantation shall use HLA testing laboratories that are capable of carrying out DNA–based intermediate and high resolution HLA typing and are appropriately accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), European Federation for Immunogenetics (EFI), or other accrediting organizations providing histocompatibility services appropriate for hematopoietic cellular therapy transplant patients.*

Explanation:

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

In addition to ASHI and EFI, other HLA typing laboratory accrediting organizations may be deemed appropriate based on standards that adequately address HPC transplantation and on accreditation processes that utilize qualified inspectors and a consistent review procedure. The FACT-JACIE

Guidelines for Histocompatibility Typing Standards and Accreditation Programs will be used to evaluate accrediting organizations that wish to be considered appropriate for HPC transplantation. It is incumbent on those other accrediting organizations to provide demonstrable evidence that they meet the guidelines. If a Clinical Program wishes to use a histocompatibility laboratory with accreditation other than ASHI or EFI, that Clinical Program must ensure the alternative accreditation has been determined to be acceptable.

Evidence:
A copy of the current (in-date) certificate of ASHI, EFI, or other accrediting organization must be submitted, including at least the competencies listed above. If ASHI accreditation is not for "HSC and BM Transplantation", the Clinical Program must describe the role the HLA testing laboratory fulfills in donor selection and demonstrate adequate HLA expertise in the program.

Example(s):
If the HLA testing laboratory is ASHI accredited for the appropriate technologies and methods, but not in HSC and BM Transplantation, the Clinical Program must have sufficient expertise to select the best matched donor for the recipient.

STANDARD:
B2.15 Chimerism testing shall be performed in laboratories accredited for the techniques used.

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

Chimerism testing may be performed using various methods, and interlaboratory variability may be significant. Appropriately credentialed laboratories that utilize validated methods, routinely utilize quality controls, and participate in proficiency testing are essential to reliable chimerism testing results.

Example(s):
EFI and other organizations provide external laboratory accreditation and quality assurance in chimerism testing specifically. Laboratories are not required to be specifically accredited for chimerism testing, but must be accredited for the techniques they use to perform the testing. For example, laboratories using molecular methods must be accredited for molecular testing. Clinical Programs using laboratories that are not accredited could send samples to an accredited laboratory for the chimerism testing.

Evidence
A copy of the current (in-date) external certification should be provided from the laboratory providing chimerism testing and be available at the on-site inspection. Inspectors should inspect proficiency testing results and SOPs that guide clinical interpretations.

STANDARD:

B2.16 *The Clinical Program shall be operated in a manner designed to minimize risks to the health and safety of employees, recipients, donors, visitors, and volunteers.*

B2.17 *The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to liquid nitrogen; communicable disease; and to chemical, biological, or radiological hazards.*

Explanation:

The Clinical Program's policies and SOPs, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to applicable safety regulations. It is critical that the Clinical Program has a safety manual, and that staff members have ready access to instructions for prompt response. In case of exposure to a hazardous material (e.g., liquid nitrogen; communicable disease; or chemical, biological, or radiological hazard), the response and action taken might be time sensitive and thus could affect the outcome of the exposure. If an institution-wide manual is used, safety, infection risks, and/or biohazard waste disposal procedures that are unique to the program must be covered in the program's SOP Manual.

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

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

An adequate means of egress in areas where liquid nitrogen is stored, moved (e.g., elevators), or transported is required for the safety of personnel, and potentially, the public.

Evidence:

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

The inspector should examine how cellular therapy products are handled and discarded, and compare his/her observations with the written protocols. The inspector should examine selected employee files for appropriately documented safety training.

Example(s):
The safety manual may be an institution-wide document available by hard copy or electronically. Access to the institutional safety manual solely by computer is not acceptable without a written policy describing how to access the information in the event of a computer failure or down time. An SOP that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice.

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

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

STANDARD:
B2.18 *All waste generated by the Clinical Program activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable laws and regulations.*

Explanation:
Poor management of medical waste exposes personnel, waste holders, and the community to injuries, infections, and toxic effects. Hazardous waste generated by the Clinical Program's activities includes a broad range of materials, including used supplies, sharps, chemicals, radioactive material, viral vectors, genetically modified cells, and the cellular therapy products themselves. All medical waste shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste and in accordance with applicable governmental laws and regulations. Contaminated materials shall be placed in appropriate bags and containers marked with the international infectious substance symbol. Radioactive and chemical waste must be discarded using methods approved by appropriate governmental agencies. General waste that contains information that would constitute a breach of confidentiality if it became available to unauthorized persons, such as paper, CDs, disks etc., should be stored in a secured container before disposal and ultimately shredded or destroyed.

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

Example(s):
Contaminated materials may be typically discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, through the use of a sanitary landfill. Sharps like needles, blades, etc., whether or not they are infected, should be considered highly hazardous health care waste and placed for disposal in puncture proof containers. Chemicals such as cytostatic drugs, used in purging procedures, shall be discarded in accordance with applicable regulations.

STANDARD:

B2.19 *Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.*

Explanation:

When handling potentially hazardous substances, personnel must use appropriate protective attire. To prevent the spread of hazardous substances, protective attire must be removed before leaving the workspace.

B3: PERSONNEL

STANDARD:

B3.1 *CLINICAL PROGRAM DIRECTOR*

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

Explanation:

The Clinical Program Director must be licensed or registered according to applicable laws and regulations to practice medicine in the state, province, or country in which the Clinical Program is located.

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

Maintenance of specialty and sub-specialty certification requires time, effort, and financial resources, and the value of maintaining certification has become controversial as recently discussed (NEJM 372(2):104-108; 2015). It is recognized that board certification exam questions in hematology/oncology may not extensively cover or be relevant to cellular therapy and HPC transplantation. Maintenance of specialist certification is recommended, however, it is not required for the Program Director or for attending physicians. There may be circumstances under which expiration of board certification or specialist registration can be allowed, if permitted by applicable laws and regulations. For example, if a significant portion of a Clinical Program Director's duties includes the direct care of cellular therapy patients, he/she will have the experience to maintain and continuously update the knowledge and skills required.

Those physicians who completed their medical training prior to the availability of specific training in transplantation may qualify as Clinical Program Directors if they have at least 10 years of documented experience in transplantation. This includes immunologists who were involved in the advent of HPC transplantation and/or had specific training in transplantation.

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

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

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

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

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

Example(s):
Specialist certification in the U.S. means sub-specialty certification by the American Board of Medical Specialties. The equivalent European Union requirements include specialist registration or completion of the higher specialist training (Certificate of Completion of Specialist Training or CCST) in one of the specialties listed in B3.1.1.

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

STANDARD:

B3.1.2 *The Clinical Program Director shall have two (2) years of experience as an attending physician responsible for the direct clinical management of HPC transplant patients in the inpatient and outpatient settings.*

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

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

STANDARD:

B3.1.3 *The Clinical Program Director shall be responsible for administrative and clinical operations, including compliance with these Standards and applicable laws and regulations.*

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

Explanation:
This standard is not intended to preclude the prerogative of the Clinical Program Director to delegate some of the duties associated with the operation of the Clinical Program to other qualified individuals. An overall Transplant Program Director who oversees clinical, collection, and cell processing functions may assume some of these duties. Similarly, a Quality Manager may facilitate the execution of a process improvement program. Because cell collection and processing services play a major role in patient outcomes, the Clinical Program Director must monitor whether these services meet the Standards and contractual requirements (see B4). The final responsibility for all delegated duties remains with the Clinical Program Director.

"Design" in this standard refers to the current structure of the Clinical Program. The Clinical Program Director is responsible for ensuring the program is designed in a manner that meets each FACT-JACIE standard through a process.

Example(s):
Individual transplant physicians may accept patients or donors for entry into the Clinical Program according to institutional policies and SOPs. It is the responsibility of the Clinical Program Director to ensure such policies exist and are followed.

STANDARD:

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

B3.1.5.1 The Clinical Program Director or designee shall be responsible for verifying the knowledge and skills of members of the Clinical Program once per accreditation cycle, at minimum.

Explanation:
This standard is not meant to imply that the Clinical Program Director is directly responsible for the medical activity of another physician, APP, or other member of the program. The Clinical Program Director is responsible for reviewing their knowledge and skills. This review must be documented by some means, such as evidence of Continuing Medical Education (CME), Continuing Professional Development (CPD), annual faculty evaluations (in the case of academic programs), minutes of meetings in which the medical care of donors and recipients was specifically addressed, etc. Provisions should be made for verification of knowledge and skills of new staff within the first year of employment including a plan to evaluate competence.

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

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

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

STANDARD:

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

B3.1.6.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:
The field of transplant medicine continues to evolve rapidly. Clinical Program Directors must participate regularly in educational activities related to cellular therapy. The purpose of this requirement is for key personnel to keep up with current advancements in the field.

There are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use his/her judgment to determine whether or not a Clinical Program Director meets this standard. Recognized educational activities include both certified continuing medical education credits (preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are included in this Accreditation Manual, and may include topics specific to cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

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

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

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

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

Examples of appropriate continuing education activities include:

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

ASBMT offers its members two Practice Improvement Modules (PIMs) that are applicable to this standard. The PIMs address chronic GVHD and Infectious Disease; each PIM provides 20 Category 1 CME credits through the American Board of Internal Medicine's Maintenance of Certification (MOC) program. The PIMs can be accessed by ASBMT members at
http://asbmt.org/professional-development/practice-improvement-modules.

ASBMT also offers an Online Learning center that hosts recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning.

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at:
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

B3.2 ATTENDING PHYSICIANS

B3.2.1 Attending physicians shall be appropriately licensed to practice medicine in the jurisdiction of the Clinical Program and should be specialist certified or trained in one of the following specialties: Hematology, Medical Oncology, Immunology, or Pediatric Hematology/Oncology.

B3.2.1.1 Clinical Programs performing adult transplantation shall have at least one attending physician who has achieved specialist certification in Hematology, Medical Oncology, or Immunology.

B3.2.1.2 Clinical Programs performing pediatric transplantation shall have at least one attending physician who has achieved specialist certification in Pediatric Hematology/Oncology or Pediatric Immunology.

Explanation:

This Standard is applicable for clinical attending physicians other than the Program Director, and is parallel to the requirements for the Clinical Program Director. However, it allows specialist training rather than requiring specialist certification for attending physicians. This implies that the attending physician has completed the formal training and all other requirements to be eligible to take examinations required for certification. The Standard also allows for attending physicians certified in Adult Immunology in adult programs, though this specialty does not meet the requirement for the Clinical Program Director. Additionally, for adult transplantation programs, at least one of the attending physicians must have achieved specialist certification as described in B3.2.1.1. Similarly, for pediatric transplantation, at least one of the attending physicians must have achieved specialist certification as described in B3.2.1.2. It is recommended but not required that continuing specialist certification be maintained to demonstrate competence.

Evidence:
A copy of the current medical license or non-U.S. equivalent of each attending physician is required to document licensure in the state, province, or country in which the Clinical Program is located. For sub-specialty board certification/eligibility or equivalent, a copy of the current certificate or documentation of completion of the requisite fellowship and primary board certification in Internal Medicine or Pediatrics is required.

Example(s):
Specialist certification in the U.S. means sub-specialty certification by the American Board of Medical Specialties. The equivalent European Union requirements include specialist registration or completion of the higher specialist training (Certificate of Completion of Specialist Training or CCST) in one of the specialties listed in B3.2.1.

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

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

Most training programs prior to 1985 had little, if any, specific training in transplantation, and there were few, if any, transplant-related questions on the written certification exams (board exams in the U.S.). Those physicians who completed their medical training prior to the availability of specific training in transplantation (i.e., prior to 1985) may be qualified if they have at least 10 years of documented experience in transplantation.

STANDARD:

B3.2.2 Attending physicians shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

B3.2.2.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:
The field of transplant medicine continues to evolve rapidly. Clinical attending physicians must participate regularly in educational activities related to cellular therapy. The purpose of this requirement is for key personnel to keep up with current advancements in the field. The Clinical Program Director should evaluate the continuing education obtained by attending physicians periodically, for example, as part of the annual performance review required in B.

There are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use his/her judgment to determine whether or not each attending physician meets this standard. Recognized educational activities include both certified continuing medical education credits

(preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are included in this Accreditation Manual, and may include topics specific to cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

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

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

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

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

Examples of appropriate continuing education activities include:

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

ASBMT offers its members two Practice Improvement Modules (PIMs) that are applicable to this standard. The PIMs address chronic GVHD and Infectious Disease; each PIM provides 20 Category 1 CME credits through the American Board of Internal Medicine's Maintenance of Certification (MOC) program. The PIMs can be accessed by ASBMT members at
http://asbmt.org/professional-development/practice-improvement-modules.

ASBMT also offers an Online Learning center that hosts recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning.

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at:
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

B3.3 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

B3.3.1 Attending physicians shall each have had a minimum total of one year of supervised training in the management of transplant patients in both inpatient and outpatient settings.

B3.3.2 Clinical training and competency shall include the management of autologous and/or allogeneic transplant recipients, as applicable.

Explanation:

Clinical Program Directors and attending physicians must have written confirmation of their training or experience and documentation of competency. Specialist certification is fulfillment of the training requirement. Other documentation could include a letter from each of the directors of the programs, departments, and/or institutions where this training and/or experience were obtained. The letter must include at least the following information: an estimate of the number of patients the applicant has managed, whether patient management included both inpatient and outpatient care, whether the training/experience was exclusively in autologous or allogeneic transplantation or both, and an estimate of the actual number of weeks committed to this training and/or experience. If appropriate, the letter could also document initial competency and/or knowledge (as required) in each of the subjects and procedural skills listed in B3.3.2 – B3.3.5.

STANDARD:

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

Explanation:

Competency in each of the areas must be documented for each attending physician (in the U.S.) or consultant/senior physician (in Europe) by the Clinical Program Director. Some competency evaluation must be documented annually. Clinical Programs do not have to assess competency for all items listed in B3.3.4 each year; however, each area should be addressed at least once during each accreditation cycle.

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

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

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

STANDARD:

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

Example(s):
The American Society for Blood and Marrow Transplantation provides Practice Improvement Modules that may be used for training and competency assessment for GVHD and Infectious Complications (available at
http://www.asbmt.org/displaycommon.cfm?an=1&subarticlenbr=81).

The British Society of Blood and Marrow Transplantation (BSBMT) also has training guidelines and curriculum available at: http://bsbmt.org/download-documents/.

Other organizations offer conferences on specific transplant topics, such as the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities may be considered at
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

B3.3.4.1 Indications for allogeneic and autologous HPC transplantation.

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

STANDARD:

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

B3.3.4.3 Donor selection, evaluation, and management.

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

STANDARD:

B3.3.4.4 Donor and recipient informed consent.

B3.3.4.5 Administration of preparative regimens.

B3.3.4.6 Administration of growth factors for HPC mobilization and for post-transplant hematopoietic cell reconstitution.

B3.3.4.7 Cellular therapy product administration and patient management.

Example(s):
The requirement for training and competency in HPC product administration and patient management may be documented with copies of administration reports for each physician or by competency evaluations developed by the Clinical Program.

STANDARD:

B3.3.4.8 Management of neutropenic fever.

B3.3.4.9 Diagnosis and management of infectious and non-infectious pulmonary complications of transplantation.

B3.3.4.10 Diagnosis and management of fungal disease.

B3.3.4.11 Diagnosis and management of sinusoidal obstruction syndrome, veno-occlusive disease of the liver, and other causes of hepatic dysfunction.

B3.3.4.12 Management of thrombocytopenia and bleeding, including recognition of disseminated intravascular coagulation.

B3.3.4.13 Management of hemorrhagic cystitis.

B3.3.4.14 Blood transfusion management.

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

STANDARD:

B3.3.4.15 Use of irradiated blood products.

Explanation:

Donors may require a blood transfusion during the apheresis collection procedure. Cellular therapy programs, especially their Apheresis Collection Facilities need to be prepared to provide appropriate blood products. Autologous units may be collected prior to apheresis, or allogeneic CMV-appropriate and irradiated units may be used. The decision to use autologous or allogeneic blood depends on the benefits and risks to the donors, especially in the case of pediatric donors.

A special concern for the allogeneic donor is the fact that transfused allogeneic blood contains lymphocytes that can become part of the collected cellular therapy product. Therefore, these transfusions must be gamma-irradiated to prevent engraftment of third-party lymphocytes in the transplant recipient. Because of the occasional need for a second cellular therapy product collection, it is advisable to continue irradiating blood transfused to the donor in the postoperative period[1].

It is expected that normal sized, adult marrow donors would donate autologous blood and therefore not require allogeneic blood. However, in the situation of small marrow donors and large recipients, transfusion is expected. Many places have difficulty collecting autologous blood from donors <40 kilograms (kg). If the recipient is adult size and the donor is 25 kg (common in sibling transplants), transfusion is expected, frequently occurs during the collection, and the blood products must be irradiated. Additional information can be found in Transfusion Support of the Marrow Donor[2].

The use of irradiated blood components during the immediate post-operative period may be necessary if there is any consideration that the donor may need to donate a second product in that immediate timeframe. Under most circumstances, the requirements for irradiated blood products are during collection, but physicians might want to consider the use of irradiated blood components during the immediate post-operative period. For example, if children need to be harvested twice, or if the target yield was not achieved, a supplemental peripheral blood product from the donor may be necessary.

References cited:

1. Snyder El and Haley NR (eds): Cellular Therapy: A Physician's Handbook. Published by AABB, 2004:15.

2. Petz LD and Swisher SW, eds: CLINICAL PRACTICE OF TRANSFUSION MEDICINE, Second edition, 1981; Third edition 1996.

STANDARD:

B3.3.4.16 Management of mucositis, nausea, and vomiting.

B3.3.4.17 Monitoring and management of pain.

B3.3.4.18 Cytokine release syndrome.

B3.3.4.19 Tumor lysis syndrome and macrophage activation syndrome.

B3.3.4.20 Cardiac dysfunction.

B3.3.4.21 Renal dysfunction.

B3.3.4.22 Respiratory distress.

B3.3.4.23 Anaphylaxis.

B3.3.4.24 Infectious and noninfectious processes.

B3.3.4.25 Diagnosis and management of HPC graft failure.

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

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

STANDARD:

B3.3.4.27 Evaluation of late effects of transplantation.

B3.3.4.28 Documentation and reporting for patients on investigational protocols.

B3.3.4.29 Applicable regulations and reporting responsibilities for adverse events.

B3.3.4.30 Palliative and end of life care.

B3.3.4.31 Age-specific donor and recipient care.

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

STANDARD:

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

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

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

STANDARD:

B3.3.5.2 Donor eligibility determination.

B3.3.5.3 Methodology and implications of human leukocyte antigen (HLA) typing.

B3.3.5.4 Management of patients receiving ABO incompatible HPC products.

B3.3.5.5 Diagnosis and management of immunodeficiencies and opportunistic infections.

B3.3.5.6 Diagnosis and management of acute graft versus host disease.

B3.3.5.7 Diagnosis and management of chronic graft versus host disease.

Explanation:
Clinical Program Directors and attending physicians must have current training and documentation of competency that reflect evolution in the current understanding, classification, and management of acute and chronic GVHD. Pertinent references include:

- Fillipovich AH, Weisdorf D, Pavletic S et al: *National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report*. Biology of Blood and Marrow Transplantation 11:945-955 (2005). Available at:

http://www.ncbi.nlm.nih.gov/pubmed/16338616. (Standardizes criteria for diagnosis of GVHD, proposes clinical scoring system (0-3) based on the extent and severity of chronic GVHD, and proposes new guidelines for global assessment of chronic GVHD.)

- Couriel D, Carpenter PA, Cutler C et al: *Ancillary Therapy and Supportive Care of Chronic Graft-versus-Host Disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: V. Ancillary Therapy and Supportive Care Working Group Report*. BBMT 12:375-396 (2006). Available at

http://www.ncbi.nlm.nih.gov/pubmed/16545722. (Recommendations for prevention of infections, osteoporosis, and steroid myopathy, and management of neurocognitive and psychosocial adverse effects related to chronic GVHD.)

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

The American Society for Blood and Marrow Transplantation provides Practice Improvement Modules that may be used for training and competency assessment for GVHD and Infectious Complications (available at
http://www.asbmt.org/displaycommon.cfm?an=1&subarticlenbr=81).

The British Society of Blood and Marrow Transplantation (BSBMT) also has training guidelines and curriculum available at
http://bsbmt.org/download-documents/.

The combined annual meetings of the CIBMTR and ASBMT offer the BMT Clinical Education Conference for NPs, PAs, Fellows, and Junior Faculty.

STANDARD:

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

B3.3.6.1 Bone marrow harvest procedures.

B3.3.6.2 Cellular therapy product cryopreservation.

B3.3.6.3 Cellular therapy product processing.

B3.3.6.4 Washing and diluting of cellular therapy products.

B3.3.6.5 Apheresis collection procedures.

B3.3.6.6 Extracorporeal photopheresis for GVHD.

B3.3.6.7 Cellular therapy product administration procedures.

Explanation:

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

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

Every physician must be knowledgeable about the procedure and its risks and benefits in order to counsel patients and donors regarding the alternative sources of stem cells, the advantages and disadvantages of each, and to make a recommendation for a specific patient. In addition, each Clinical Program must have access to at least one physician who is trained and competent in bone marrow harvesting.

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

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

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

For attending physicians at Clinical Programs administering immune effector cellular therapy products, such as chimeric antigen receptor (CAR) T cells, patient management includes responses to cytokine release syndrome and other similar adverse events.
The Clinical Program Director may document each physician's knowledge in these areas utilizing a letter, evidence of CME, a copy of a publication authored by the physician, or other documents.

STANDARD:
B3.4 PHYSICIANS-IN-TRAINING

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

Explanation:
This standard applies to Clinical Programs in which physicians-in-training, including residents, fellows, registrars, play a role in the direct clinical care of hematopoietic stem cell transplant recipients and/or donors.

Evidence:
In the US, documentation that the physician-in-training is a resident or fellow in an Accreditation Council for Graduate Medical Education (ACGME)-accredited training program will be accepted by FACT as evidence of medical licensure, appropriate attending medical staff supervision, and an appropriate curriculum. If all physicians-in-training in a Clinical Program are part of the ACGME-accredited training program, it is sufficient for the program to submit one certification of accreditation to cover all trainees. The ACGME is a private, nonprofit organization that accredits residency programs in 140 specialties and subspecialties. Its mission is to improve health care by assessing and advancing the quality of resident physicians' education through accreditation. Accredited training programs are inspected every two to five years, and accreditation is based upon substantial compliance with common and specialty-specific standards. Documentation will be required for BMT training programs that are accredited by a state or other agency. Individuals with less formal training arrangements may be required to submit individual credentials. FACT may audit a training program if needed. Equivalent programs to review and accredit training programs exist in Australia, Asia, and elsewhere.

Example:
There are approved fellowships available in the US for training in Oncology, Hematology, Pediatric Hematology/Oncology, and various other specialties. Fellows in these programs may be involved in care of transplant recipients; documentation of their credentials may be achieved through the submission of ACGME certificate. At the time of publication, there is no approved training program in the US under this structure for specifically bone marrow/stem cell transplant fellows, although many programs have such training opportunities available. Programs would be expected to provide documentation for these persons that include licensure and appropriate supervision.

STANDARD:

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

Explanation:
Physician training programs may differ depending on the goals of the physician in training and the purposes of the program. Training duration (e.g., a year or month of training) and type (e.g., training as a medical or pediatric resident, an oncology fellow versus a transplant fellow) will determine the level of transplant-related knowledge and competence a physician in training is expected to achieve. The training and competencies in this standard and in B3.3.4 and B3.3.5 refer specifically to the training of an HPC transplant fellow. It is important to note that training should include both allogeneic and autologous transplantation for all fellows.

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

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

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

ASBMT and NMDP developed a BMT Curriculum to give physicians-in-training exposure to the biology and clinical practice of blood and marrow transplant. (BMT) leading transplant physicians developed 16 didactic curriculum modules and several testimonial videos on "why I chose BMT". These modules provide the history and future of BMT, fundamentals of the science behind transplant, state-of-the-field disease summaries, immunobiology and donor selection, early and late effects and more. Visit https://bethematchclinical.org/Resources-and-Education/Education-Courses-and-Events/Curriculum/ for more details.

ASBMT also offers its members two Practice Improvement Modules (PIMs) that may be useful in training programs. The PIMs address chronic GVHD and Infectious Disease, and can be accessed at:
http://asbmt.org/professional-development/practice-improvement-modules

ASBMT also offers an Online Learning center that hosts recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning

Other organizations offer conferences on specific transplant topics, such as the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are detailed at: http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

The combined annual meetings of the CIBMTR and ASBMT offer the BMT Clinical Education Conference for NPs, PAs, Fellows and Junior Faculty.

STANDARD:
B3.5 ADVANCED PRACTICE PROVIDERS/PROFESSIONALS (APPs)

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

Evidence:
Evidence of current licensure to practice in the jurisdiction of the Clinical Program will be submitted with the accreditation application. If the APPs are a part of the cellular therapy team, a written description of clinical responsibilities of the APP and the expected physician oversight should be available within the Clinical Program. Note that the role of an APP is not found in all countries, nor do all programs have APPs. The Clinical Program is not required to have APPs participate in the direct care of transplant recipients.

STANDARD:

B3.5.2 *APPs shall have received specific training and maintain competence in the transplant-related skills that they routinely practice included within but not limited to those listed in B3.3.4 and B3.3.5.*

Evidence:
Competency in each of the areas described in B3.3.4 and B3.3.5, as applicable to the procedural skills they routinely practice in their facility, must be documented for APPs by the Clinical Program Director or designee. Pediatric APPs must have training in pediatrics as specified by B3.6.1.

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

The ASBMT Nurse Practitioners and Physicians Assistants Special Interest Group (SIG) has developed a website with additional resources for APPs, including a guideline for training in hematopoietic cell transplantation, available at http://www.asbmt.org/?page=NPPASIG#.

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

The American Society for Blood and Marrow Transplantation provides Practice Improvement Modules that may be used for training and competency assessment for GVHD and Infectious Complications, available at
http://www.asbmt.org/displaycommon.cfm?an=1&subarticlenbr=81.

The British Society of Blood and Marrow Transplantation (BSBMT) also has training guidelines and curriculum available at
http://bsbmt.org/download-documents/.

Other organizations offer conferences on specific transplant topics, such as the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities may be considered at
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

The combined annual meetings of the CIBMTR and ASBMT offer the BMT Clinical Education Conference for NPs, PAs, Fellows and Junior Faculty.

STANDARD:

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

B3.5.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:

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

There are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use his/her judgment to determine whether or not each APP meets this standard. Recognized educational activities include both certified continuing education credits (preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are included in this Accreditation Manual, and may include topics specific to cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Evidence:

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

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

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Example(s):

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

Examples of appropriate continuing education activities include:

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

ASBMT offers its members two Practice Improvement Modules (PIMs) that are applicable to this standard. The PIMs address chronic GVHD and Infectious Disease; each PIM provides 20 Category 1 CME credits through the American Board of Internal Medicine's Maintenance of Certification (MOC) program. The PIMs can be accessed by ASBMT members at
http://asbmt.org/professional-development/practice-improvement-modules

ASBMT also offers an Online Learning center that hosts recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning.

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

B3.6 CLINICAL TRANSPLANT TEAM

B3.6.1 Clinical Programs performing pediatric transplantation shall have a transplant team trained in the management of pediatric recipients.

Explanation:

Teams treating children must include at least one attending physician who has achieved specialist certification in Pediatric Hematology/Oncology or Pediatric Immunology. Pediatric expertise and experience is also required among the nursing, pharmacy, and social services staff. Teams treating adults must include at least one attending physician who has achieved specialist certification in Internal Medicine Hematology, Medical Oncology, or Immunology. After achieving specialist certification, re-certification is not required.

Example(s):
Evidence of compliance with these standards may include age-specific competencies and proficiencies, attendance at age-specific continuing educational activities, and/or age-specific preceptorships.

STANDARD:

B3.6.2 *The Clinical Program shall have access to licensed physicians who are trained and competent in marrow collection and utilize a marrow collection facility that meets these Standards.*

Explanation:
This standard requires that the Clinical Program either have at least one physician who is trained and competent in marrow collection within the Clinical Program, or have an agreement with another accredited facility to provide marrow collection services from trained and competent physician(s). While one is the minimum requirement, it is recommended that the program should have a trained back-up physician. If a program's SOPs state that marrow collection will be performed in the event apheresis collection is not an option (e.g., if a donor fails to mobilize adequately), the program must comply with this standard. Alternatively, if the program SOPs state that recipients requiring marrow products will not be transplanted in that program, this standard does not apply.

Marrow collection must be performed in a facility that meets FACT-JACIE Standards. The increased use of peripheral blood as a source of HPC has been associated with a marked decline in the number of bone marrow harvests in many programs. The minimum activity required for accreditation as a Marrow Collection Facility is one procedure in the 12 months prior to initial accreditation and an average of one procedure per year in each accreditation cycle, as defined in CM1. Clinical Programs collecting marrow must document compliance with all requirements of Part CM of the Standards.

Example(s):
Evidence of training may include documentation by a letter from a fellowship program director or procedure notes. Evidence of competency may include credentials for hospital privileges, quality audits, components of annual evaluations, or reports of marrow harvest procedures performed, demonstrating appropriate donor management and cell collection yields.

STANDARD:

B3.6.3 *The Clinical Program shall have access to personnel who are trained and competent in cellular therapy product collection by apheresis and utilize an apheresis collection facility that meets these Standards.*

B3.7 NURSES

B3.7.1 *The Clinical Program shall have nurses formally trained and experienced in the management of patients receiving cellular therapy.*

B3.7.2 *Clinical Programs treating pediatric recipients shall have nurses formally trained and experienced in the management of pediatric patients receiving cellular therapy.*

B3.7.3 Training and competency shall include:

B3.7.3.1 Hematology/oncology patient care, including an overview of the cellular therapy process.

B3.7.3.2 Administration of preparative regimens.

B3.7.3.3 Administration of blood products, growth factors, cellular therapy products, and other supportive therapies.

B3.7.3.4 Care interventions to manage transplant complications, including, but not limited to, cytokine release syndrome, tumor lysis syndrome, cardiac dysfunction, respiratory distress, neurologic toxicity, renal and hepatic failure, disseminated intravascular coagulation, anaphylaxis, neutropenic fever, infectious and noninfectious processes, mucositis, nausea and vomiting, and pain management.

B3.7.3.5 Recognition of cellular therapy complications and emergencies requiring rapid notification of the transplant team.

B3.7.3.6 Palliative and end of life care.

B3.7.4 There shall be written Standard Operating Procedures or guidelines for nursing procedures, including, but not limited to:

B3.7.4.1 Care of immunocompromised recipients.

B3.7.4.2 Age-specific considerations.

B3.7.4.3 Administration of preparative regimens.

B3.7.4.4 Administration of cellular therapy products.

B3.7.4.5 Administration of blood products.

B3.7.4.6 Central venous access device care.

B3.7.4.7 Detection and management of immune effector cellular therapy complications including, but not limited to, those listed in B3.7.3.4.

Explanation:
These are core competencies for nurses in HPC transplantation and cellular therapy. The Standards require that nurses be trained in the management of children or adults as appropriate for the age ranges of recipients being treated at that program. The Standards do not define pediatric age limits as these vary by institution. Age-specific training is often provided through orientation for new employees, attendance of age-specific continuing educational activities, and/or age-specific preceptorships.

Specific transplantation training is required for each nurse who is involved in the care of transplant recipients. Training may be a part of the formal job orientation, and/or may be provided in increments over a specified period of employment. Specific training may also be obtained through agreements with another established transplant institution. Nurse competencies should be evaluated and documented according to a defined process. Nursing personnel must be able to recognize when rapid notification of another transplant team member is required. The Clinical Program is responsible for identifying what situations would constitute a need for rapid notification.

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

Nurses who occasionally treat transplant recipients, such as nurses in an intensive care unit, may not have the degree of training and experience in management of neutropenic patients or immunosuppressive medications that exist on the transplant unit, but they must have sufficient expertise to safely care for the transplant recipient. How these issues are addressed when the recipient must be treated on a unit other than the transplant unit must be defined.

The Oncology Nursing Certification Corporation (ONCC) offers a certification program in blood and marrow transplantation nursing. ONCC initiated this certification in 2014 after identification of the tasks involved in blood and marrow transplantation nursing, and the knowledge needed to perform those tasks competently. Certification requires passing a written examination that covers autologous and allogeneic transplant in adult and pediatric recipients. Nurses who meet eligibility requirements, including a minimum of 1000 hours of nursing practice experience, may apply to take the examination. Nurses with BMTCN™ certification will have evidence of competence in this specialty. Additional information, eligibility, reference lists, and practice exams are available at:
http://www.oncc.org/TakeTest/Certifications/BMTCN

Evidence:
Because on-going education and documentation of continued competency are required, inspectors will expect to review documentation of in-service training and/or attendance at conferences. Evidence of compliance with the Standards will also include age-specific competencies.

Example(s):
Formal training can include in-service and annual review classes that address the relevant transplant-related topics, local or regional conference attendance, and/or on-the-job training. All of these training experiences must be documented, using tools such as a conference attendance record, a list of attendees at an internal class, a checklist for training of new employees or documented continued competency, an individual employee's continuing education record, and/or similar documents.

As new cellular therapies are provided by the Clinical Program, additional training modules may be required to adequately train nursing staff.

STANDARD:

B3.7.5 *There shall be an adequate number of nurses experienced in the care of transplant recipients.*

B3.7.6 There shall be a nurse/recipient ratio satisfactory to manage the severity of the recipients' clinical status.

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

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

Example(s):
Nurse staffing laws enacted in the U.S. are referenced by the American Nurses Association at: http://www.nursingworld.org/MainMenuCategories/Policy-Advocacy/State/Legislative-Agenda-Reports/State-StaffingPlansRatios.

"The National Database of Nursing Quality Indicators (NDNQI)," a report from *The Online Journal of Issues in Nursing* on U.S. nursing structure, process, and outcome indicators, is a growing effort to assess nursing numbers and quality. It is located at: http://nursingworld.org/MainMenuCategories/ANAMarketplace/ANAPeriodicals/OJIN/TableofContents/Volume122007/No3Sept07/NursingQualityIndicators.aspx.

STANDARD:
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 shall include:

B3.8.2.1 Hematology/oncology patient care, including the process of cellular therapy transplant.

B3.8.2.2 Adverse events, including but not limited to, cytokine release syndrome and neurological toxicities.

B3.8.2.3 Therapeutic drug monitoring, including, but not limited to, anti-infective agents, immunosuppressive agents, anti-seizure medications, and anticoagulants.

B3.8.2.4 Monitoring for and recognition of drug/drug and drug/food interactions and necessary dose modifications.

B3.8.2.5 Recognition of medications that require adjustment for organ dysfunction.

Explanation:
Training of pharmacists would ideally include one year of supervised training in the management of hematology/oncology patients, including hematopoietic stem cell transplant recipients. Documentation of training may include a list of pharmaceutical related transplant topics, such as:

- Prevention and treatment of viral, bacterial and fungal infections.
- Febrile neutropenia.
- Nausea/vomiting and mucositis.
- Treatment of acute and chronic GVHD.
- Stem cell mobilization regimens.
- High-dose chemotherapy preparative therapy.
- Long-term follow-up medication, including vaccinations.
- Prevention and treatment of other complications associated with cellular therapy, including, but not limited to, veno-occlusive Disease (VOD)/sinusoidal obstruction syndrome (SOS), bronchiolitis obliterans syndrome (BOS), bronchiolitis obliterans organizing pneumonia (BOOP), hemorrhagic cystitis, iron overload, and management of toxicities related to CAR-T therapy.
- Pain and palliative care.
- Different types of conditioning regimens

STANDARD:

B3.8.3 Pharmacists shall be involved in the development and implementation of guidelines or Standard Operating Procedures related to the pharmaceutical management of cellular therapy recipients.

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

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

STANDARD:

B3.8.4 Designated pharmacists shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

B3.8.4.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation and cytokine release syndrome and neurological toxicities resulting from cellular therapies.

Explanation:
The field of transplant medicine continues to evolve rapidly. The purpose of this requirement is for key personnel to keep up with current advancements in the field.

There are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use his/her judgment to determine whether or not each designated transplant pharmacist meets this standard. Recognized educational activities include both certified continuing education credits (preferable) and non-credit educational hours, including internal presentations and conferences. Examples of acceptable forms of education are included in this Accreditation Manual, and may include topics specific to cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Evidence:
To assess the appropriateness of the amount and type of continuing education in which the designated transplant pharmacists participated, the following information for each of the completed continuing education activities within each accreditation cycle:

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

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

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

Examples of appropriate continuing education activities include:

- The annual meeting of several professional societies includes information directly related to the field.
- Grand Rounds, if specifically related to cellular therapy or diseases for which transplantation is a therapeutic option. The continuing education log must include the title, subject, and date of the presentation.
- Presentation of Continuing Education lectures.
- Presentation of a paper at a scientific meeting.
- Publication of a manuscript related to cellular therapy,
- Participation in a webinar or on-line tutorial.
- Review of an article in the medical literature related to cellular therapy; including those where the journal offers CME credits.
- Local or regional journal club, potentially including the preparation time.
- Morbidity and Mortality conferences.

Additional resources are available through the ASBMT Pharmacists' Special Interest Group (SIG) at http://www.asbmt.org/?page=PharmacySIG. The Pharmacy SIG exists to provide a forum for pharmacists to network and share ideas, and move the field of hematopoietic stem cell transplantation forward.

ASBMT offers its members two Practice Improvement Modules (PIMs) that are applicable to this standard. The PIMs address chronic GVHD and Infectious Disease; each PIM provides 20 Category 1 CME credits through the American Board of Internal Medicine's Maintenance of Certification (MOC) program. The PIMs can be accessed by ASBMT members at
http://asbmt.org/professional-development/practice-improvement-modules.

ASBMT also offers an Online Learning center that hosts recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning.

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at: http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

B3.9 CONSULTING SPECIALISTS

B3.9.1 The Clinical Program shall have access to certified or trained consulting specialists and/or specialist groups from key disciplines who are capable of assisting in the management of recipients and donors requiring medical care, including, but not limited to:

Explanation:
In addition to the specialties specifically listed in these standards, Clinical Programs should also have access to other specialists directly related to the diseases being treated, such as metabolic diseases or immunodeficiencies.

STANDARD:

B3.9.1.1 Surgery.

B3.9.1.2 Pulmonary medicine.

B3.9.1.3 Intensive care.

B3.9.1.4 Gastroenterology.

B3.9.1.5 Nephrology.

B3.9.1.6 Infectious disease.

B3.9.1.7 Cardiology.

B3.9.1.8 Pathology.

B3.9.1.9 Psychiatry.

B3.9.1.10 Radiology.

B3.9.1.11 Radiation oncology with experience in large-field (e.g., total body or total lymphoid) irradiation treatment protocols, if radiation therapy is administered.

B3.9.1.12 Transfusion medicine.

B3.9.1.13 Neurology.

B3.9.1.14 Ophthalmology.

B3.9.1.15 Obstetrics/Gynecology.

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

STANDARD:

B3.9.1.16 Dermatology.

B3.9.1.17 Palliative and end of life care.

B3.9.2 A Clinical Program treating pediatric donors and recipients shall have consultants, as defined in B3.9.1, qualified to manage pediatric 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 these Standards or the performance of the Clinical Program.

B3.10.2 The Clinical Program Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.

B3.10.3 The Clinical Program Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy and quality management annually at a minimum.

B3.10.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:
The Clinical Program must identify at least one person with the responsibility for quality management (QM). This individual can be the Program Director or a qualified designee. Delegation to a qualified designee must be documented in the QM Plan, in a related SOPs, job description, or other document. The title held by this individual is not mandated by the Standards, and may differ among facilities. This is acceptable as long as the duties include those described in the Standards. The Quality Manager should be an individual with at least an undergraduate degree or equivalent in the field of health sciences or biological sciences with training, education, or experience in either QM or cellular therapy. Formal training may include practical work experience in a facility, fellowship, or certification program. This person could be a member of another department, such as an institutional Quality Assurance Department, who devotes some time to the QM activities of the Clinical Program, or it could be a member of the program who has these additional responsibilities.

There are many ways to meet this standard, and the standard is not meant to be prescriptive. A total of 10 hours in combination of these topics is required. Each topic does not need to be covered in 10 hours individually. The inspector should assess the documented number and content of the continuing education activities and use his/her judgment to determine whether or not a QM Supervisor meets this standard.

Formal training and certification in one or more aspects of QM is encouraged, but not required. Additional information related to certification in quality is available from the American Society for Quality at www.asq.org.

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

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

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

While continuing education in hematopoietic stem cell transplantation is important, it is also vital that the quality manager continue to improve knowledge in the field of quality, including the knowledge and skills necessary for auditing; occurrence reporting; deviation management, including complaints, adverse events and reactions; corrective and preventive action; and process improvement.

The inspector may ask about membership in professional organizations, and/or attendance at meetings, webinars, or other online training activities, publications, etc.

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

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

The FACT *Quality Handbook: A Guide to Implementing Quality Management in Cellular Therapy Organizations* is an excellent resource, available at: www.factwebsite.org.

STANDARD:
B3.11 SUPPORT SERVICES STAFF

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

B3.11.1.1 Dietary staff.

B3.11.1.2 Social Services staff.

B3.11.1.3 Psychology Services staff.

B3.11.1.4 Physical Therapy staff.

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

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

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

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

B4: QUALITY MANAGEMENT

STANDARD:

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

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

Explanation
The QM Program includes a description of the strategy (QM Plan) and the associated policies and SOPs that drive the operation of the QM Program. Development of a comprehensive QM Program is often the most challenging and time-consuming exercise that a Clinical Program encounters when preparing for FACT or JACIE accreditation.

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

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

STANDARD:

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

Explanation:

The QM Plan is a written document that outlines how the QM Program (quality assurance, control, assessment, and improvement activities) is implemented.

The QM Plan must detail all key elements that affect the quality of recipient and donor care and cellular therapy products. The specific SOPs to be followed for each of these elements does not have to be fully described in the QM Plan, but must be referenced within the plan and linked to the appropriate document where the details are described.

The thoroughness and attention to detail of the written QM Plan is an indication of how QM is perceived and executed within the Clinical Program.

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

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

Evidence:

The written QM Plan for the Clinical Program will be provided to the inspector prior to the on-site inspection. If policies and SOPs are referenced in the QM Plan, they may be requested in advance to enable the inspector to review the details of the QM Program. The inspector is expected to evaluate implementation of the QM Plan at the facility and assess the understanding of QM by the staff. An incomplete, too broad (i.e., a shared plan covering an entire Transfusion Medicine department), or poorly written QM Plan may be an indication that QM is not deemed an integral and important component of the facility.

Under these circumstances, the inspector should pay particular attention to evaluating the QM efforts of the facility during the on-site inspection process. The inspector should specifically look for documentation of compliance for QM activities not directly performed by program staff and seek evidence that QM activities link to the Clinical Program, Collection Facility, and Processing Facility.

STANDARD:

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

Explanation:

There shall be an individual (i.e., the Clinical Program Director or designee) at the Clinical Program in charge of the elements of the QM Plan that are directly related to the facility. A designee must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. Delegation must be documented, either in the QM Plan or in SOPs related to it.

Evidence:

QM Plan review and approval should provide evidence of the Clinical Program Director's and designee's (if applicable) involvement.

Example(s):

A designee can be a member of another department, such as an institutional Quality Assessment and Improvement or Compliance Department, who devotes some time to the QM activities of the Clinical Program, or he/she could be a member of the clinical team. The same person may be responsible for QM of all components of the cellular therapy program or each individual area (clinical, collection, processing) may have a distinct individual responsible for QM, as long as there is a mechanism for sharing of information to all participating entities.

STANDARD:

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

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

Explanation:
The overall organizational chart should include the titles of key positions and the reporting structure of the Clinical Program and the QM Program. The chart should also depict the relationship among the participating sections of the cellular therapy program (clinical, collection, and processing at a minimum) even if supporting functions are performed by contract with another facility or by individuals within the program.

The inspector will verify that the organization and daily function is as described.
The description of the operation of the QM Program should include the processes in place to accomplish the goals (e.g., meetings, participants, schedules, reporting, and documentation). Lines of responsibility and communication must be clearly defined in a way that is understood by all involved.

Evidence:
The organizational chart for the Clinical Program, and the charts for collection and processing, will be provided to the inspector prior to the on-site inspection.

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

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

STANDARD:
B4.4 *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:*

Explanation:
The QM Plan, as approved by the Clinical Program Director, identifies the key personnel for whom documentation of training, competency, and continuing education is expected. These must include all individuals responsible for critical elements of the Clinical Program. Documentation of training for each individual must include all procedural skills routinely practiced. These requirements are detailed in B3.

Evidence:
The inspector should review training records to verify compliance with these regulations. Organization-specific issues and safety training are generally covered by orientation programs and continuing education programs, but inclusion of this content should be confirmed by the inspector. The inspector should review policies or SOPs describing the elements of staff training and continued competency as described in B4.4.

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

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

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

Legal and regulatory context can be demonstrated by including training related to GTP, GMP, and the Standards.

STANDARD:

B4.4.1 A current job description for all staff.

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

B4.4.2.1 Initial qualifications.

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

STANDARD:

B4.4.2.2 New employee orientation.

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

Evidence:
Organization-specific issues are generally covered by institutional orientation programs, but this should be confirmed by the inspector.

STANDARD:

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

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

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

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

STANDARD:

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

Explanation:
Competency is the ability to adequately perform a specific procedure or task according to direction. Clinical Programs must have a system for documenting competency for each critical function performed by a staff member (see Part A for the definition of "critical").

Example(s):
Competency may be assessed by direct observation, the use of written tests, successful completion of proficiency surveys, review of outcomes, and/or self-assessment and discussion with the Clinical Program Director or appropriate supervisor. SOPs for personnel training and competency assessment must be documented and reviewed.

STANDARD:

B4.4.2.5 Continuing education.

Explanation:

Staff should adhere to local and governmental continuing education requirements. The inspector should find evidence of suitable educational opportunities for staff related to their duties, such as quality-related meetings, webinars, and/or FACT or JACIE training sessions, if applicable.

Evidence:

The inspector should review policies or SOPs describing the elements of staff training and continued competency as described in B4.4.

The inspector will review the records of one or more employees to determine whether all of the required elements are documented.

STANDARD:

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

B4.5.1 There shall be a current listing of types of documents that are considered critical and shall comply with the document control system.

Explanation:

The QM Program must maintain a list of all active critical documents. For example, all SOPs required by these Standards must be considered to be critical documents, and must be controlled. Clinical Programs may call documents different names (such as patient guidelines instead of protocols), and may identify additional types of documents as critical within the scope of the document control system.

Evidence:

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

STANDARD:

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

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

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

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

STANDARD:

B4.5.3 The document control system shall include:

B4.5.3.1 A standardized format for each document type including, but not limited to, policies, Standard Operating Procedures, guidelines, worksheets, forms, and labels.

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

Documents authored by the Clinical Program should follow the document control system; however, departmental and institutional documents may differ.

In this standard, labels refer to marrow collection labels and the awareness of other cellular therapy product labels. This does not include labels for other types of products (e.g., diagnostic samples).

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

STANDARD:

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

Explanation:

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

Evidence:

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

STANDARD:

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

Explanation

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

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

Evidence:

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

STANDARD:

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

Explanation:
The methods of document distribution and storage should control or prevent unwanted or unauthorized document modification or duplication. Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software (to lock specific areas or a specific document to prevent printing) or having copies clearly printed with an expiration date or watermarked as copies. The intention is to make sure that only the currently approved document is available for use.

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

STANDARD:

B4.5.3.5 *Controlled documents shall be reviewed every two years at a minimum.*

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

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

The effective date of a controlled document is an assigned date following approval when the controlled document, such as an SOP, worksheet, form, or other document must be followed by trained personnel. For instance, a staff member may not perform a new or modified procedure until he/she has reviewed the SOP and completed required training and competency assessment. The amount and format of training and competency assessment may differ based on complexity of the changes.

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

STANDARD:

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

Explanation:

Documentation is especially important for the investigation of errors, accidents, suspected adverse events, biological product deviations, and complaints, since these investigations are frequently retrospective in nature. If outcomes change over time, one needs to be able to go back to previous versions of controlled documents to determine if an operational change is the cause.

Evidence:

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

Example(s):

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

STANDARD:

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

Example(s):

Clinical Programs may have forms, worksheets, patient brochures, etc., that are printed and distributed. There should be a system in place to recover these obsolete documents to prevent unintended use.

STANDARD:

B4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the establishment and maintenance of written agreements with external parties providing critical services that could affect the quality and safety of the cellular therapy product or welfare of the donor or recipient.

B4.6.1 Agreements shall be established with external parties providing critical services.

B4.6.2 *Agreements shall include the responsibility of the external party performing any step in collection, processing, testing, storage, distribution, or administration to comply with applicable laws and regulations, these Standards, and the standards of other required accreditation agencies.*

B4.6.3 *Agreements shall be dated and reviewed on a regular basis.*

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

The burden to determine compliance with the requirements of the accrediting organizations is on the Collection Facility, not on FACT or JACIE. Agreements must address other accreditations required by FACT.

Written agreements should clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements should be dated, reviewed, revised and approved by both parties and legal if necessary, on a regular basis as defined by the program, and at least every two years. The policy or SOP for written agreements, or each individual agreement should describe the maintenance of records following termination of the agreement.

Programs should have an awareness of, and a review plan for, all agreements including those that the program does not control (i.e. does not develop or provide authorized signature), but which are relevant to the clinical care of the recipient and/or donor or impact upon the cellular therapy product. A master list of written agreements and a checklist could assist with appropriate review and ensure that important elements are included, and a designee in the program is notified when changes are made.

The standard does not require Clinical Programs to monitor third-party manufacturing entities' compliance with laws and regulations when they are operating under regulatory oversight such as INDs or BLAs. It does, however, require that programs specify in written agreements that those entities are responsible for complying with laws and regulations, and requires that the relationship between the program and manufacturer (i.e., who is responsible for specific tasks) is defined.

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

Example(s):
A transplant program within a single institution is not required to have written agreements for the Collection and Processing Facilities. However, it is recommended that a Clinical Program have a contingency plan in the event that the Collection or Processing Facility is unable to provide services as intended (e.g., significant personnel change or natural disaster). The contingency plan may require a written agreement with an external facility.

Examples of written agreements with external parties include memorandums of understanding, purchasing arrangements, service level agreements, contracts and preventive maintenance arrangements. Specific examples include written agreements with donor registries, external laboratories performing testing of donors, recipients, and cellular therapy products and external facilities used for the storage of cryopreserved cellular therapy products.

STANDARD:

B4.7 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for documentation and review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.*

Evidence:
The inspector should confirm documentation of all activities from definition of expected outcome to process improvement, when indicated. There must be evidence of ongoing analysis of data in addition to mere data collection. The inspector should ask to see the data and/or minutes of meetings, including the personnel in attendance and where data are presented.

STANDARD:

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

Explanation:
Product efficacy based on patient outcome may be more difficult to document for cellular therapy products other than hematopoietic progenitor cells, and that assessment will differ for each product type. Minimally the QM Plan must address the need for the development of a validated potency assay as regulated products enter the later stages of clinical trials.

Predefined outcome criteria for investigational cellular therapy products (e.g., chimeric antigen receptor [CAR] T-cells, vaccines) may be found in the clinical research protocol and may include clinical outcomes or only safety endpoints, depending on the trial phase.

It is expected that criteria for which reasonable data can be obtained (product safety, product efficacy, and the clinical outcome) be determined and reviewed.

STANDARD:

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

Explanation:

Outcome analysis should include each individual product or recipient to assess efficacy or safety as appropriate; however, that assessment alone is insufficient to meet this standard. The intent of the standard is that similar recipients of a similar product be assessed together for efficacy, safety, trends, and opportunities for improvement. Individual programs will choose how to aggregate data based upon the size and complexity of the Clinical Program.

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

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

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

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

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

Performance measures may include survival, treatment-related mortality, specific complication rates, adherence to selected policies or SOPs, and other clinical outcomes in addition to overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after transplantation. Morbidity may include rehospitalization, prolonged hospitalization, or other measures as defined by the Clinical Program. The measures may include overall outcomes in certain groups of recipients, which may be compared to existing internal or published data, for example, by the International Bone Marrow Transplant Registry or the European Blood and Marrow Transplant Registry.

STANDARD:

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

B4.7.3.1 For HPC products intended for hematopoietic reconstitution, time to engraftment following product administration shall be analyzed.

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

The Clinical Program is responsible for communicating clinical outcomes data to associated Collection Facilities, Processing Facilities, or any other relevant party. The National Marrow Donor Program does provide engraftment data to collection facilities for products provided through this program.

Evidence:
The Clinical Program should be prepared to provide the engraftment data, the methods used to evaluate consistency in engraftment, and the documentation of review of the analyses to the on-site inspector. Graft failure may be reviewed as an adverse event. There must be evidence of ongoing analysis of engraftment data among clinical, collection, and processing in addition to collection.

STANDARD:

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

Example(s):
In addition to overall and treatment-related morbidity and mortality at certian time points listed below (which are required), examples of clinical function endpoints include:

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

STANDARD:

B4.7.3.3 Overall and treatment-related morbidity and mortality at thirty (30) days, one hundred (100) days, and one (1) year after cellular therapy product administration.

B4.7.3.4 Acute GVHD grade within one hundred (100) days after allogeneic transplantation.

B4.7.3.5 Chronic GVHD grade within one (1) year after allogeneic transplantation.

B4.7.3.6 Central venous catheter infection.

Example(s):
A central venous catheter infection is an outcome that has long-term implications on patient management, quality of life, and survival. Review of such infections is defined by the Clinical Program (with or without input from the institutional infection control department), but should at a minimum include central line-associated bloodstream infections (CLABSI). Programs are encouraged to assess all catheter, catheter site, and blood stream infections as part of adverse event monitoring.

STANDARD:

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

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

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

The Clinical Program should inform the Collection Facility of the results of the product administration so that the Collection Facility can track cellular therapy product engraftment or effectiveness If collection involves an unrelated donor through an external donor registry, programs must provide the data to the registry so it can in turn give the information to the Collection Facility.

STANDARD:

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

B4.7.5.1 If expected one year survival outcome is not met, the Clinical Program shall implement a corrective action plan that meets FACT or JACIE requirements.

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

In the U.S., it expected that Clinical Programs performing allogeneic transplant will utilize the CIBMTR Stem Cell Therapeutic Outcomes Database reports to demonstrate patient outcomes within the expected range at a minimum. Reporting center-specific survival rates is a requirement of the Stem Cell Therapeutic and Research Act of 2005 (reauthorized in 2010). CIBMTR has the contract to report these data.

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

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

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

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

- The corrective action plan must identify specific causes of death.
- The corrective action plan must provide quantitative data.
- The assessment must identify reasonable causes of the low one-year survival rate.
- The corrective action plan must address the identified causes.
- There must be measurable outcome improvement.
- The program must provide updates on corrective actions at the time of inspection., at the time annual reporting, or s otherwise directed by the FACT Clinical Outcomes Committee.

Example(s):
In the U.S., Clinical Programs will provide their outcomes as published in the CIBMTR Transplant Center Survival Report. European programs will use similar national schemes, for example, the British Society of Blood and Marrow Transplantation (BSBMT) and Swiss Blood Stem Cell Transplant Group (SBST).

STANDARD:

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

Explanation:

This Standard requires Clinical Programs to set benchmarks for non-relapsed mortality at 100 days. The QM Plan must describe the rationale for the determined benchmark, how the program analyzes non-relapsed mortality at 100 days and how frequently, and actions to take when the benchmark is not met.

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

The benchmark(s) that the Clinical Program sets should allow the program to assess non-relapsed mortality at 100 days, and identify specific corrective actions to take when the benchmark is not met. Small programs may not have a substantial amount of data in just one year, and statistically significant analysis is not required. Programs may use cumulative data over multiple years (i.e., the accreditation cycle) to conduct the analysis and trend results.

STANDARD:

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

Explanation:

There is an emphasis on audits in Part B of the Standards, in part because of the difficulty of validating clinical practices. Audits represent one of the principal activities of the QM Program. Audits are conducted to determine that the QM Program is operating effectively and to identify trends and recurring problems in all aspects of facility operation. Processes to be audited should include those where lack of compliance would potentially result in an adverse event. The head of the QM Program should identify areas to be audited and audit frequency.

A schedule of prospective audits is expected. There may be other audits required in response to specific events. Required audits for the Clinical Program are listed in B4.8.3. The audit process should occur throughout the year in accordance with the Clinical Program's QM Plan and schedule, with reporting of audit results, corrective action, and follow-up on a regular schedule, at least once a year. Review by the

Clinical Program Director is to be documented. There should be evidence that audit reports are shared with the clinical staff and the Collection Facility Director and Processing Facility Director as appropriate. Further information is available in the FACT *Quality Handbook* (http://factwebsite.org/qm).

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

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

Example(s):
Examples of audits in the Clinical Program include:

- Adherence to policies and SOPs (e.g., chemotherapy administration or patient/donor selection).
- Timely distribution of correctly written medical orders (e.g., for collection, processing, and administration of cells).
- Turn-around time for laboratory results.

An audit process or report could include the following elements:

- Audit title.
- Audit type (e.g., Yearly Key Element, 2-Year Key Element, Focused, Follow-up).
- Clinical site or unit (e.g., pediatric, adult).
- Date audit is assigned, including name and title of staff who assigned the audit.
- Name and title of staff assigned to complete the audit.
- Audit period (date range).
- Audit parameter description.
- Date audit started and completed.
- Audit findings and recommendations.
- Timeline for follow up.
- Signatures and Comments.
    - Auditor signature and date.
    - Quality Manager signature, date, and comments.
    - Clinical Program Director signature, date, and comments.
    - BMT quality committee chair signature, date, and comments.
- Documented staff review and date of review.
- Quality meeting results presentation date, if required.

STANDARD:

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

Explanation:

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

The auditor must be knowledgeable in auditing techniques.

Example(s):

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

- If donor eligibility determination is normally performed by outpatient clinic staff, the audit could be performed by an inpatient nurse or by an apheresis nurse.
- In a joint adult and pediatric Clinical Program, pediatric staff could audit functions performed by the adult team and vice versa.
- Cell processing laboratory staff, particularly those with audit experience, could also audit clinical processes.

STANDARD:

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

Explanation:

There must be regular auditing of critical activities; frequency will depend on the importance of these activities, and to some extent on the results. Where there are published studies, these should be used to help assess audit results. For example, product yields may be expected to fall within a certain range based on national or international data. Although the yields continue to fall within that range, a trend downward to the lower end of the expected range may indicate a need to investigate the cause (e.g., new staff, a new piece of equipment, a reagent unexpectedly received from a different supplier).

Evidence:

The audit process and example audits must demonstrate that this is an ongoing process and that the QM records demonstrate corrective actions or process improvement activities that are based on audit findings.

Additionally, when audit results identify corrective action or process improvement, there should be a date designated as the expected date of completion of the corrective action, and a planned time to re-audit the process to verify that the corrective actions were effective.

Example(s):
Topics to be audited may include completion of consent, adherence to clinical guidelines, transplant protocols, etc.

For example, product yields may be expected to fall within a certain range. Although the yields continue to fall within that range, a trend downward to the lower end of the expected range may indicate a need to investigate the cause (e.g., new staff, a new piece of equipment, a reagent unexpectedly received from a different supplier).

STANDARD:

B4.8.3 Audits shall include at a minimum:

B4.8.3.1 Annual audit of donor screening and testing.

B4.8.3.2 Annual audit of verification of chemotherapy drug administered against the written order.

B4.8.3.3 A periodic audit of the prescription ordering system against the protocol.

B4.8.3.4 Annual audit of management of cellular therapy products with positive microbial culture results.

B4.8.3.5 Annual audit of safety endpoints and immune effector cellular therapy toxicity management.

B4.8.3.6 Annual audit of documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

B4.8.3.7 Periodic audit of the accuracy of data including clinical data and data contained in the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A Forms of the EBMT.

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

The Clinical Program should have a system in place verifying that the prescription matches the protocol or standard of care guidelines (e.g., indications for dose reduction). Prior to administration, there should be a documented mechanism to confirm the prescription is consistent with the protocol or standard of care defined by the program. This is to prevent dosage errors. Whether the mechanism is written or electronic, the system must have a two-point verification process involving more than one person and more than one document.

Example(s):
An example of another recommended audits is the compliance of the Clinical Program with revisions to the Standards within the 3-months following publication as expected.

STANDARD:

B4.9 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results 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.*

B4.9.3 *Recipient follow-up and outcome analysis.*

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

B4.9.5 *Investigation of cause.*

B4.9.6 *Reporting to regulatory agencies if appropriate.*

Explanation:
The cellular therapy program (i.e., Clinical Program and Collection and Processing Facilities) must develop an integrated approach to the management of cellular therapy products with positive microbial culture results that are identified before or after the products have been administered. Policies and SOPs are required across areas of an integrated cellular therapy program to manage the aspects for which the particular area of the program is responsible. This requirement may be satisfied with a single policy or SOP or there may be separate documents. For each topic, SOPs should detail what action is to be taken, who is responsible to take the action, and the expected timeframe of the actions. Different approaches to management may be acceptable if these approaches are consistently followed and meet regulatory requirements.

The Clinical Program's policies and SOPs cover timely notification of the transplant physician caring for the patient, and if applicable, the Collection and Processing Facilities. The Clinical Program's policies and SOPs should cover investigation of the cause of the positive microbial culture and the reporting to regulatory authorities if applicable. In many cases, the actual responsibilities for these activities may be in the Processing or Collection Facility; however, the documents should include this overview. In some cases a positive microbial result may only become known after the product has been administered.

In some cases a positive microbial result will be detected prior to administration. The Clinical Program must have criteria at a minimum for use of a cellular therapy product with a positive microbial culture, when another collection should be pursued, and, if administered, guidelines for recipient management, such as prophylactic antibiotics, increased monitoring, or other precautions.

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

Example(s):
Each area in a cellular therapy program may have responsibilities that do not apply to another area. In this case, an over-arching document for the management of cellular therapy products with positive cultures is recommended.

An example of donor follow-up is a situation in which the investigation found that the donor was infected at the time of collection. This is most common in the case of an autologous donor, particularly when a central venous catheter may have become colonized. However, it is advisable to also verify the well-being of an allogeneic donor, particularly if a positive culture result is noted within hours of the end of collection. The Clinical Program is generally responsible for donor follow up, however, a donor center or collection center may have a role in follow up of the unrelated donor.

Criteria for administration of a positive cellular therapy product could include when no other collection is possible and/or no other donor is available.

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

STANDARD:

B4.10 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for occurrences (errors, accidents, biological product deviations, adverse events, adverse reactions, and complaints). The following activities shall be included at a minimum:*

Evidence:

The inspector should expect to find a documented process for occurrences including detection, investigation, documentation, corrective action, preventive action, and follow-up. This should be reviewed by the Program Director and Quality Manager or designee, and reported, as appropriate, to the Collection Facility, the Processing Facility, and appropriate governmental agencies.

STANDARD:

B4.10.1 *Detection.*

Explanation:

A goal of a QM Program is to continuously improve processes. Monitoring occurrences and trends facilitates recognition of improvement opportunities. There must be a process to detect, evaluate, document, and report occurrences in a timely fashion to key individuals, including the Clinical Program Director and appropriate governmental agencies, as appropriate. The Clinical Program should define errors, accidents, deviations, adverse events, adverse reactions and complaints in SOPs and describe when, how, by whom and to whom each is reported. Programs can use the definitions stated by applicable regulatory agencies. See the definitions of each of these types of occurrences in the Standards, Part A (Definitions). Management of each of these types of occurrences is slightly different; however, the same steps (detection, evaluation/investigation, documentation, determination of corrective and preventive action, and reporting) apply to all types.

Errors, accidents, adverse events, adverse reactions, biological product deviations, and complaints (collectively referred to as occurrences) can be tracked for outcomes that are not necessarily related to cellular therapy products. Examples include:

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

A biological product deviation (see definition in A4) is an event that represents a deviation from applicable regulations or established specifications that relate to the prevention of communicable disease transmission or cellular therapy product contamination; or that is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to product contamination. Such products are used by Clinical Programs only when

the benefit outweighs the risk to the recipient and no alternative is available, although in some cases, the information is not known until after administration of the product. The most common biological product deviations encountered by Clinical Programs involve cellular therapy products with a positive microbial culture or products from ineligible donors. The Clinical Program should have a sufficiently detailed plan in place that describes whether products with a positive microbial culture can be used, and if so, under what circumstances it is allowable, how the recipient is best protected, and how this is documented. Issues regarding products from ineligible donors are addressed under B6.

The Clinical Program is expected to comply with institutional requirements and applicable laws and regulations pertaining to the documentation and reporting of adverse events or reactions in the Clinical Program.

STANDARD:

B4.10.2 Investigation.

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

Example(s):

When investigating an incident involving a licensed cellular therapy product in the U.S., it is helpful to inform the manufacturer of the batch number.

STANDARD:

B4.10.3 Documentation.

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

Explanation:

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

STANDARD:

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

B4.10.3.3 Cumulative files of occurrences shall be maintained.

B4.10.3.4 Cumulative files shall include written investigation reports containing conclusions, follow-up, corrective and preventive actions, and a link to the record(s) of the involved cellular therapy products, donor(s), and recipient(s), if applicable.

Evidence:

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

Example(s):

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

STANDARD:

B4.10.4 Reporting.

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

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

Explanation:
The FDA defines an adverse reaction as an adverse event involving the transmission of a communicable disease, cellular therapy product contamination, or failure of the product's function and integrity if the adverse reaction a) is fatal, b) is life-threatening, c) results in permanent impairment of a body function or permanent damage to body structure, or d) necessitates medical or surgical intervention. Adverse reactions may also include unexpected reactions to the graft that are designated as possibly, probably, or definitely related. For suspected adverse reactions to administration of products, the results of investigation and any follow-up activities must be documented. Adverse reactions meeting the FDA definition of products regulated under GTP (allogeneic HPC, Apheresis and HPC, Cord Blood, T Cells) or GMP (products produced under IND or IDE) must be reported to FDA within their specified guidelines. Reporting to other oversight organizations may also be necessary (e.g., accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees).

The EU Directive 2004/23/EU distinguishes between serious adverse events, which are incidents, errors etc., which have potential consequences, and serious adverse reactions, which are actual reactions in donor or recipient. Both must be documented and reported. "Serious adverse event" is defined as any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells that might lead to the transmission of a communicable disease; to death or life threatening, disabling, or incapacitating conditions for patients; or which might result in or prolong hospitalization or morbidity.
"Serious adverse reaction" means an unintended response, including a communicable disease, in the donor or in the recipient, associated with the procurement or application of tissues and cells that is fatal, life threatening, disabling, incapacitating, or which results in or prolongs hospitalization or morbidity.

EU Commission Directives 2006/17/EC and 2006/86/EC include equivalent requirements for non-conforming products.

If an unexpected or serious adverse reaction occurs due to cellular therapy product collection or administration for which there is a reasonable possibility that the response may have been caused by the product, the report of the adverse reaction and its outcome and investigation should be communicated to all facilities associated with collection, processing, and/or administration of the product. This includes graft failure. Usually the Clinical Program is responsible for making the initial report; however, each involved facility must participate in the investigation and evaluation of the potential cause, particularly related to its own procedures that were involved.

Examples:
The following are examples of adverse events that must may need to be reported :

- Adverse events involving the transmission of communicable disease.
- Product contamination.

- Adverse reactions that are fatal, life threatening, result in permanent impairment of a body function or permanent damage to body structure, or necessitate medical or surgical intervention.

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

STANDARD:

B4.10.5 Corrective and preventive action.

B4.10.5.1 Appropriate action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.

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

Explanation:

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

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

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

STANDARD:

B4.10.5.3 Investigations shall identify the root cause and a plan for short- and long-term corrective and preventive actions as warranted.

Explanation:

It is critical to investigate the cause(s) of events that pose significant risk or severity, and to establish and determine what corrective and preventive action will most likely be effective. The focus of the investigation should be to learn and improve, not to cast blame or be punitive. Often "systems" play a role in causation. Clinical Programs should be encouraged to stratify occurrences according to risk or severity, and invest more time and energy into management of the more critical issues. Only an understanding of cause allows creation and implementation of new or revised systems and controlled documents that will correct the issue and may prevent the recurrence of an occurrence.

STANDARD:

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

Explanation:

The Clinical Program must document a policy or SOP for tracking and traceability of each cellular therapy product through all steps from collection to administration or final disposition. Documentation in the medical record should include the proper product name, unique product identifier (ISBT 128 donation identification number or DIN, or Single European Code or SEC), content of the cellular therapy product, identification of the donor including medical record numbers, unrelated donor registry identifiers including Global Registry Identifier for Donors (GRID), allogeneic donor eligibility status, and the unique identity of the intended recipient including registry identifiers, where appropriate. There must be a process, including the use of the ISBT128 barcode or other barcode or unique numbering system, to track and trace specimens removed from a cellular therapy product for testing at an external facility such as an HLA testing facility, transfusion service, or microbiology laboratory. This process must ensure linkage between the results of testing and the original product. There should also be a means, direct or indirect, that will allow outcome information to be related back to any other facilities involved in collection, processing, and distribution of the product. The final disposition of the product must be documented, whether the product was administered, destroyed, released, or used for research, remains in storage, or other disposition. The tracking and tracing system must comply with all applicable laws and regulations and the Standards.

Evidence:
The inspection team will review examples of collection and processing records including worksheets and reports and final product labels, to determine if tracing and tracking from donor selection through final product disposition and recipient identification is possible. All critical steps should identify who performed the procedure and when it was completed. The Clinical Program or Marrow Collection Facility must have a system in place to request information, if not initially provided, to identify manufacturing procedures performed by external facilities (e.g., gene modified cellular therapy product).

Example(s):
A Clinical Program may assign an ISBT 128 DIN as a unique product identifier upon reception of a cellular therapy product from an unrelated donor collection facility that does not use ISBT 128 labeling, as long as tracking and tracing from the donor to the recipient is possible (i.e., the unique product number assigned at the collection facility is recorded in the medical record to maintain the linkage).

Full implementation of ISBT 128 labeling ensures tracking and traceability of the cellular therapy product and associated pilot vials and segments in a facility. However, if a Clinical Program or Marrow Collection Facility removes specimens from a cellular therapy product and sends these to an external laboratory such as an HLA testing laboratory or a transfusion service for testing, the laboratory information system at the testing laboratory might not be compatible with ISBT 128 barcodes. If the testing laboratory assigns a new laboratory or barcode number to these specimens, there must be a system to link the reports generated following testing to the original cellular therapy product.

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

Explanation:
Clinical Programs should be prepared for situations that may interrupt typical operations so that such interruptions do not adversely affect recipients, donors, or cellular therapy products. While a policy or SOP is required that addresses emergencies and disasters (see B5.1), the program/facility must also have a plan for the management of interruptions that do not rise to the disaster level. It is difficult to anticipate every possible situation that may occur. Therefore, the Standards do not require the program to outline actions for specific events; rather, the program/facility is required to describe actions to take when an interruption presents, including who needs to be contacted, how to prioritize cases, key personnel to be involved in identifying alternative steps to continue functions, and notification of staff.

A contingency plan specific to the program would convey evidence that risk has been assessed for program-defined potential events of varying impact, such as a failure of the scheduling system, a water supply interruption, or shortage of a chemotherapy agent. The plan should reflect differences between specific program needs and general hospital needs, and complement the hospital plan.

As more and more of the Clinical Program's documents exist on an electronic platform, there is an increasing risk of temporary or permanent document loss. The institutional Information Technology Department generally confirms that software in use is validated for its function, and that there is a regular schedule of back up to allow for retrieval of information when necessary. Freestanding facilities, as well as programs utilizing desktop storage, must have a plan to create a similar level of security. In either case, the program also needs a method to produce current versions of critical documents, such as preprinted orders, consent forms, SOPs, etc., when the electronic format is not available.

Policies, SOPs, and associated worksheets and forms must be available to (Processing Facility) staff at all times. Arrangements must be made so that these documents are available in the event that the computer system goes down. Staff should have periodic training and review of alternate systems so they will be competent in the use of these systems should the need arise.

Evidence:
The inspector should review policies and forms to be used in case the electronic record system is unavailable.

Example(s):
Examples include malfunctioning electronic records systems, drug shortages, power outages, equipment failures, supply shortages, etc. Particularly important drug shortages would include chemotherapy agents typically used as part of the preparatory regimen, or antibiotic/antifungal agents. A contingency procedure would identify alternative sources of supplies, alternative supplies, and/or alternative preparative regimens.

STANDARD:

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

Explanation:
Quality can be maintained only if there is control over critical manufactures, vendors, supplies, reagents, equipment, facilities, and services. The QM Plan must include a process to qualify reagents and supplies to safeguard their consistent function in validated procedures. This process must include the establishment of minimal standards for the acceptance of critical supplies and reagents and must document that those standards are met before they are made available for use.

Even if supplies, reagents, and equipment are qualified, the manner in which they are used must also be qualified to prevent product mix-ups, contamination, or cross-contamination.

It is not the intent of this standard for the Clinical Program to qualify licensed pharmaceutical products, but rather a risk-based approach should be taken to identify items which require qualification.

For further definitions and examples of qualification , see the JACIE *Quality Management Guide* (www.jacie.org/document-centre) or the FACT *Quality Handbook* (http://factwebsite.org/qm).

STANDARD:

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

Explanation:

The rationale for requiring Clinical Programs that perform marrow collections to include qualification in their QM Plans is that the attending physician is generally responsible for the marrow collection procedure. A Marrow Collection Facility that operates independently of an accredited Clinical Program is required to establish and maintain an independent QM Plan. Programs also utilize the assistance of Processing Facilities or institutional quality departments to assist with this task, which is in compliance with the Standards. The Clinical Program does have ultimate responsibility for ensuring qualification has been performed.

This standard requires qualification of materials used for the marrow collection procedure, but it is not the intent to require Clinical Programs to qualify materials for the delivery of anesthesia or other materials outside of those directly used in the collection.

STANDARD:

B4.13.2 Qualification plans shall include minimum acceptance criteria for performance.

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

Explanation:

A plan for qualification must be reviewed and approved prior to performing a qualification. Qualification of critical items should include:

- Design Qualification (DQ).
- Installation Qualification (IQ).
- Operation Qualification (OQ).
- Performance Qualification (PQ).

The qualification plan should be reviewed after the qualification to determine if all acceptance criteria were met. This process must include the establishment of minimal standards for acceptance and must document that those criteria are met before use.

Clinical Programs may choose to delegate review of qualification studies to the Marrow Collection Facility.

The Clinical Program must have a system in place that confirms that vendors provide materials in a timely and consistent manner that meets their acceptance criteria. Supplier qualification must also confirm that vendors are compliant with applicable governmental laws and regulations and that there is a system in place that is consistent with the Standards, such that they can demonstrate process control. Suppliers of infectious disease testing must also be qualified.

Evidence:
The inspector should find evidence of qualification of manufactures, vendors, supplies, equipment, facilities, services, and critical reagents. Qualification procedures should include instructions for requalification and under which circumstances qualification is required.

Example(s):
There are several ways to qualify a vendor of supplies, reagents, and services. The most effective is to perform an audit of the provider. Other, often more practical, methods may include one or more of the following:

- A review of third-party assessments by accrediting organizations such as FACT, JACIE, AABB, CAP or others.
- Remote audits by questionnaire.
- An ongoing dialog of resolution of service complaints or suggested process improvements.
- The sharing of internal audit findings and implemented corrective action plans from the provider back to the facility as evidence that deficiencies have been recognized and corrected.
- A documented review of the suppliers' past performance history.

Suppliers with pre-existing service agreements preceding the implementation of this standard can be qualified as meeting expectations by a retrospective review of the quality of service provided. Documentation, in the form of a brief written statement, that the service provider has met the Processing Facility's requirements and worked with the facility to identify the cause of service failures and taken corrective actions in the past may serve as documentation of service provider qualification.

Critical reagents and supplies, that come into contact with donors, recipients, or cellular therapy products shall be sterile and approved for human use (appropriate grade for intended use).

General medical equipment qualification is performed by institutional support to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. An example might be the qualification of a new administration pump or marrow collection set.

Facility qualification is based on the level of services being provided, but in a new clinical area might include air-handling and air-filtration or drug security.

STANDARD:

B4.14 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

B4.14.1 Critical procedures to be validated shall include at least the following: marrow collection procedures, labeling, storage, and distribution.

B4.14.2 Each validation shall include at a minimum:

B4.14.2.1 An approved validation plan, including conditions to be validated.

B4.14.2.2 Acceptance criteria.

B4.14.2.3 Data collection.

B4.14.2.4 Evaluation of data.

B4.14.2.5 Summary of results.

B4.14.2.6 References, if applicable.

B4.14.2.7 Review and approval of the validation plan, validation report, and conclusion by the Quality Manager and the Clinical Program Director or designee.

Explanation:

Validation is confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process or SOP is validated by establishing objective evidence that the process consistently produces an expected endpoint or result that meets predetermined acceptance criteria. Validations can be performed prospectively, concurrently or retrospectively.

Verification is the confirmation of the accuracy of something or that specified requirements have been fulfilled. Verification differs from validation in that validation determines that the process performs as expected whereas one verifies that the products of a process meet the required conditions.

Validation studies should be performed according to a validation procedure, utilizing a consistent format for approval of the validation plan, conducting of the studies, collection and documentation of results, data analysis, conclusions, and approval of the studies. A validation study performed because of a proposed change in a process or SOP shall include a documented assessment of the risk involved in the change to donor and recipient welfare and the quality and safety of cellular therapy products.

The design of the validation study should be adequate to determine if the process reproducibly achieves the purpose for which it is intended. The validation plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. Any change in the planned study that occurs during the study requires explanation. There should be an explanation, follow-up, and/or repeat of any test that fails to meet the expected outcome.

Marrow collection validation should confirm acceptable endpoints can be achieved while maintaining purity, potency, and safety of the cellular therapy product. Examples of acceptable endpoints may include, but are not limited to, nucleated cell recovery, viability, sterility, and red cell reduction.

In the Clinical Program, the following should be validated:

- Marrow collection procedures. Validation of the HPC, Marrow collection procedure should include all the variables used in the collection of each product, such as donor variables (e.g., WBC or CD34 cell count at initiation of collection, blood volume, or weight) and procedural variables (e.g., marrow volume collected, duration of collection). The validation study should demonstrate that the process reproducibly results in a product that is sterile and is of a predetermined volume and nucleated cell content.
- Labeling of cellular therapy products collected from marrow.
- Storage of cellular therapy products prior to distribution.
- Distribution of the product. This may include packaging, temperature, and monitoring for products transported or shipped within or between facilities.
- Electronic records system, if applicable.

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

Evidence:
The inspector should ask to see the SOPs for conducting validation studies and review a sample of validation studies. The inspector should note that studies are properly designed, objectively collect the required data, that outcome and intended actions are summarized, and that both the finalized plan and report are reviewed and approved by the Clinical Program Director and Quality Manager.

Example(s):
It is acceptable, but not required, for the Clinical Program to utilize validation plans, formats, and personnel from the Collection Facility or Processing Facility to perform validation studies, or to contract these validation studies to a contract vendor.

Use of a new system for collection of bone marrow would require validation to confirm the system performed as expected with no compromise of bone marrow product purity, potency, or safety.

For further definitions and examples of validation, see the JACIE Quality Management Guide (www.jacie.org/document-centre) or the FACT Quality Handbook (http://factwebsite.org/qm).

STANDARD:

B4.15 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for inclusion of risk assessment in document control, change control, occurrence investigations, qualification, and validation.*

B4.15.1 *Changes to a process shall include evaluation of risk to confirm that the changes do not create an adverse impact or inherent risk elsewhere in the operation and shall be validated or verified as appropriate.*

Explanation:
Risk assessment is a process to assess and document the risks involved in a change in a practice, process, SOP, or environment that has the potential to affect a critical procedure; direct patient care; and/or the cellular therapy product integrity, sterility, viability, and/or recovery. Risk assessment shall be completed for changes in processes to critical procedures including collection, labeling, and storage.

Risk assessment is a process that may be documented in a validation plan or exist as a separate document and should include:

- Identification of a risk.
- Context.
- Evaluation.
- Risk assessment and impact.
- Management response.

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

Example(s):
Identification of a risk can be made by providing a description of a potential or known risk. Establishing the context or scope means all the possible risks are identified and the possible ramifications or impact in all areas are analyzed thoroughly. Once the context or scope has been established successfully, the next step is identification and evaluation of potential risks either source or effect. During source analysis, the source of risks is analyzed and appropriate mitigation measures are put in place. This risk source could be either internal or external to the system. During problem analysis the effect rather than the cause of the risk is analyzed.

A general description of the issue and identity of the specific risk(s) should be included. After the risk(s) has been identified, it must be assessed on the potential of criticality or on their likelihood of occurrence and the potential impact including quantitative and qualitative evaluation. Risk prioritization is when the 'likelihood of occurrence × impact' is equal to risk.

There are many different approaches to calculating risk, and there are tools that can help assist in defining the probability of the effect occurring, the root cause, effects and magnitude of risk under different scenarios.

Once the risk assessment is established then a risk management plan can be developed and implemented. It comprises of the effective controls for mitigation of risk. Risk Management includes justification and rationale for accepting the risk and how to manage the impact if applicable. This can often be established in a simple one-page document for change with low impact and risk. An example might be a change in using another reagent or supply item of suitable grade.
Below is a risk assessment matrix that combines the concept of likelihood and severity. This may be useful for programs to utilize when assessing risk:

Risk Matrix		Probability (Likelihood of occurrence)		
		Occasional (Possible to occur in time, if not corrected)	**Likely** (Will probably occur in most circumstances)	**Frequent** (Expected to occur in most circumstances)
Severity of Incidence	**Minor** (low risk to the product or patient)	**Low (1)**	**Low (1)**	**Medium (2)**
	Moderate (Probable risk to product or patient)	**Medium (2)**	**Medium (2)**	**High (3)**
	Major (High risk to product or patient)	**High (3)**	**High (3)**	**High (3)**

STANDARD:

B4.16 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining feedback from donors and recipients or legally authorized representatives.*

Explanation:

Feedback (including complaints) from donors, recipients, and legally authorized representatives may be obtained directly by the Clinical Program; however, it is also acceptable to use a hospital-wide system, such as patient satisfaction surveys, as long as the cellular therapy program is included and relevant issues can be readily identified.

STANDARD:

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

B4.17.1 *Key performance data and review findings shall be reported to staff.*

B4.17.2 *The meetings should have defined attendees, documented minutes, and assigned actions.*

Explanation:

QM activities shall be reported, at a minimum, quarterly to review the performance of the QM Program and its objectives. This is to determine whether the elements in the QM Plan are relevant and effective and necessary actions are taken in a timely manner.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported with each audit while others may be retrospectively analyzed and reported at defined intervals. The data should be analyzed, assessed, and trended over time to identify improvement opportunities on a regular basis, such as at each QM meeting. Strategies for improvement should be identified and implemented. The results of these implemented strategies should be measured and the improvement strategies either continued or new alternatives developed depending on the results.

The minutes and attendance lists of regularly scheduled QM meetings are effective ways to document QM activities and communication of quality assessments to key individuals within participating facilities in the cellular therapy program.

Evidence:
The inspector should ask to see evidence that the outcome of quality assessments is communicated to key individuals within all participating entities in the cellular therapy program. The inspector should ask to see the minutes of the QM meetings, which should document who was in attendance and what topics were covered. At a renewal inspection, it is particularly important to ask for QM meeting minutes that represent the time since the previous accreditation in order to determine that the QM Program is and has been ongoing. Minutes should summarize activities such as training performed, documents reviewed, audits performed, and SOPs introduced or revised.

Example(s):
Documentation of quarterly reports can be based on minutes from the regular quality management meetings (if the frequency of the meetings is sufficient) and should summarize activities such as training performed, documents reviewed, audits performed, and SOPs introduced or revised.

STANDARD:

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

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

STANDRD:

B4.18 *The Clinical Program Director or designee shall annually review the effectiveness of the overall Quality Management Program.*

B4.18.1 *The annual report and documentation of the review findings shall be made available to the Clinical Program staff, Collection Facility Director, and Processing Facility Director.*

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

The overall effectiveness of the QM Program must be reviewed and reported to staff on an annual basis. The annual report will provide a year-long view of the overall function of the QM Program, its effect on and interactions with the Collection Facility and Processing Facility, and provide clues on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated.

The annual report should also contain trending information related to key indicators that are monitored, patient outcomes, patient satisfaction, adverse events, and other important elements utilizing data from prior years.

Example(s):
The Clinical Program Director(s) may wish to report on the effectiveness of the QM Program more frequently than once a year. If so, the report should utilize some data from the previous 12 months to provide a longitudinal perspective of how the QM Program is functioning over time.

Examples of sections to include in the report on the performance of the QM Program are:

- Overall programmatic indicators (e.g., accreditation achieved, new faculty, moves, data update);
- Quality measures (including clinical, collection, and processing):
    - Clinical outcomes,
    - Audits,
    - Validations,
    - Process improvements,
    - Biological product and other deviations and nonconformances, and
    - Adverse events; and
- Goals for the coming year.

In the case of shared manufacturing arrangements, such as multi-center trials and centralized processing, the Clinical Program must have arrangements to report and share quality management data among all participating entities.

B5: POLICIES, STANDARD OPERATING PROCEDURES AND CLINICAL GUIDELINES

STANDARD:

B5.1 *The Clinical Program shall establish and maintain policies or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in B4. These documents shall include all elements required by these Standards and shall address at a minimum:*

Explanation:
The policies and SOPs required in B5 are operational in nature, whereas those required in B4 pertain to the QM Program. The policies and SOPs must be detailed, unambiguous, and adequately define all operational aspects of the Clinical Program. It is recognized that the practice of medicine requires some flexibility and that the Clinical Program may choose to describe some elements of clinical practice in clinical guidelines, rather than as policies or SOPs. Unlike SOPs, which must be strictly followed, clinical guidelines provide recommendations for patient care while allowing for variations in practice depending on the clinical situation(s).

When a clinician decides that a variation or alternative intervention from a clinical guideline is warranted, the reasoning behind that decision shall be documented in the recipient's or donor's chart, but pre-approval of the variation or alternative intervention is not necessary. Clinical guidelines must comply with the document control system.

The Clinical Program is not required to have a controlled document titled for every item on the list, as long as each item is addressed within one (e.g., policy, SOPs, or clinical guideline). In those circumstances where program or institution standards vary from these minimal requirements, the program will be held to the higher standards.

Evidence:
Documents addressing the elements listed in B5 must be present. A list of all controlled documents shall be provided to inspectors prior to the inspection to determine if in-depth review of any documents is necessary. When multiple topics are covered by a single document, it will aid the inspection process if the Clinical Program prepares a crosswalk between the list of required SOPs in B5 and the program's own list of controlled documents.

There will not be time to read all policies and SOPs during the on-site inspection. The list of controlled documents should be examined for evidence of documents addressing each item before arriving at the inspection site. Prior confirmation that a specific document has been generated will reserve limited on-site inspection time for activities that can only be verified in person at the inspection site. When necessary, specific documents may be requested and read in their entirety by the inspector.

Example(s):
An example of the use of guidelines rather than SOPs is for the use of antibiotics for fever. The Clinical Program may need to have flexibility if the patient is allergic to the recommended antibiotic or has a past history of infection that would dictate a particular antibiotic combination.

The policies and SOPs can be generated within the Clinical Program or in collaboration with other institutional infrastructures. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and emergency response. In cases where general policies and SOPs are inadequate to meet standards or where there are issues that are specific to the program, the facility must develop its own policies and SOPs. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for review and approval of revisions within the program initially and two years thereafter.

STANDARD:

B5.1.1 Recipient evaluation, selection, and treatment.

B5.1.2 *Donor and recipient confidentiality.*

B5.1.3 *Donor and recipient consent.*

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

Explanation:
Depending on patient characteristics, cells from marrow, peripheral blood, or umbilical cord blood may be advantageous over the other options. The Clinical Program should determine general plans for how a physician may choose the best source of cells for a recipient and how those cells should be sought (e.g., which registries are available for searching).

STANDARD:

B5.1.5 *Management of donors who require central venous access.*

B5.1.6 *Administration of the preparative regimen.*

B5.1.7 *Administration of blood products.*

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

B5.1.9 *Administration of ABO-incompatible products to include a description of the indication for and processing methods to be used for red cell or plasma reduction.*

B5.1.10 *Management of toxicities of immune effector cellular therapies, including cytokine release syndrome and central nervous system complications.*

Explanation:
Cytokine release syndrome and central nervous system complications are adverse events that are common with the administration of immune effector cells. The Clinical Program must be aware of this and other nervous system issues resulting from these cellular therapy products.

STANDARD:

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

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

STANDARD:

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

B5.1.13 *Disposal of medical and biohazard waste.*

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

Evidence:
Compliance with most of the standards in this section can be determined before the on-site inspection by review of the document control system and SOPs submitted in the pre-inspection material. However, additional SOPs should be reviewed during the inspection for compliance.

Example(s):
For the emergency and disaster plan, the Clinical Program may use institutional policies for the general responses; however, specific SOPs relating to the chain of command and necessary SOPs to address the safety of stored cellular therapy products are needed to augment the institutional policies (such as the need for a plan for back up storage facilities). Examples of disasters include fires, hurricanes, floods, earthquakes, nuclear accidents, etc. Specific natural disaster policies may be more pertinent dependent on geographic location. In cases where institutional policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the cellular therapy program, the program must develop additional policies and SOPs. Examples of the latter include, for instance, contingency plans for major environmental or infectious threats, such as failure of isolation facilities or outbreak of aspergillosis, RSV or (para)influenza, leading to an emergency closure of the clinical unit. The article *Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program* (Wingard et all, 2006) provides a framework for disaster plans that can be customized for individual Clinical Programs (available at http://asbmt.affiniscape.com/associations/11741/files/EmergencyPreparednessGuidelines.pdf).

The U.S. Food and Drug Administration offers information on its webpage titled, "The Impact of Severe Weather Conditions on Biological Products," at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ProductSecurity/ucm147243.htm.

STANDARD:

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

Explanation:
Controlled documents must be maintained in an organized fashion so that all current documents can be found. Many Clinical Programs have adopted an electronic method of compiling its controlled documents.

Evidence:
The detailed list should be organized in such a manner that the inspector can ascertain that the controlled documents are comprehensive and define all aspects of the Clinical Program.

Example(s):
A Clinical Program may choose to have one detailed list of controlled documents, or divide controlled documents into several manuals by subject. A technical procedure manual in conjunction with a quality, a policy, and a database manual may serve to better organize information if the program chooses this format.

STANDARD:

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

Explanation:
This standard defines the minimum elements required in each SOP. SOPs are controlled documents and must comply with the requirements in B4.

STANDARD:

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

B5.3.2 *A description of equipment and supplies used.*

B5.3.3 *Acceptable 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.*

Explanation:
Pediatric and geriatric recipients and donors require adjustments that address issues of co-morbidity, age, and size of the donor. A Clinical Program that collects a cellular therapy product from a minor donor must have appropriate SOPs that address at least issues of informed consent, donor size, and venous access. A program that includes geriatric patients should do a geriatric assessment.

Depending on the age range of recipients and donors treated in the program, Clinical Programs should be able to demonstrate the processes by which age-specific issues are addressed. For example, a program admitting teenage patients should demonstrate processes that accommodate the psychological, educational, family, and social needs of this age group, including routine peer group contact. Geriatric recipients (greater than 65 years of age) should have appropriate access to rehabilitation and social support.

Example(s):
Examples of age-specific issues include Total Parenteral Nutrition (TPN) guidelines, blood product administration volume for pediatric recipients, delirium management, geriatric evaluation service, and medication management.

STANDARD:

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

B5.3.8 *Reference to a current version of orders, worksheets, reports, labels, and forms.*

B5.3.9 *The Clinical Program Director or designated physician shall approve, prior to implementation, new or revised controlled documents.*

Explanation:
Although the FACT-JACIE Standards indicate that an individual designated by the Clinical Program Director may review SOPs every two years, the Clinical Program Director remains ultimately responsible for this process. The designated individual should be qualified to review SOPs. If a process changes, the SOP must be updated at that time and reviewed before the changes are implemented; unchanged SOPs must be reviewed at a minimum every two years.

Copies of worksheets, reports, labels, and forms, where applicable, must be identified in or be attached to each SOP as paper copies or via electronic links. The Clinical Program may use the format of its choice, as long as all listed elements are present. The purpose of this standard is to assure that these documents are easily accessible to a reader of the SOP and that it is clear what documents may be required for the performance of that SOP. Review of SOPs should include review of the applicable worksheets, forms, and attachments.

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

Evidence:
Review of SOPs can be documented in several ways, including but not limited to:

- Signature and date on each individual SOP.
- Signature and date for each title and version of individual SOPs listed on a master document.
- Electronic approval via an authenticated electronic document management system.

Orders, worksheets, etc., can be referenced rather than included in the actual SOP as long as the forms are under document control and can be easily accessed by personnel and presented to the inspector on request. The Standards do not prescribe that a review date must appear on a document printed from an electronic document management system; however, the document control system must be validated so that printed documents are the current implemented versions. Such a system would archive obsolete versions or have a method to convey the printed version is an archived version (e.g., watermark).

Example(s):
In some Clinical Programs, the actual SOP may be limited to minimal work instructions, and required elements such as a reference list may be found only in higher-level documents. Such variability is acceptable if all elements can be found within the associated controlled documents.

Though not required, the Clinical and Laboratory Standards Institute (CLSI) standard format can be useful in preparing these SOPs (see www.clsi.org for more information). Some Clinical Programs may utilize a format consistent with ISO 9000 in which all documents, policies, SOPs, and work instructions exist in a specific hierarchy. In this case, the inspector must be certain to review all relevant documents.

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

Explanation:
The written copy or electronic version (with provisions for hard copies as necessary) of the Clinical Program's policies and SOPs relevant to the work schedule and duties must be immediately available to all relevant staff in their working environment. Documents that an employee must comply with must be readily available to him/her for reference when needed.

Evidence:
The written copy or electronic version of the SOPs should be readily identifiable to the inspector. The inspector should expect to see the SOP manual or electronic access to SOPs in all performance areas of the Clinical Program. These include all locations of sustained patient care (BMT inpatient and outpatient facilities). The SOPs should be organized in such a manner for the inspector to ascertain that the SOPs are comprehensive, defining all aspects of the Clinical Program.

STANDARD:
B5.5 *Staff training and, if appropriate, competency shall be documented before performing a new or revised policy, Standard Operating Procedure, or guideline.*

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

Example(s):
Sometimes a revision to a policy or SOP is minor, such as an update to a referenced regulation or grammatical corrections. In these cases, full training may not be necessary. Review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

It is recommended that there be a specific signoff sheet for every policy and SOP and associated revisions to document that each staff member required to review a policy or procedural revision has done so prior to performing the tasks described. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each procedure and to any major revision also facilitate documentation of appropriate training of staff.

STANDARD:

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

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

Explanation:

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

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

Explanation:

The Standards are intended to promote the safety of the donor and recipient as well as the safety and efficacy of the cellular therapy product.

For allogeneic donors, nearly all the requirements in B6 apply, including standards to safeguard appropriate confidentiality, confirm histocompatibility matching, and protect the recipient from the risks of transmissible disease.

For autologous-only Clinical Programs, many, but not all, of the requirements in this section apply. The standards and substandards under B6.1, B6.2, and B6.3 apply to autologous transplantation except for those that specify allogeneic donors only. The term "donor" is used by the Standards even in the autologous setting because considerations for informed consent and suitability (i.e., safety) of the individual include issues above and beyond the individual's status as a cellular therapy recipient. The following table lists the standards and substandards in this section that apply to autologous transplantation:

Required Standards for Autologous-only Clinical Programs

Subject	Substandards	
B6.1 Written criteria		
B6.2 Informed Consent	B6.2.1	B6.2.1.1
		B6.2.1.2
		B6.2.1.3
		B6.2.1.4
		B6.2.1.5
	B6.2.2	
	B6.2.3	
	B6.2.4	
	B6.2.5	
	B6.2.6	
	B6.2.7	
	B6.2.9	
	B6.2.10	
B6.3 Donor Suitability	B6.3.1	B6.3.1.1 B6.3.1.3
	B6.3.2	B6.3.2.1
		B6.3.2.2
		B6.3.2.3
	B6.3.3	
	B6.3.4	
	B6.3.5	
	B6.3.6	
	B6.3.7	
	B6.3.8	
	B6.3.9	

STANDARD:

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

Explanation:

The Clinical Program must have in place written SOPs defining all aspects of donor identification, evaluation, selection, and management, including identification of the personnel responsible for each aspect (when in the control of the program).

In addition, this standard requires that the Clinical Program identify the institutional criteria for allogeneic and autologous donor medical suitability and selection.

Written criteria for allogeneic donors should include criteria to determine the number of cellular therapy product donations permitted by a single donor. This includes criteria for both related and unrelated donors. The Clinical Program should be aware of the number of times an unrelated donor has donated, as it may factor into whether that donor should be selected or not.

Clinical Programs performing allogeneic transplantation should endeavor to receive only voluntary and unpaid donations of cells. Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation. This is based on national and international standards for donation.

Evidence:
The inspector may ask to verify compliance with these SOPs by reviewing a specific donor evaluation. If a Clinical Program only performs allogeneic transplants, then the written criteria need only pertain to allogeneic donors. If a program performs only autologous transplants, then the written criteria need only reflect autologous donors. If the program performs both allogeneic and autologous transplants, then criteria for both types of transplant must be written.

Example(s):
Examples of written criteria for allogeneic donors include:

- Infectious disease markers obtained within the appropriate time frame before collection from a donor.
- Criteria for an ineligible but acceptable donor (e.g., an international donor may be ineligible but acceptable if all other donor criteria are fulfilled).
- The number of times a sibling donor can donate cells.
- The role of the donor advocate.

STANDARD:

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

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

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

Explanation:
Sufficient information for allogeneic donors should be provided before the potential donor undergoes HLA typing to protect the potential donor from undue pressure should he/she be the only suitable donor. The Clinical Program may not always have control over the allogeneic donor consent process, but should attempt to provide information to the donor if possible, or review available documentation to verify that the donor received such information.

Example(s):
A full informational session regarding the donation process is not required to meet this standard. Other acceptable methods include, but are not limited to, a brochure, pamphlet, or telephone conversation. Information provided by unrelated donor registries may be useful sources of information, such as the information on the websites of the NMDP (http://www.bethematch.org) and the Anthony Nolan Trust (http://www.anthonynolan.org).

STANDARD:

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

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

Explanation:

The informed consent substance and process is determined by the law in the jurisdiction of the Clinical Program. The SOP for obtaining consent from donors must comply with applicable laws and regulations. The essential elements of informed consent are that donors are told, in terms they can reasonably be expected to understand and in their native language via an approved interpreter when indicated, the reasons for the proposed therapy or procedure, alternative therapies or procedures, the risks associated with the treatment or procedure, and potential benefits. In addition, the donor should be given the opportunity to ask questions and to have those questions answered to their satisfaction.

The discussion that ensues is the important part of the process of obtaining informed consent; however, it is the documentation of this process that can be easily audited. Informed consent is to be documented according to institutional standards and criteria.

The information must be given by a trained person able to transmit it in an appropriate and clear manner, using terms that are easily understood. The health professional must confirm that donors have a) understood the information provided, b) had an opportunity to ask questions and had been provided with satisfactory responses, and c) confirmed that all the information they provided is true to the best of their knowledge and documented in the medical record.

Evidence:

If the informed consent process is performed verbally, the clinic note must detail discussion of the protocol, including the documentation of required elements consistent with institutional policy and applicable laws and regulations.

Example(s):

This process may take place over several visits. A preprinted consent form detailing all of the above elements is an easy method of documentation; however, informed consent does not specifically require such a form. In the absence of a form, the clinical notes detailing the consent discussion must be significantly detailed.

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

Informed consent requirements of the WMDA or NMDP may be more detailed, and Clinical Programs facilitating unrelated transplants should consult those current requirements.

STANDARD:

B6.2.1.1 The risks and benefits of the procedure.

B6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

B6.2.1.3 The rights of the donor or legally authorized representative to review the results of such tests according to applicable laws and regulations.

B6.2.1.4 Alternative collection methods.

B6.2.1.5 Protection of medical information and confidentiality.

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

B6.2.3 Family members and legally authorized representatives should not serve as interpreters or translators.

B6.2.4 The donor shall have an opportunity to ask questions.

B6.2.5 The donor shall have the right to refuse to donate or withdraw consent.

B6.2.5.1 The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal in the event that consent is withdrawn after the recipient has begun the preparative regimen.

Explanation:
This standard is not meant to be coercive, but to require full disclosure of the effects a donor's decisions has on a recipient. Donors shall be informed that the consequences to the recipient of the donor's refusal to donate are significantly different depending on the stage of transplant. If the potential donor declines prior to typing versus refusing after selection and the day before the administration, then the degree of risk incurred to the recipient will be very different.

STANDARD:

B6.2.6 Donor informed consent for the cellular therapy product donation shall be obtained and documented by a licensed health care professional familiar with the collection procedure.

B6.2.6.1 Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

Explanation:
In the allogeneic setting, to prevent conflict of interest that may exist when a physician or other healthcare provider cares for both the donor and the recipient, donors must be consented by a member of the team other than the primary health care professional of the intended recipient or a clinician who is not a member of the clinical team but is knowledgeable with the collection procedures. It should be strongly considered that the physician or healthcare provider is not a part of the cellular therapy program.

STANDARD:

B6.2.7 *In the case of a donor who is a minor, informed consent shall be obtained from the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.*

Explanation:
Donors must be of legal age of consent (in the jurisdiction of the collection) or the informed consent for donation must be signed by the legally authorized representative. Specific consent is required for the use of growth factors in a minor, allogeneic donor.

Clinical Programs must be compliant with institutional policy and governmental laws when addressing issues of assent of a minor who may be unwilling to donate. The age of assent and consent varies depending on the legal jurisdiction. Conferring with appropriate legal counsel is indicated in complex cases.

Example(s):
It is appropriate to discuss the donation procedure with the pediatric donor in terms he/she can understand. For minor donors, although consent is obtained from legally authorized representatives in accordance with local regulations, assent should also be obtained in an age appropriate manner. It may be helpful to include a child life specialist, a social worker, or another qualified individual in the consent process to determine whether the minor donor has age-appropriate understanding.

STANDARD:

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

Explanation:
The purpose of this standard is to protect donor confidentiality regarding his or her health information and appropriateness to donate. Factors that determine whether or not it is appropriate to select a potential donor include HLA matching, eligibility (i.e., lack of a communicable disease risk), suitability (medical fitness to undergo the collection procedure), desire to donate his/her cells, etc. Donors do have the option to specifically limit disclosure of certain information upfront.

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

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

STANDARD:

B6.2.9 *The donor shall be informed of the policy for cellular therapy product discard or disposal, including actions taken when an intended recipient no longer requires the cellular therapy product.*

Example(s):
Registries that facilitate unrelated transplants may have specific requirements for what information must be provided to the donor regarding cellular therapy product discard.

STANDARD:

B6.2.10 *Documentation of consent shall be available to the Collection Facility staff prior to the collection procedure.*

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

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

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

Example(s):
Vulnerable donors (e.g., children) and donors at increased medical risk from donation (e.g., those with cardiac disease) are examples for when donor suitability assessment is crucial.

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

STANDARD:

B6.3.1.1 Clinically significant findings shall be reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

Explanation:
Abnormal findings in a donor, including, but not limited to testing and physical evaluation results, may have important implications for the donor apart from his/her role in the collection process. Appropriate care of the donor requires that clinically significant abnormalities be communicated to him/her and that recommendations be made for follow-up care. These actions should be documented in the individual's medical record.

Evidence:
The inspector may need to specifically request a record of a prospective donor undergoing collection who had abnormal findings, since this may not be a common occurrence in many Clinical Programs. Review of a chart from an ineligible donor will aid in verification of documentation of abnormal results.

Example(s):
For donors with abnormal test results, it is recommended that appropriate follow-up evaluations be completed or a referral be made to an appropriate physician.

STANDARD:

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

Explanation:
An independent physician or health care professional must be utilized for evaluating donor suitability to minimize potential bias of the recipient's health care professional(s). This individual must not be the primary health care professional of the recipient and should have knowledge of the risks of the donation procedures.

Medical literature supports the idea that having the allogeneic donor evaluated by a physician or health care professional who is not the primary health care provider of the recipient decreases the potential conflict of interest with regard to the welfare of the recipient and the welfare of the donor (see "Family Donor Care Management: Principles and recommendations," (Walraven et al, 2010). Furthermore, the American Academy of Pediatrics (AAP) and the American Society of Blood and Marrow Transplantation (ASBMT) recommend this practice for related donations.

Evidence:
The Clinical Program's policy on donor evaluation and medical charts can be used to verify that an individual other than the recipient's primary licensed health care professional evaluates the donor for suitability.

Example(s):
A potential donor could be evaluated by another attending physician of the Clinical Program; however, programs are not required to have sufficient staffing to evaluate donors using their own attending physicians. Small programs may not have enough attending physicians to separately evaluate donors within their own programs. Physicians and licensed health care professionals outside of the program may perform this function, including a clinician who is a member of a different program, the donor's primary care physician (if he/she possesses knowledge of the donation procedure), a general internal medicine clinic, or a clinic not directly associated with the program.

STANDARD:

B6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

Explanation:
Testing or screening of autologous donors in connection with product collection is not required by the Standards. However, consistent with B1, testing required by local laws or regulations is required.

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

STANDARD:

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

B6.3.2.1 Possible need for central venous access.

Explanation:
The appropriate and safe positioning and function of central venous catheters (CVCs) is critical to the performance of cellular therapy product collection by apheresis. A licensed, trained, and qualified health care provider (such as a physician or a nurse) is responsible for obtaining central venous access. Credentialing of health care providers for this activity is the responsibility of the individual institution.

It is ultimately the health care provider's responsibility to confirm the adequacy and safety of placement of a CVC by appropriate methods. Confirmation that the line is satisfactorily positioned and functioning prior to the collection episode must be provided. The methods should be appropriate for the site of placement (e.g., subclavian/jugular access – fluoroscopy or ultrasound) while femoral line placement could be confirmed by ultrasonography. The records describing the position and function of the catheter and that both are appropriate to proceed with the collection must be available to the collection team.

Prior to collection and use of a CVC, the Apheresis Collection Facility staff must receive the documentation of placement and its appropriateness for use. This step will allow the facility staff the assurance to use the CVC and include documentation of satisfactory venous access in the donor record. Appropriate care should be taken to protect donor safety when a CVC is inserted solely for a collection procedure and that collection extends over more than one day. Donors need to be assessed for the risks of CVCs, including significant complications such as hematomas, pneumothorax, hemothorax, and bacterial infections.

Evidence:
The inspector should inquire about the nature and frequency of CVC complications including significant hematomas, pneumothorax, hemothorax, and bacterial infections. These adverse events should also have been discussed during quality assurance meetings of the Apheresis Collection Facility.

The inspector should look at the documentation of central line placement by the Apheresis Collection Facility, including documentation of line position and function prior to collection.

Example(s):
The WMDA S(P)EAR Committee has provided recommendations for policies in response to reported adverse events (Document Reference: 0110824-CLWG-SEAR-August 2011):

- Stem cell donor registries should review their policies concerning the placement of CVCs.
- If a stem cell donor registry does not have a policy concerning CVC placement, one should be written.
- Insertion of a CVC for PBSC collection should only be used in exceptional circumstances, e.g., only when peripheral venous access is not deemed feasible after skilled assessment or cannot be obtained or has failed.
- The policy should cover, at a minimum, the need for the following:
    - Requirement for careful peripheral venous assessment at the time of donor medical evaluation.
    - Evidence that alternative methods of donation have been discussed if appropriate.
    - Written justification for placement of a CVC.
    - Consenting procedures (and counselling) for CVC insertion, including who should obtain informed consent.
    - Qualifications and expertise of the person(s) permitted to insert the CVC.
    - Permissible sites for CVC insertion.
    - The requirement for radiological guidance for all CVC inserted above the umbilicus, if locally available.
    - The need for care for all patients with CVCs, cared for by appropriately trained personnel.
    - The requirement for reporting SAE/AEs.

The National Health Service National Institute for Health and Clinical Excellence (NHS NICE) provides guidelines regarding the placement of CVCs. Visit http://guidance.nice.org.uk/TA49 to obtain these guidelines and additional information. The American Society of Anesthesiologists Task Force on Central Venous Access has also published guidelines available for review (Anesthesiology 2012; 116:539–73).

STANDARD:

B6.3.2.2 Mobilization for collection of HPC, Apheresis.

Explanation:
Mobilization requires that evaluation occur for any medical condition that would expose the donor to the risk for thrombotic events. This evaluation must be documented, including the pre-collection and collection time frames specific to growth factor administration.

If the donor is at risk of failure to mobilize, the Clinical Program must also evaluate the donor for fitness to undergo a marrow collection if necessary, and inform the donor, to protect the recipient who has already begun the preparative regimen.

Evidence:
The donor's medical records for pre-collection workup results will contain evidence of compliance.

STANDARD:

B6.3.2.3 Anesthesia for collection of HPC, Marrow.

Evidence:
The donor's medical records for pre-collection workup results will contain evidence of compliance.

STANDARD:

B6.3.3 The donor shall be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen.

Explanation:
Hemoglobinopathy assessment is required since administration of mobilization agents such as G-CSF may pose a risk to the donor as it was associated with morbidity (e.g vaso-occlusive crisis) and mortality in donors with sickle cell disease (HbSS), HbSC, and also with compound hemoglobinopathies such as sickle-beta-thalassemia (S/β thal). Testing is not required, although it is an acceptable method.

Of note, donors with sickle trait were safely mobilized and collected. While the sickle trait donors did have higher symptom score than control donors, there were no symptoms suggestive of sickle crisis. Thus, in this group, the risk is limited.

References:
Granulocyte Colony-Stimulating Factor (G-CSF) Administration in Individuals with Sickle Cell Disease: Time for a Moratorium? Fitzhugh Cd et al ,Cytotherapy. 2009; 11(4): 464–471.

Granulocyte Colony-Stimulating Factor-Based Stem Cell Mobilization in Patients with Sickle Cell Disease. Rosenbaum C et al, Biology of Blood and Marrow Transplantation 2008; 14:719-723.

Mobilization, collection, and processing of peripheral blood stem cells in individuals with sickle cell trait. Kang et al, Blood 2002;99:850.

STANDARD:

B6.3.4 *A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to starting the donor mobilization regimen, undergoing anesthesia, and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.*

Explanation:

Pregnancy testing is required since the donation of cells from marrow or peripheral blood and anesthesia may pose a risk to the fetus. The intent is to confirm the donor is not pregnant before the initiation of the mobilization agent or administration of anesthesia and before the recipient starts the conditioning regimen. Child-bearing potential is meant to include all female donors from puberty through menopause, unless there is some definite medical indication that pregnancy is impossible (e.g., a past hysterectomy).

The purpose of the required timeframe is to prevent donor mobilization and recipient conditioning occurring before finding out that the donor is pregnant. There are some obvious situations in which pregnancy testing would not occur within seven days prior to recipient conditioning. For example, if a cellular therapy product is collected from the donor and subsequently cryopreserved for administration weeks later, the donor does not have to be retested for pregnancy. However, if a recipient is on a 21-day conditioning regimen, a pregnancy test must be performed within seven days prior to beginning that regimen.

Evidence:

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

Example(s):

A pregnancy test is required; serologic assays or urinalysis may be used.

STANDARD:

B6.3.5 *Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, or licensed in accordance with applicable laws and regulations.*

Explanation:

All laboratory tests must be performed by a laboratory accredited for the relevant tests. Testing may be performed at any time prior to the initiation of the recipient's preparative regimen except for infectious disease tests for allogeneic donors, which must be done within 30 days prior to collection of HPC products and within seven days prior to or after collection of other cell products as required by the FDA or as required by non-U.S. equivalent regulations.

Example(s):

Some governmental authorities, such as the U.S. FDA, allow for testing up to seven days after collection of HPC products; however, this is intended only for rare occasions. To be compliant with the Standards, HPC products for which infectious disease testing is not performed within 30 days prior to collection must be approved, investigated, and evaluated per the requirements for biological product deviations in B4.

Examples of relevant accreditation organizations include CLIA, CAP, ASHI, AABB, JCAHO, HCFA, EFI, UKAS (United Kingdom Accreditation Services), and Australasian College of Pathologists.

STANDARD:

B6.3.6 *The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.*

B6.3.7 *There shall be a written order from a physician specifying, at a minimum, anticipated date and goals of collection and processing.*

Explanation:
In addition to the specific requirements in the Standards, Clinical Programs must assess the overall health of the donor.

Example(s):
The HCT Comorbidity Index is a useful tool for determining if any comorbidities put donors at unacceptable risk. See Hematopoietic cell transplantation (HCT)–specific comorbidity index: a new tool (Sorror et al, 2005) and the NMDP/CIBMTR index for more details.

STANDARD:

B6.3.8 *Collection from a donor who does not meet collection safety criteria shall require documentation of the rationale for his/her selection by the donor's physician.*

Explanation:
These standards are meant to require the Clinical Program Director or designee to review all donor data prior to collection, and to document in the record that the donor is appropriate for the intended recipient and is suitable to undergo the collection procedure. Critical factors impacting donor suitability must be included in the documentation (e.g., age, weight, co-morbidities).

Autologous donors in particular may have health-related issues that need to be known by Collection Facility staff in order to maximize the safety of the collection procedure. This information is important enough that it needs to be clearly communicated in writing in advance of the procedure so that appropriate precautions are taken.

Example(s):
Clinical Programs may include information regarding donor health issues on the collection order form, or may communicate needed information by a documented note in the collection chart record. Such records may include the electronic medical record.

STANDARD:

B6.3.8.1 *Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff prior to collection.*

B6.3.9 *There shall be a policy or Standard Operating Procedure for the management of collection-associated adverse events and follow-up of donors that includes routine management .*

Explanation:
Collection-associated adverse events should be addressed in accordance with the Clinical Program's QM Plan (see B4).

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

Example(s):
The World Health Organization (WHO) guiding principles of Human Cell, Tissue and Organ Transplantation (guiding principle 10) recommends long-term follow-up of donors. These guiding principles can be found at
http://www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf.

"Allogeneic hematopoietic stem cell donation-standardized assessment of donor outcome data: a consensus statement from the Worldwide Network for Blood and Marrow Transplantation (WBMT)" (Halter et al, 2013) provides additional recommendations for donor follow up.

STANDARD:
B6.4 *ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS*

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

Explanation:
A donor advocate is an individual distinct from the recipient's primary treating physician whose primary obligation is to help the donor understand the risks and benefits of donation and promotes the interests, well-being, and safety of the donor. According to Donor Registries for Bone Marrow Transplantation: Technology Assessment (NIH Office of Medical Applications of Research, 1985), the role of the advocate is to help safeguard that the consent is made without time pressure and with full information, to enhance the personal attention given to the donor during all procedures, to help prevent unnecessary inefficiencies and discomfort, to mobilize official expressions of gratitude after the donation, and to aid in the resolution of subsequent problems.

For donors who are mentally incapacitated or not capable of full consent, a donor advocate must be utilized to appropriately counsel the donors and protect them from unsafe or futile donation procedures. For these individuals, donor advocates do not need to be routinely appointed, but should be available if concerns are raised regarding whether the best interest of these individuals are being adequately protected.

The donor advocacy role should be documented and should not be fulfilled by an individual involved in the recipient's care. A court-appointed advocate is not required.

Evidence:
For Clinical Programs using minor or mentally incapacitated donors, there must be documentation that a donor advocate was available in the donor selection process.

Example(s):
Examples of donor advocates include chaplains, patient advocates, social workers, etc. "Family Donor Care Management: Principles and recommendations," (Walraven et al, 2010) provides recommendations for donor advocacy in the related transplant setting. The American Academy of Pediatrics (AAP) and the American Society of Blood and Marrow Transplantation (ASBMT) are also sources of information.

STANDARD:

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

Explanation:
Donors are often asymptomatic, and infectious disease tests must be sensitive enough to produce a positive result when a disease has not yet manifested in the donor. In some countries, the relevant governmental authorities may require use of approved or cleared tests for any tests performed in their jurisdiction, even if the recipient is in a different country. If such tests are not used, the donor eligibility is considered incomplete, but the donor may be used provided that all requirements for urgent medical need in the recipient's country are met.

STANDARD:

B6.4.3 *Allogeneic donors and allogeneic recipients shall be tested for ABO group and Rh type using two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.*

Explanation:
ABO group and Rh typing is performed on blood and/or cellular therapy products from allogeneic donors and recipients to avoid the unintentional use of ABO incompatible products containing red blood cells (RBCs) that might result in a transfusion reaction. The Standards require testing on two independently collected samples. The timing of the collection of these samples is not specified; however, the entire process of collecting the two samples must be distinct from one another (i.e., different needle sticks and different phlebotomists if staff allows). It is not acceptable to collect the two samples at the same time. The results of both tests should be available to clinical, collection, and processing. The cellular therapy program determines who collects the samples and who performs the testing. Note that these are minimum requirements, and the cellular therapy program may elect to perform more testing, more frequent testing, or testing on the first day of collection as it determines to be appropriate. Testing and documentation should occur according to written SOPs. SOPs to manage ABO and Rh mismatches between the donor and recipient should also be established.

If cord blood products are selected for cellular therapy, two independent ABO tests can only be performed when additional CB samples are available for testing.

Example(s):
Allogeneic donors may be tested at the time they are initially evaluated for donor suitability and eligibility and a second test may be performed at the time of cellular therapy product collection. Alternatively, both tests may be performed prior to collection.

STANDARD:

B6.4.4 *A red cell antibody screen shall be performed on allogeneic recipients.*

Explanation:
Red cell antibody screening is important for recipients who receive cellular therapy products containing red blood cells. Red cell antibodies other than those that naturally occur in relation to the recipient's ABO blood group can cause hemolysis of red cells that bear the antigens the antibodies recognize. Not all recipients have red cell antibodies other than those to ABO antigens. The only way to know if the antibodies are present is to test a panel of RBCs using serum from the recipient to detect them. Recipients only develop antibodies to red cells other than anti A or anti B if they have been previously exposed to red cells bearing other blood group antigens the patient lacks. Pregnancy can immunize a woman, and previous blood transfusions can immunize women or men. It is far less likely that a healthy donor will have antibodies to other blood group antigens, and even if they do, the antibodies are rarely potent enough (in high enough concentration) to cause a reaction if administered with the product. The rare times this could be a problem do not justify testing all allogeneic donors. Red cell antibody screening is needed to mitigate clinical problems and development of a management strategy.

Evidence:
Records of ABO and Rh typing results and antibody screening in the clinical records provide documentation of compliance.

Example:
Tests can be performed on the product itself, although the plasma that would be available for red cell antibody screening is diluted, potentially causing weak but significant antibodies to be missed.

STANDARD:

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

Explanation:
In some cases, such as resistant disease or relapse/progressive disease, it may be medically necessary to administer donor lymphocytes or other cellular therapy products before availability of repeat transmissible disease testing. The recipient must be informed of this deviation, and the discussion of the deviation with the recipient must be documented in the medical record.

Testing must occur in accordance with written SOPs and using appropriate donor-screening tests licensed, approved, or cleared by applicable governmental authorities in accordance with the manufacturer's instructions. The results of donor eligibility determination must be recorded. For products in which donor testing results are not yet available, these products should be quarantined until the results are available.

Products from autologous donors known to be positive for agents listed in these standards must be labeled in the same fashion as an allogeneic donor but do not require the statement: "Warning: Advise Patient of Communicable Disease Risks" since the patient is already infected with the agent. However, autologous donors with a positive communicable disease test are not considered to be ineligible and such products do not require physician notification or patient consent for release for allogeneic donors. Clinical Program personnel are required to adhere to universal precautions and should treat all products as potentially infectious.

Evidence:
The medical records should document that allogeneic donors were tested for these infectious agents within the specified time period and that the results were obtained prior to the initiation of the cellular therapy procedure. Donor eligibility determination must be recorded.

Example(s):
For donors of allogeneic cellular and tissue-based products, the FDA regulations on donor eligibility determination require that donor evaluation includes risk factor screening by health history questionnaires, review of medical records, physical examination, and testing for relevant communicable disease agents and diseases. The donor is determined to be eligible if he/she is 1) free from risk factors for and clinical evidence of relevant communicable disease agents and diseases, 2) free from communicable disease risks associated with xenotransplantation, and 3) tests negative or non-reactive for relevant communicable disease agents within the specified timeframe for the product. It is the responsibility of the Clinical Program to document that donor evaluation procedures are in place to protect the recipient from the risk of disease transmission from the donor.

It is recommended that Clinical Programs and their testing laboratories use the most advance tests available for these diseases and disease agents to minimize the window period.

STANDARD:

B6.4.6 The medical history for allogeneic donors shall include at least the following:

B6.4.6.1 Vaccination history.

B6.4.6.2 Travel history.

B6.4.6.3 Blood transfusion history.

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

B6.4.6.5 Questions to identify persons at risk of transmitting inherited conditions.

B6.4.6.6 Questions to identify persons at risk of transmitting a hematological or immunological disease.

B6.4.6.7 Questions to identify a past history of malignant disease.

B6.4.6.8 The allogeneic donor shall confirm that all the information provided is true to the best of his/her knowledge.

Explanation:
The Standards require that all donors be screened for medical history and risk factors for human transmissible spongiform encephalopathy, Creutzfeldt-Jakob disease (CJD), and potential transmissible infectious disease agents through xenotransplantation as there are no tests for these agents. Travel history is essential for this screening. Information about areas of the world where CJD is a risk factor should be established using trusted sources, such as national or international health agencies' websites or publications.

Evaluation of risk factors for disease transmission by medical history, physical examination and, examination of relevant medical records must be done within an appropriate period of time according to applicable laws and regulations. If the particular period of time has passed, the risk factors for disease transmission must be updated.

Other risks may be associated with unlicensed vaccines, receipt of human-derived growth hormone or clotting factor concentrates, or hepatitis B immune globulin. Prospective donors should be questioned about these issues.

In some donors, risks assessments may be necessary based on the donor medical history. In the case of child donors born of mothers with HIV, hepatitis C, hepatitis B, or HTLV infection, the evaluation of risk of transmitting infection should include consideration of the age of the child, history of breastfeeding, and results of infectious disease marker testing; eligibility criteria must be in accordance with applicable governmental laws and regulations.

There are standard deferral times after immunization for allogeneic blood donation that can be used to determine the potential risk that may exist. Blood donors are typically deferred for four weeks after attenuated live virus vaccines such as oral polio, herpes zoster, and measles. In those cases in which a potential donor has recently been vaccinated, both the reason for the vaccination and the time interval should be evaluated to estimate the potential risk to a recipient. There should be specific SOPs in dealing with donors who had received smallpox vaccination. Donors must be screened for travel to the area that would put them at risk for malaria, human transmissible spongiform encephalopathy, SARS (severe acute respiratory syndrome) during periods of world-wide prevalence, or rare strains of HIV, which may not be detected by current screening tests.

Evidence:
Donor medical examination notes and questionnaire records can be reviewed to determine if all of the required screening elements were included in the eligibility determination.

Example(s):
It is recommended that the Clinical Program utilize a screening tool used by an unrelated donor registry even for related donors, such as the National Marrow Donor Program's "Donor Health History Screening Questionnaire."

Information about areas of the world where CJD is a risk factor can be obtained from the interorganizational Uniform Donor History Questionnaire developed for donors of HCT/Ps and the algorithm that accompanies it. This information is available on the FACT website at: http://factwebsite.org.

Specific diseases for which screening is required by the FDA can be found in 21 CFR 1271.75 and at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/.

Additional FDA requirements can be found at:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm.

STANDARD:

B6.4.7 *Allogeneic donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests required by applicable laws and regulations:*

Explanation:
The purpose of this standard is to prevent transmission of communicable diseases from the donor to the recipient in the allogeneic setting. A Clinical Program may wish to also perform such testing on autologous donors for patient care issues or for additional protection of personnel; however, this is not required unless mandated by applicable laws and regulations. If an autologous donor is not tested for transmissible disease, or if testing is performed and found to be positive, the applicable labeling requirements apply.

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

Example(s):
The FDA announces through published guidance additional relevant communicable diseases. See FDA Guidance Document ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Product [HCT/Ps], 2007) at:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm for additional information.

Other communicable disease tests should be added to the donor evaluation as they become available and recommended to increase cellular therapy product safety. There are other relevant communicable diseases besides those specifically listed in the FDA regulations. In making this determination, the factors considered in naming a disorder a "relevant communicable disease" are:

- There might be a risk of transmission through an CTP.
- It is sufficiently prevalent as to affect the potential donor population.
- There could be fatal or life-threatening consequences as a result of transmission.
- Effective screening mechanisms and/or an approved screening test for donor specimens have been developed.

STANDARD:

B6.4.7.1 Human immunodeficiency virus, type 1.

B6.4.7.2 Human immunodeficiency virus, type 2.

B6.4.7.3 Hepatitis B virus.

B6.4.7.4 Hepatitis C virus.

B6.4.7.5 Treponema pallidum (syphilis).

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

B6.4.8.1 Human T cell lymphotropic virus I.

B6.4.8.2 Human T cell lymphotropic virus II.

B6.4.8.3 West Nile Virus.

B6.4.8.4 Trypanosoma cruzi (Chagas Disease).

Explanation:
In the US, HCT/P donors must be tested for HTLV I and HTLV II. Clinical Programs in EU member states are required to perform a risk assessment to determine if testing for HTLV I and II or other diseases is appropriate for their patient populations. In the US, testing for West Nile Virus is required on a seasonable basis. Testing results may influence the timing of recipient conditioning (when using autologous or allogeneic donors) or lead to selection of an alternative donor when possible.

Example(s):
Clinical Programs in EU member states are required to perform a risk assessment to determine if testing for HTLV I and II or other diseases is appropriate for their patient populations.

STANDARD:

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

B6.4.9.1 Blood samples for communicable disease testing from allogeneic HPC donors shall be obtained within thirty (30) days prior to collection.

B6.4.9.2 For viable, lymphocyte rich cells, including mononuclear cells and other cellular therapy products, blood samples from allogeneic donors shall be obtained within seven (7) days prior to or after collection in the U.S. or 30 days prior to collection in European Union member states.

B6.4.10 Allogeneic donors shall be tested for Cytomegalovirus (unless previously documented to be positive).

Explanation:
Cytomegalovirus (CMV) is not a relevant communicable agent or disease. However allogeneic donors must be tested for evidence of infection with CMV, although the time frame for this testing is not restricted. A prospective donor who was previously positive for anti-CMV should be considered to be a seropositive donor. Use of CMV-seropositive donors is permissible and a positive CMV test alone does not make a donor ineligible. Such a cellular therapy product may be used so long as the Clinical Program has a clearly defined policy or SOP that addresses the use of CMV-seropositive donors. Product labels from CMV positive donors do not require the statements or biohazard label required for products positive for the other agents listed in these standards. However, there must be a SOP for communicating test results of donors who are positive or reactive for CMV antibody.

Example(s):
CMV testing results may accompany the cellular therapy product as part of the administration form or other information available at product release.

STANDARD:

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

Evidence:
Medical record documentation will demonstrate that a risk assessment (e.g., based on season, geography, time/day of testing, CDC/EU/WHO reports) was conducted to determine the need for additional donor testing.

STANDARD:

B6.4.12 *Allogeneic donors and recipients shall be tested for HLA alleles by a laboratory accredited by ASHI, EFI, or other appropriate organization. Typing shall include at a minimum HLA-A, B, and DRB1 type for all allogeneic donors and also HLA-C type for unrelated allogeneic donors and related allogeneic donors other than siblings.*

Explanation:
Some cord blood banks may not test for all HLA loci or at the level of resolution required by the Standards. In this situation, the Clinical Program must test for these requirements using a cord blood unit sample if one is available.

The following table outlines HLA typing guidance for various cellular therapy products as written in ASHI and EFI standards:

	ASHI 2014	EFI 2015
Version of Standard	CMS approved January 8, 2015	6.3 effective from October 1st 2015
Agreement between Histocompatibility Laboratory and Transplant Center	Transplant center agreements between lab and transplant center is essential in order to define the testing which will be performed by the accredited lab.	A Transplant Protocol between the Histocompatibility Laboratory and the Transplant Center must be written, signed and regularly updated. In agreement with EFI standards, it should define for the different types of HSC transplants, HLA loci to be typed, level of resolution and acceptability criteria.
Matched related transplant (2 samples required)	D.5.3.3.1.5 Perform adequate testing of relatives to determine genotypes for patient and donor or high resolution molecular typing	I2 Perform A,B, and DR and enough adequate testing to establish HLA genotype identity. If only phenotype identity is established, perform high resolution for relevant loci I5 Crossmatching must be performed if required by the Transplant Protocol
Unrelated transplant recipient (2 samples required)	* D.5.3.3.1.1	I4.3 HLA-A/B/C and DRB1 typing at high resolution as a minimum requirement. Include additional loci and/or resolution levels if required by transplant protocol. HLA typing must be performed by the laboratory affiliated with the Transplant Center. I5 Crossmatching must be performed if required by the Transplant Protocol

	ASHI 2014	EFI 2015
Haplo transplant recipient and donor (2 samples required)	* D.5.3.3.1.1	I2.2.3 Include high resolution typing for recipient and potential intra-familial donors who are not HLA identical siblings I5 Crossmatching must be performed if required by the Transplant Protocol
Unrelated donor (1st sample on registry/2nd sample in transplant center)	D.5.3.3.1.3.2 High resolution typing	HLA-A/B/C and DRB1 typing at high resolution Include additional loci and/or resolution levels if required by transplant protocol. I5 Crossmatching must be performed if required by the Transplant Protocol
Cord (verification typing)	D.5.3.3.1.4 Low res A,B High res DRB1	I4.4 Low res A,B High res DRB1 Extended typing if required by the transplant protocol I5 Crossmatching must be performed if required by the Transplant Protocol

*As defined in transplant center agreement including any additional loci or resolution.

*ASHI standard D.5.3.3.1.1 - Laboratories must type the specified HLA loci at the specified level of resolution as defined in their HLA testing agreements with the transplant center(s). Testing agreements may require more stringent HLA typing resolution based on the standards of the specific accrediting organization(s) /registries that dictate transplant center practices. For example, high resolution typing of one or more loci may be required even if HLA identity at low resolution between donor and recipient is confirmed via descent in family studies.

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

ASHI standards are currently under CMS review and expected to be released in the near future.

Evidence:
HLA typing results must be available to the inspector to verify the use of the appropriate resolution and the performance of verification typing.

Example(s):
Clinical Programs performing allogeneic cellular therapy are encouraged to create broad policies and SOPs related to the various HLA typing that may or may not be relevant to specific settings.

While only the HLA loci specified in this standard are required, testing other loci may be useful for selecting donors. For example, typing for additional loci may be useful for assigning alleles and narrowing down the number of potential donors to test at high resolution. There may even be future studies demonstrating that other loci have an impact on patient outcomes. However, there is no clear mandate for testing additional loci at this time.

STANDARD:

B6.4.12.1 DNA high resolution molecular typing shall be used for DRB1 typing.

Example(s):
A Clinical Program may choose to use high resolution typing for Class I and Class II genes other than DRB1 also.

In the case of related donors, it may be possible to deduce that parents are heterozygous for DRB1 at low resolution when all four parental haplotypes are identified. ASHI Standards allow for this assessment by testing enough relatives to determine genotypes for recipient and donor. The Clinical Program may wish to use this approach for related donors so long as it is in accordance with HLA typing accreditation guidelines and follows the planned deviation process.

STANDARD:

B6.4.12.2 Verification typing shall be performed on the selected allogeneic donor using an independently collected sample. Results shall be confirmed prior to administration of the preparative regimen.

B6.4.12.3 There shall be a Standard Operating Procedure to confirm the identity of cord blood units if verification typing cannot be performed on attached segments.

Explanation:
Verification typing does not need to be performed on all potential donors, but it is required for the final selected donor. Results must be available and confirmed prior to administration of the preparative regimen so that any discrepancies may be resolved in advance. Verification typing should be performed according to ASHI or EFI standards. Repeat testing of HLA-A, B and DRB1 is usually sufficient to establish identity. The same resolution is not required for the verification typing.

Although HLA laboratories perform the technical work of HLA typing, Clinical Programs are responsible for qualifying those laboratories for performing work in accordance with applicable laws and regulations and these Standards.

Example(s):
High resolution typing for DRB1 is required; however, the verification typing can be performed at low resolution. There must be concordance between the two results.

STANDARD:

B6.4.12.4 There shall be a policy for anti-HLA antibody testing for mismatched donors and recipients.

Explanation:
This standard refers only to the testing of the mismatched recipient for antibodies against the donor in the event there are mismatched donors and recipients. The Clinical Program must have a policy to define when the program performs such testing and who will be tested for specific antibodies.

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

STANDARD:

B6.4.13 Allogeneic donor eligibility, as defined by applicable laws and regulations, shall be determined by a physician after history, exam, medical record review, and testing. The donor eligibility determination shall be documented in the recipient's medical record before the recipient's preparative regimen is initiated and before the allogeneic donor begins the mobilization regimen.

B6.4.14 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

Example(s):
For products that are manufactured in or distributed for use in the U.S., FDA requires that an accompanying statement of authenticity be present for records translated into English.

STANDARD:

B6.4.15 The use of an ineligible allogeneic donor, or an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of the rationale for his/her selection by the transplant physician, urgent medical need documentation, and the informed consent of the donor and the recipient.

Explanation:
If chosen allogeneic donors are ineligible according to applicable laws and regulations or do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented. There must also be documentation in the medical record by the transplant physician of urgent medical need for the cellular therapy product. There should be clear documentation of the intended recipient and informed understanding of the donor.

Urgent medical need means that no comparable stem cell or cellular therapy product is available and the recipient is likely to suffer death or serious morbidity without the stem cells or cellular therapy products. The product should be accompanied by a summary of records to the Collection and Processing Facilities stating reasons the donor is ineligible, including results of health history screening, physical examination, and results of infectious disease testing.

FDA regulations and the Standards require labeling with a biohazard legend for cellular therapy products collected from ineligible donors with the statement "Warning: Advise patient of communicable disease risk" and in the case of reactive test results, "Warning: Reactive test results for (name of disease agent or disease)." This regulation for urgent medical need or labeling does not apply to an autologous donor. For additional information regarding labeling of products, see Appendix II of the Standards.

Evidence:
The rationale and informed consent for a specific donor who did not meet the institution's donor criteria should be available to the inspector for verifying the appropriate urgent medical need documentation and labeling.

Example(s):
According to U.S FDA Final Guidance ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Product [HCT/Ps]," August 2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This guidance document is available at:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm.

Conditions other than communicable diseases would include, but are not limited to, a recipient or donor with inherited, acquired, or immunological conditions.

STANDARD:

B6.4.16 Allogeneic donor eligibility shall be communicated in writing to the Collection and Processing Facilities.

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

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

Explanation:
There should be a written SOP covering the creation and retention of allogeneic donor records. The recipient records would be regulated by the clinical standards regarding patient care. The policy should address the following:

- For each donor, there should be a record containing:
  - The donor identification (first name, family name, and date of birth).

- Age, sex, and medical and behavioral history (the information collected must be sufficient to allow application of exclusion criteria, where required).
- Consent/authorization form(s), where applicable.
- Clinical data, laboratory test results, and the results of other tests performed.
- The donor's eligibility and suitability. For unrelated donations, when the organization responsible for collection has limited access to recipient data, the Clinical Program must be provided with donor data relevant for confirming eligibility.

- All the records should be clear and legible, protected from unauthorized amendment and retained and readily retrieved in this condition throughout their specified retention period in compliance with data protection legislation.
- Donor records required for full traceability must be kept for a minimum duration as dictated by institutional practice and/or governmental regulatory requirements.

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

B7: RECIPIENT CARE

STANDARD:

B7.1 *Recipient informed consent for the cellular therapy shall be obtained and documented by a licensed health care professional familiar with the proposed cellular 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 verify the final availability and suitability of a donor or cellular therapy product prior to initiating the recipient's preparative regimen.*

Explanation:
Due to the potentially serious toxicity associated with preparative regimens, Clinical Programs must verify that cellular therapy products or suitable donors will be available prior to administering preparative regimens.

There are risks involved in the distribution of cellular therapy products, such as damage to the product container and significant warming events. Loss of a product intended for a recipient who has already received his/her preparative regimen affects the recipient's safety. Ordinarily, cryopreserved cellular therapy products should be chosen, ordered, and transported and/or shipped early enough in the process that the unit(s) will be on-site prior to the start of the preparative regimen. In the event there are problems encountered during transport and/or shipping or discovered upon arrival of the product, the recipient will not be at risk.

Cellular therapy products should be assessed to confirm quality and adequacy of dose. A responsible member of the Clinical Program must review donor information to confirm HLA typing, consent, eligibility, and any other issues are correct and documented.

Evidence:
SOPs, standardized orders, and checklists (with signatures) are examples of preinspection documentation that may provide evidence this standard is met. Alternatively, Clinical Programs may include a description of a process evident in dictated notes.

STANDARD:

B7.2.1 *The Clinical Program shall notify the Processing Facility prior to requesting a cellular therapy product from a cord blood bank, registry, or other facility.*

Explanation:
Cellular therapy products obtained from registries or manufacturers outside of the cellular therapy program may differ in important ways for which the Processing Facility must be prepared. Required preparations may include special storage arrangements, necessary supplies and reagents, and developing personnel competency in order to process the product for administration while protecting cell viability and product safety. Refer also to B1.2 if novel cellular products provided by third parties will be implemented.

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STANDARD:

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

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

STANDARD:

B7.4 *There shall be a policy addressing safe administration of the preparative regimen.*

Explanation:
Preparative regimens encompass various modalities, such as biologic, radiologic, and chemotherapy. It is recommended that a tracking system regarding mixture, delivery, and completed administration be instituted for all these regimens . Staff administering the preparative regimen shall be appropriately credentialed as defined by institutional policies and in accordance with governmental laws and regulations.

If there are differences between inpatient and outpatient processes, these should be addressed in applicable SOPs and specified on pre-printed or electronic orders used by the Clinical Program.

Example(s):
Administration of chemotherapy in the preparative regimen context requires specific policy(ies) for safe administration due to the risk of adverse outcomes related to high doses. The policy(ies) must include timing and clearance of chemotherapy agents.

Melphalan is an example of a chemotherapy drug that requires careful timing of administration and for which there should be a written policy and pre-printed or electronic orders for administration. One formulation must be reconstituted and infused within a 60-minute period; a newer formulation remains stable for five hours (or more if refrigerated).If a Clinical Program begins collaboration on immune effector cell programs with hematologists/oncologists not experienced with cellular therapy, some explanation of the preparative regimen will be necessary. For example, lymphodepletion is currently supported in medical literature to reduce tumor bulk before administration of CAR-T cells. Use of anti-tumor conditioning chemotherapy regimens may also enhance tumor antigen presentation and improve the persistence and function of the CAR-T cells (Davila & Brentjens, *CAR Therapy for CLL: What are the Challenges?*, Hematol Oncol Clin North Am. 2013 Apr: 27(2): 341-353, doi: 10.1016/j.hoc.2012.12.004).

STANDARD:

B7.4.1 *The treatment orders shall include the patient height and current weight, specific dates of administration, daily doses (if appropriate), and route of administration of each agent.*

Explanation:

It is recognized that treatment orders must be approved by various individuals; however, the height and current weight should be measured and recorded before treatment administration. The Clinical Program should also have a policy regarding when it is more appropriate to use Body Mass Index (BMI), ideal body weight, or other calculation (e.g., adjusted body weight) on the treatment orders. Verification of Body Surface Area (BSA), automated or verified by a second qualified designee (e.g., pharmacy), should be performed.

STANDARD:

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

Explanation:

A protocol or standard of care-specific set of orders that are preprinted and readily available in written or electronic form is an important measure of control; however, it is still critical that the drug doses are verified and documented by an attending physician prior to transmitting the order to the pharmacy.

Evidence:

It is recommended that the Clinical Programs implement a SOP containing a process for regular review of preprinted orders or electronic equivalents and incorporate the review into the audit process.

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

STANDARD:

B7.4.3 *The pharmacist preparing the drug shall verify and document the doses against the protocol or standardized regimen listed on the orders.*

B7.4.4 *Prior to administration of the preparative regimen, one (1) qualified person using a validated process or two (2) qualified people shall verify and document the drug and dose in the bag or pill against the orders and the protocol or standardized regimen, and the identity of the patient to receive the therapy.*

Explanation:

Even if a validated electronic system is used (e.g., bar coding), there must be a method to document the verification of the drug and dose in the final container against the orders and the protocol, and the identity of the recipient to receive the chemotherapy by a qualified person.

Written instructions should be available for reconstitution, dilution, mixing, labeling, and packaging. There should be a standard process in place to retrieve the batch number and expiry of all drugs and diluents used in the preparation of the therapy regimens.

Evidence:

Copies of standard treatment or research protocols in areas of recipient care such as inpatient and outpatient units and the pharmacy can provide evidence of compliance. Specific patient charts can be used to check that treatment orders and documentation are compliant with the guidelines. In case of time-sensitive chemotherapy agents (e.g., Melphalan), the inspector may review documentation of the time elapsed between drug reconstitution and administration.

There should be written documentation by the two (2) staff members that they have verified the drug and dose against the orders and the protocol, as well as the recipient's identity.

While touring patient care areas, the inspector may also ask the pharmacists about their normal practice and if they retain ultimate responsibility for verification against the protocol or standard regimen listed on the orders. Nurses may be asked about the normal procedures for treatment administration to confirm this.

STANDARD:

B7.5 *There shall be a policy addressing safe administration of radiation therapy.*

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

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

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

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

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

Explanation:
"In writing" as used in the Standards includes electronic documentation. Information from the radiation oncology consultation, including factors that may increase the toxicity of the radiation, should be discussed with the patient and informed consent should be documented.

Evidence:
Written information available to the radiation oncologist, the radiation oncology consult, and radiation report at the end of treatment can be reviewed in recipient's chart. Documentation that the radiation was given on a specific date and its dose can be compared to the consultation documentation. The inspector can also ask to see copies of treatment protocols that include radiation and verify the protocol by comparing it to patient charts.

STANDARD:
B7.6 *There shall be a policy addressing safe administration of cellular therapy products.*

Explanation:
Non-cryopreserved (often referred to as "fresh") cellular therapy products must be administered within the time specified by Clinical Program policies, registry and tissue bank requirements, and applicable laws and regulations. Thawed product administration should be completed as soon as possible. It may be optimal to thaw individual bags to reduce the time thawed products sit before administration.

Clinical Programs must identify appropriate timeframes between the end of the preparative regimen and administration of the cellular therapy product to confirm that the administered product is not affected by the preparative regimen. The program must verify that the preparative regimens were given at the scheduled time and delay administration of the cells if required. Programs are responsible for communicating with the Processing Facility regarding any delayed administration.

Clinical Programs need to determine the composition of the cellular therapy product to determine how it should be prepared for administration. Characteristics of the product, including the cell source (e.g., marrow, peripheral blood, or cord blood), cell counts, etc. should be taken into consideration. Unless otherwise specified, the B7.6 standards apply to all products. Programs should work with their Processing Facilities to verify appropriate processing and preparation of the product for administration.

Evidence:
Staff should be prepared to discuss their normal practice and their training in the administration of cellular therapy products. Specific patient charts can be used to determine that two persons checked the product and that the documentation in the chart is complete. If there is time and an administration is scheduled on the day of inspection, the inspector should be notified so that he/she may watch parts of the procedure. If not, a mock procedure should be performed for inspector observation.

Example(s):
Autologous transplants may include significantly more administration of DMSO, and allogeneic bone marrow may include administration of significantly more ABO incompatible red blood cells.

One way Clinical Programs can communicate date and time of administration to the Processing Facility is to use a facesheet or other written documentation of the start and end date of the preparative regimen and the date and time, if needed, of the cellular therapy product administration. If plans change, updated information is provided to the laboratory prior to the planned day of administration.

Monitoring of vital signs is generally part of routine hospital policy for blood products; however, given the potential for administration reactions (e.g., hypoxia, bradycardia, hypertension.), the Clinical Program should monitor vital signs at least one hour after administration. Some cellular therapies are known to elicit early adverse reactions.

The policy must also address failure of the cellular therapy product to graft. Management might include back-up plans such as an alternative donor, repeating a collection procedure, or performing an emergency marrow collection.

STANDARD:

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

Explanation:
Clinical Programs need to determine the appropriate volume, DMSO (and other additives), and red cell load for recipients. Volume issues will differ depending on the cellular therapy product. Clinicians must consult with the Processing Facility to make clinical decisions based on methods of cellular therapy product preparation.

STANDARD:

B7.6.2 *There shall be a policy for the infusion of ABO-incompatible red cells in allogeneic cellular therapy products.*

B7.6.3 *There shall be consultation with the Processing Facility regarding cord blood preparation for administration.*

B7.6.3.1 *Cord blood units that have not been red cell reduced prior to cryopreservation shall be washed prior to administration.*

Example(s):
For cord blood units, the NMDP requires washing of red cell replete CB units due to unexpected adverse events.

STANDARD:

B7.6.3.2 Cord blood units that have been red cell reduced prior to cryopreservation should be diluted or washed prior to administration.

B7.6.4 Two (2) qualified persons shall verify the identity of the recipient and the product and the order for administration prior to the administration of the cellular therapy product.

B7.6.5 For transplants utilizing cellular therapy products from more than one donor, the first cellular therapy product shall be administered safely prior to administration of the second cellular therapy product.

Explanation:
In the case of transplants using more than one cellular therapy product (e.g., double cord blood transplant), the program must wait to administer the second product until it is determined that the first unit was administered safely with no adverse events.

Example(s):
For double cord blood transplants, preferably the second unit should not be thawed until administration of the first unit is completed and the Clinical Program is reasonably certain that no adverse reactions are occurring.

STANDARD:

B7.6.6 There shall be documentation in the recipient's medical record of the administered cellular therapy product unique identifier, initiation and completion times of administration, and any adverse events related to administration.

B7.6.7 A circular of information for cellular therapy products shall be available to staff.

Example(s):
The inter-organizational Circular of Information for the Use of Cellular Therapy Products may be used to fulfill this requirement. The current version can be found on the FACT website.

STANDARD:

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

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

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

B7.7.3 Monitoring of infections and use of antimicrobials.

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

B7.7.5 Monitoring of graft failure and institution of treatment.

Explanation:
Administration of preparative regimens and HPC is known to be associated with diverse and potentially serious complications. Clinical Programs are expected to have a system in place to monitor for these complications and provide appropriate courses of action if they occur. Written policies and SOPs addressing appropriate management plans, developed after critical review of current literature and thoughtful deliberations, will enable the clinical team to have increased consistency in management approach and enhanced quality improvement. To allow for the flexibility often needed in clinical practice, the program may choose to address these critical elements of post-transplant management in the form of clinical guidelines rather than SOPs (see also Standard B5.1).

STANDARD:

B7.7.6 Allogeneic recipients should be assessed regularly for evidence of acute GVHD using an established staging and grading system.

B7.7.7 Allogeneic recipients should be assessed regularly for evidence of chronic GVHD using an established staging and grading system.

Explanation:
Adverse events attributable to acute or chronic GVHD occur within and outside of the 100-day post-transplant window. GVHD should be assessed at the transplant center, with close communication with the referring physician. Weekly assessment for the first three post-transplant months for acute GVHD as clinically indicated is generally recommended. Thereafter less frequent assessment and documentation is widely accepted as standard of care; however, a minimum frequency of at least every three months during the first year post-transplant is recommended for assessment of chronic GVHD and late effects.

SOPs should include post-transplant vaccination schedules and indications, as well as procedures for monitoring late effects. GVHD staging and grading and post-transplant surveillance for late effects should be documented in the recipient's medical record.

Example(s):
Examples of established GVHD grading systems include the NIH consensus criteria for chronic GVHD and the CIBMTR data management guidelines.

STANDARD:

B7.8 There should be policies and Standard Operating Procedures in place for planned discharge and provision of post-transplant care.

B7.8.1 The Clinical Program shall refer planned discharges and post-transplant care to facilities and health care professionals adequate for post-transplant care.

B7.8.1.1 Recipients that have not achieved hematological stability shall only be discharged to Clinical Programs that met these Standards.

B7.8.2 *The Clinical Program shall provide or secure oversight of care that meets applicable standards.*

B7.8.3 *The Clinical Program shall provide appropriate instructions to recipients prior to discharge.*

B7.8.4 *There should be policies and Standard Operating Procedures in place for post-transplant vaccination schedules and indications.*

Explanation:
Discharges should normally take place after recipients have achieved clinical and hematological stability. A Clinical Program may adopt a policy of discharging recipients before they have achieved clinical and hematological stability, with ongoing inpatient care undertaken by another clinical unit. In these instances, the standard of care at a receiving unit should be equivalent to that of the accredited program, with similar policies and SOPs which should be made available to the inspection team. Equally, a program may adopt a policy of post-transplant care to be delivered in local and regional facilities. These patients must receive care according to established guidelines and with documented oversight of the cellular therapy program.

Evidence:
The working relationships between the Clinical Program and receiving unit should be clearly documented, including explicit criteria for transfer back to the transplant center. There should be a policy or SOP describing criteria for referring patients to other facilities or care providers, and oversight of care by the transplant center.

Programs should provide a thorough justification for the necessity of the shared care arrangement within their QM Plan and monitor patient outcomes under this type of arrangement.

Inspectors will determine how and if the Clinical Program adequately evaluates that receiving facilities are adequate for post-transplant care and have the right to arrange direct inspection of receiving facilities to confirm compliance with the Standards. Audit and outcome data related to the shared care arrangement may be requested.

Example(s):
A shared care arrangement may be justified by a balance of clinical, economical, and geographical factors that clearly benefit overall patient care without compromising safety.

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

Explanation:
Extracorporeal photopheresis (ECP) is a leukapheresis-based immunomodulatory therapy used in the treatment of acute and chronic graft versus host disease (GVHD), along with other non-transplant indications involving the separation of leukocytes by apheresis followed by addition of a psoralen, usually 8-methoxypsoralen (8-MOP) and exposure to UVA light. It is probable that inspectors will increasingly encounter the use of ECP within and associated with transplant programs undergoing inspection, both within and outside of clinical trials.

There are different methodologies for ECP that include both closed and open circuits. In the former, which is the most common, collected leukocytes remain integral to the circuit of the cell separator, while a minority of ECP procedures involve detaching, the leukapheresis product at some point (e.g., for addition of psoralen and/or UV irradiation).

STANDARD:

B7.9.1 *There shall be a consultation with the facility or physician that performs ECP prior to initiation of therapy.*

Explanation:
If ECP is a part of therapy for GVHD or other indications for BMT patients within a Clinical Program or Collection Facility applying for FACT or JACIE accreditation, the activities must meet the Standards as they apply. However, it is quite common for patients requiring ECP to attend a hospital or unit (such as dermatology) that may have no other relationship with the program aside from the provision of ECP. If ECP is performed at a site not applying for accreditation, then the program must be able to demonstrate a written agreement that meets the requirements in B7.9.

The term "consultation" in this standard is interpreted broadly. Clinical Programs that perform ECP within their own programs must still review the patient's medical status in relation to how it presents a need for ECP and how the therapy should be administered.

Example(s):
Clinical Programs may perform ECP within their own facilities, utilize a separate unit of the hospital, or refer patients to an external facility. When not performed within the program itself, written agreements must require compliance with the Standards.

STANDARD:

B7.9.2 *Before ECP is undertaken, there shall be a written therapy plan from an attending physician specifying the patient's diagnosis and GVHD grade, involved organs, timing of the procedure, and any other factors that may affect the safe administration of ECP.*

B7.9.3 *A report of the details of ECP administered, including an assessment of the response, shall be documented in the recipient's medical record.*

Explanation:
The provision of ECP is not required of Clinical Programs; however, if it is used as a treatment for cellular therapy patients, it must comply with the Standards.

It is acceptable for the transplant physician to rely on the ECP provider to create the therapy plan; however, the physician must confirm that a treatment plan has been established and agree to the details prior to the intended procedure.

If national or international standards in ECP are available, they should be incorporated into organizational or transplant program policies and SOPs.

Evidence:
Inspectors should review patient medical records of ECP, both in the instance of an internal or external service, to determine the requirement for administration and response assessment are met. The inspector is not required to review records on site if the facility is external. However, the therapy plan and documentation of the date and regimen of administered ECP must be included in the recipient's medical record and can be compared to the consultation documentation. The inspector can also ask to see copies of treatment protocols that include ECP and verify the protocol by comparing it to patient medical records.

Example(s):
The Clinical Program may decide the frequency with which to report ECP in the patient's medical record. This will depend on the therapy plan; for example, depending on the length of the therapy regimen, reports may be created after every procedure, monthly, etc.

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

- Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, Ayuk F, Kiani A, Schwerdtfeger R, Vogelsang GB, Kobbe G, Gramatzki M, Lawitschka A, Mohty M, Pavletic SZ, Greinix H, Holler E. Biol Blood Marrow Transplant. 2011 Jan;17(1):1-17.
- Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process. Pierelli L, Perseghin P, Marchetti M, Messina C, Perotti C, Mazzoni A, Bacigalupo A, Locatelli F, Carlier P, Bosi A; Società Italiana di Emaferesi and Manipolazione Cellulare (SIdEM); Gruppo Italiano Trapianto Midollo Osseo (GITMO). Transfusion. 2013 Oct;53(10):2340-52.
- Extracorporeal photopheresis for treatment of adults and children with acute GVHD: UK consensus statement and review of published literature. Das-Gupta E, Dignan F, Shaw B, Raj K, Malladi R, Gennery A, Bonney D, Taylor P, Scarisbrick J. Bone Marrow Transplant. 2014 Jun 2.
- Diagnosis and management of chronic graft-versus-host disease. Dignan FL, Amrolia P, Clark A, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Shaw BE, Potter MN; Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. Br J Haematol. 2012 Jul;158(1):46-61.
- Diagnosis and management of acute graft-versus-host disease. Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Hadzic N, Shaw BE, Potter MN; Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. Br J Haematol. 2012 Jul;158(1):30-45.

- Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, Szczepiorkowski ZM, Williams ME, Wu Y, Shaz BH. J Clin Apher. 2013 Jul;28(3):145-284.

STANDARD:

B7.9.4 *The facility performing ECP shall follow written Standard Operating Procedures appropriate for the clinical condition of the patient.*

Explanation:

Clinical Programs performing ECP must have an SOP for the ECP procedure. For those programs referring patients to external facilities, written agreements should require that the facilities follow a written procedure including a written informed consent. The intent is not to dictate how ECP is performed, but that it is performed in accordance with established processes.

STANDARD:

B7.10 *There shall be policies and Standard Operating Procedures addressing the administration of immune effector cells and management of complications, if applicable.*

B7.10.1 *There shall be a consultation with the referring physician prior to initiation of immune effector cellular therapy to review the goal and plan of the treatment.*

B7.10.2 *There shall be regular assessment of the recipient to detect complications, including cytokine release syndrome and neurologic dysfunction.*

Example(s):

In addition to IND requirements, investigator experience may generate ideas for detecting complications. Attending physicians may want to request additional laboratory testing, such as C-reactive protein, lactate dehydrogenase, ferritin, and fibrinogen. For example, evaluating fibrinogen periodically after CAR administration may be useful for early detection of disseminated intravascular coagulation (DIC).

STANDARD:

B7.10.3 *There shall be a written plan for rapid escalation of care, increased intensity of monitoring, and relevant workup to address complications.*

B7.10.4 *Communication to the clinical staff, intensive care unit, emergency department, and pharmacy shall be timely.*

B7.10.5 *The Clinical Program shall have written guidelines for management of complications, including the use of cytokine-blocking agents and corticosteroid administration.*

Explanation:
Immune effector cellular therapy is increasingly being used for clinical treatment of refractory or relapsed malignancies with promising outcomes. While there are different forms of immune effector cellular therapy being used, they share important immune-related features that Clinical Programs should be cognizant of and be prepared to manage. The risk of severe cytokine release syndrome following such therapy is an example, which could occur after either immune effector cellular therapy or transplant of HPC replete with immune effector cells (see, for instance, Severe Cytokine-Release Syndrome after T Cell-Replete Peripheral Blood Haploidentical Donor Transplant is Associated with Poor Survival and Anti-IL-6 Therapy is Safe and Well Tolerated. Ramzi Abbouda, Jesse Kellera, Michael Sladea, John F. DiPersio, Peter Westervelt, Michael P. Rettig, Stephanie Meier, Todd A. Fehniger, Camille N. Abboud, Geoffrey L Uy, Ravi Vij, Kathryn M. Trinkaus, Mark A. Schroeder, Rizwan Romee. BBMT, in press, http://www.bbmt.org/article/S1083-8791(16)30145-8/abstract). The best practices for immune effector cellular therapy are still being developed by practitioners in the field and are expected to change with experience, but programs that administer immune effector cellular therapy must have current policies and SOPs that address critical aspects of such therapy and to promote the safety of its recipients.

STANDARD:

B7.11 *There shall be policies and Standard Operating Procedures in place for provision of appropriate long-term follow-up care to recipients.*

B7.11.1 *There shall be policies and Standard Operating Procedures for monitoring by appropriate specialists of recipients for post-cellular therapy late effects, including at a minimum:*

B7.11.1.1 *Endocrine and reproductive function and osteoporosis.*

B7.11.1.2 *Cardiovascular risk factors.*

B7.11.1.3 *Respiratory function.*

B7.11.1.4 *Chronic renal impairment.*

B7.11.1.5 *Secondary malignancies.*

B7.11.1.6 *Growth and development of pediatric patients.*

B7.11.2 *There shall be a policy describing the transition of long-term pediatric recipients to adult care as appropriate.*

B7.11.2.1 *There shall be a policy describing the acceptance of pediatric recipients into a long-term follow-up clinic for adults.*

Explanation:
Long-term follow-up care is a critical component of the comprehensive care that the Clinical Program is responsible for providing to recipients of cellular therapy. Long-term follow-up is essential for detecting and managing late effects of cellular therapy and it requires expertise that is different from that for acute care of recipients.

Late effects may include endocrine and reproductive function (new onset diabetes, thyroid dysfunction, hypogonadism), osteoporosis, cardiovascular risk factors (hypertension, dyslipidemia, metabolic syndrome, lifestyle factors), respiratory function, chronic renal impairment and secondary cancers. Growth and development late effects should specifically be monitored in pediatric patients.

To underscore the importance of this aspect of care, the following elements have been introduced as a new Standard in this edition: 1. Establishment of long-term follow-up guidelines for care and a plan for long term follow-up of both allogeneic and autologous patients. 2. Pediatric programs must include plans for transitioning patients to adult care, and 3. Adult transplant programs must have a plan to accept patients transplanted elsewhere (including pediatric programs) into long-term follow-up.

The following publications may be used as references when establishing long-term follow-up guidelines for care of patients after HPC transplant:

- Lost in Transition: The Essential Need for Long-Term Follow-Up Clinic for Blood and Marrow Transplantation Survivors. Hashmi S, Carpenter P, Khera N, Tichelli A, Savani BN. Biol Blood Marrow Transplant. 2015 Feb;21(2):225-232.
- Hashmi, S. and Litzow, M. R. (2013) Late Effects after Allogeneic Hematopoietic Stem Cell Transplantation, in Blood and Marrow Transplantation Long-Term Management: Prevention and Complications (ed B. N. Savani), John Wiley & Sons, Ltd, Oxford, UK.

The establishment of a dedicated survivorship clinic for cellular therapy survivors is highly recommended but not required, as long as the medical issues outlined in the Standards can be adequately addressed. The Clinical Program shall have the responsibility to either perform long-term follow-up by themselves or monitor long-term follow-up data of its former recipients already discharged to the referring physicians. In the latter case, it will still be the responsibility of the program to coordinate the long-term care with the referring physicians so that the recipients will not be lost for follow-up.

Example(s):
The publication, *"Recommended Screening and Preventive Practices for Long-Term Survivors after Hematopoietic Cell Transplantation"* is a highly recommended guideline to follow. It is accessible at: http://www.ncbi.nlm.nih.gov/pubmed/22178693.

B8: CLINICAL RESEARCH

STANDARD:

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

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

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

B8.2 *Documentation for all research protocols performed by the Clinical Program shall be maintained in accordance with institutional policies and applicable laws and regulations, including audits; approvals by the Institutional Review Board, Ethics Committee, or equivalent; correspondence with regulatory agencies; and any adverse events and their outcomes.*

Explanation:

The purpose of these standards is to confirm that the Clinical Program is obtaining appropriate review of clinical research protocols.

Investigational drugs should be secured in storage dedicated to investigational products, and clearly labeled as investigational products.

There are a variety of ways to manage cellular therapy products. Management in a cellular therapy Processing Facility may be beneficial due to staff experience, storage facilities, and validated procedures. Clinical Programs may choose to manage cellular therapy products in hospital pharmacies, and take responsibility for safe handling to protect the product and recipient.

Evidence:

The inspector may ask about the process for review of protocols, ask which Institutional Review Board (IRB) or Research Ethics Committee (REC) is used by the Clinical Program, and examine the regulatory binder for a specific study. A signed consent form in one of the patient charts can be used to cross check approval dates with IRB regulatory agency documents. If the center carries out any studies under Investigational New Drug (IND) or IDE (Investigational Device) application or non-U.S. equivalent, the regulatory binder for such studies needs to be available.

Example(s):

A Clinical Program may use its host institution's shared resources to manage its regulatory files and clinical research operations, or a program may have its own clinical research office that manages all aspects of its clinical research studies. One aspect requiring management is clinical research monitoring by institutional monitors, independent monitors contracted by industry, national cooperative group monitors, lead research center monitors, etc.

Appropriate governmental authorities include the Office for Human Research Protections under the Department of Health and Human Services and/or the FDA (U.S.) and national Research Ethics Committees (Europe) Furthermore, gene-modified immune effector cellular therapy products, such as CAR products, may also be considered gene therapies by IRBs and the Recombinant DNA Advisory Committee (RAC), which is applicable to investigators supported by the National Institutes of Health [NIH]) in the U.S.

STANDARD:

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

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

B8.3.2 *Informed consent for a research subject shall contain the following elements at a minimum and comply with applicable laws and regulations:*

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

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

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

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

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

Explanation:

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

Language the subject can understand shall be conveyed via the process of informed consent in accordance with applicable laws and regulations and institutional policy. This may include the grade-level of laymen's terms, cultural considerations, assent, language translation and interpretation, etc.

Detailed information about the scope of the clinical research, such as if the research is conducted at single or multiple sites, may influence the subject's decision as to whether or not to participate. In the U.S., sources such as clinicaltrials.gov are required by the informed consent process.

Evidence:

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

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

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

Explanation:
The purpose of this standard is to require that the Clinical Program have a conflict of interest policy. Examples of conflicts include financial, academic, or any other incentive that would unduly influence the clinical investigator to enroll patients on clinical research protocols.

Evidence:
The inspector may request to review the Clinical Program's or institution's conflict of interest policy to evaluate whether it is consistent with regulatory requirements.

Management plans for identified Conflicts of Interest (COI) shall exist in accordance with applicable laws and regulations and institutional policies and SOPs. COI policies and SOPs shall be reviewed in conjunction with informed consent processes. Plans for managing identified conflicts of interest may vary according to applicable laws and regulations.

Example(s):
The Clinical Program may follow its institution's policy on conflicts of interest or develop its own policy.

A clinical research investigator may have a potential conflict of interest in a product used in a clinical trial in which the investigator is participating, such as stock ownership, advisory boards, speaker's bureaus, or research funding. A COI management plan might include divulging the information to participating subjects, depending on governmental and institutional mandates.

In the U.S., CFR Part 54 applies.

B9: DATA MANAGEMENT

STANDARD:
B9.1 *The Clinical Program shall collect all the data necessary to complete the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A forms of the EBMT.*

Explanation:
FACT and JACIE acknowledge the importance of complete and accurate data for self-assessment in individual Clinical Programs, for research and outcome reporting, and for compliance with the Standards.

Over the years, both FACT inspectors and CIBMTR auditors have continued to observe some Clinical Programs and personnel who struggle with data accuracy and completeness. The two organizations are collaborating to help FACT-accredited programs improve through intensified support between inspections, increased emphasis on implementation of corrective action plans, and follow up to document continuous improvement. Commendable practices in data management will be widely shared.

CIBMTR audits will remain every four years as scheduled (unless a Clinical Program requests and pays for an interim special audit). Programs will respond to these audits to the principal auditor as usual and according to the time frames defined by CIBMTR. FACT will receive information from programs annually, and will manage the processes on an on-going basis, depending on the needs of the program. FACT on-site inspections will continue to occur every three years.
Initially, Clinical Programs will be given a grace period to show improvement in critical field and random error rates. During this time, programs will be expected to learn from prior difficult audits, design appropriate investigations, implement effective corrective actions, and follow up to ensure that improvements are sustained. This new process is designed to help programs identify the issues that may be barriers to improvement and to develop strategies to be successful. When this process has been fully implemented, FACT-accredited programs will be required to remain in good standing with the CIBMTR data audit program.

Clinical Programs also applying for FACT accreditation of their novel cellular therapy programs (such as CAR-T cell products or regenerative medicine) should use the appropriate CIBMTR forms for these therapies. CIBMTR frequently revises its forms to remain current in the rapidly evolving field of cellular therapy. Programs should use the forms that are appropriate for the novel cellular therapy products they administer. Some of these therapies have very specific forms and some are included on general cellular therapy forms.

Evidence:
All verification of the accuracy of data against source data will be performed by the CIBMTR audit teams on site according to their current practices and schedules. The current CIBMTR process will not change. FACT clinical inspectors will no longer perform a data audit during the on-site FACT inspection. This will eliminate the need for data sheets to be prepared only for FACT inspectors, and allow the clinical inspector to focus on adequacy of corrective actions and quality improvement.

The FACT-CIBMTR Data Audit Committee will review CIBMTR audit reports and corrective action plans to assess compliance with Standards, implementation of effective corrective action, and improvements. Timeliness and completeness of data submission will also be assessed by the committee using CPI reports from CIBMTR indicating "in good standing".

On-site, FACT clinical inspectors will have access to this information and CIBMTR reports. The expectation is that clinical inspectors will look at documentation of internal data audits and implementation of corrective action plans (CAP). Where data management is outstanding and there are no corrective action plans to review, the on-site inspectors may ask to see commendable practices that have resulted in exemplary data management.

The Clinical Program must also furnish evidence of its own periodic data audits to determine if data are accurate for evaluation of patient outcomes as specified in B4. The choice of data to be audited is a decision for the program but should include those listed in B4 at a minimum.

Example(s):
Some Clinical Programs reporting to the SCTOD are comprehensive report centers and some of their patients will have more detailed post-transplant reports instead of the post-Transplant Essential Data (TED) forms. Programs must still collect the data in the post-TED forms, which are covered in the comprehensive report forms.

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

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

STANDARD:

B9.1.1 *Clinical Programs shall submit the data specified in B9.1 to a national or international database if required by applicable laws and regulations.*

B9.1.2 *Clinical Programs should submit the data specified in B9.1 for allogeneic and autologous transplants to a national or international database.*

Explanation:
FACT and JACIE strongly recommend the publication of transplant data and strongly encourages the submission of transplant data to the CIBMTR or EBMT, as appropriate. Additionally, autologous patient data should be submitted. Standard B9.1 does not require that Clinical Program data be submitted to these registries; however, it does require that all data collected in the Transplant Essential Data (TED) or Comprehensive Report/Minimum Essential Data-A (MED-A) Form of the CIBMTR/EBMT be maintained by the program.

Evidence:
In the event that the Clinical Program does not submit data to these registries, it should provide reasonable explanations for not submitting the data.

Example(s):
Examples of the TED and Comprehensive Report Forms currently utilized by the CIBMTR may be found on the organization's website at www.cibmtr.org and examples of the MED-A forms currently utilized by the EBMT may be found on the organization's website at www.ebmt.org.

Allogeneic transplant patient information and outcomes are to be reported to the Stem Cell Therapeutics Outcome Database (SCTOD), managed by the CIBMTR, by all U.S. centers according to law. While autologous transplant information reporting is not mandatory, it is recommended. Clinical Programs in the U.S. may also receive transplant outcome data from the SCTOD.

STANDARD:

B9.1.3 *Clinical Programs should collect the data specified in B9.1 for all patients for at least one year following administration of the cellular therapy product.*

B9.2 *The Clinical Program should collect all data elements included in the applicable CIBMTR Cellular Therapy forms or EBMT forms.*

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

B10: RECORDS

STANDARD:

B10.1 *Clinical Program records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years.*

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

B10.1.2 *Cleaning and sanitation records shall be retained for at least three (3) years or longer in accordance with applicable laws or regulations, or by a defined program or institution policy. All other Clinical Program records shall be retained as in B10.1.*

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 laws and regulations for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration, whichever requires the longest maintenance period.*

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

Explanation:

Each Clinical Program has the flexibility to develop individualized systems of maintaining and organizing records as long as the objectives of the Standards are achieved. The methods for filing and transfer of records to archival storage should be specified in the SOP Manual.

Electronic records must be backed up on a regular basis and stored to prevent their loss. The Clinical Program must make provisions for all records to be maintained for the required period in the event that the program ceases operation.

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

Personnel training and competency records include all of the items referred to in B3 (Personnel), including licenses and/or board certifications for all transplant and consulting physicians in other specialties, licenses for all APPs, all letters documenting initial training, all competencies for procedural skills as routinely practiced in their facility, nursing training records, and the names of key individuals responsible for support services (coordinators, pharmacy, dietary, social services, physical therapy, and data management).

Facility maintenance records include all of the items referred to in B2 (Clinical Unit) including documentation of facility testing and validation for control of air quality and microbial contamination; dates and extent of repairs on mechanical systems; dates and extent of renovations and new construction; preventive maintenance on equipment; personnel responsible for cleaning and additional training records when required; safety training for biological, chemical, and radiation exposure and/or disposal; and the outcome of any building and/or clinical unit inspections for safety and/or compliance with governmental and/or other agencies.

Facility management records include management issues related to facility maintenance including a list of responsible individuals including job titles and areas of oversight and resolution of facility problems.

General facility records include global policies for the entire institution of which the Clinical Program is a part. These may include disaster plans; fire response and safety plans; biological, chemical, and radiation disposal policies; and confidentiality requirements.

Patient and donor files (either electronic or hard copy) include allogeneic donor eligibility determination files, including results and interpretation of testing and screening. These records must be maintained with a secure system that guarantees absolute confidentiality and is in compliance with applicable laws or regulations on confidentiality and data protection. The inspector should be alert to breaches in policy or security that potentially compromise patient confidentiality.

Patient and donor records must be maintained for a period of at least 10 years after administration (or if not known, after distribution, disposition, or expiration) or longer if required by applicable governmental laws and regulations.

Data to be provided to other facilities involved in the collection or processing of the cellular therapy product include adverse effects of administration, other adverse events related to the product such as transmission of infection, and engraftment data. Other data, such as temperature on arrival of products, may be required by the Collection and/or Processing Facilities.

Research records should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. If research records are stored independently of patient records, the same considerations regarding confidentiality apply. The sponsor of the research and/or governmental authorities may place specific requirements for long-term maintenance of research records.

An exception to the 10-year requirement for retention of Clinical Program records is for the documentation of cleaning and sanitation. These records only need to be retained for at least 3 years after creation but should include cleaning schedules, methods, and identification of personnel responsible for cleaning. There should also be documentation for the initial training and retraining of personnel as needed.

Evidence:
It is suggested that Clinical Programs have readily accessible records for at least quality control and personnel training and competency for the last three years for inspector review. A written SOP should indicate the methods for filing and transfer of records to on- or off-site archival storage and how and for how long records are archived.

Example(s):
In EU Member States, donor records required for full traceability must be maintained for a period of 30 years.

Records may be maintained in more than one location, provided that the records management system is designed to allow prompt identification, location, and retrieval of all records. However, it is recommended that recent records should be kept on-site and archived records should be readily accessible within a reasonable time frame relevant to the current operations of the facility.

Records may be maintained as original paper records, electronic files, photocopies, microfiche, or microfilm. Suitable equipment must be available for reading and/or photocopying records maintained on microfiche or microfilm.

In the case of gene-modified cellular therapy products, 15-year follow-up is required by the FDA. Consequently, records must be maintained for the duration of follow-up.

In the U.S., HIPAA regulations on confidentiality and data protection apply. In the European Union, the comparable law or regulation is Directive 95/46/EC.

STANDARD:
B10.4 ELECTRONIC RECORDS

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

Explanation:
The definition of an electronic record is, "A record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer." As programs utilize more electronic systems, it is important that they maintain a list of which ones are critical.

Electronic records are considered critical when any one of the following points occurs:

- Used as a substitute for paper.
- Used to make decisions based upon the data stored and/or created by the electronic record system (including outcome analysis).
- Used to make calculations via automated functions,

- Used to create and/or store information that are inputs into critical processes (whether the electronic record system is used during critical processes or used as source data for critical procedures).

It is not the intent of the Standards to include hospital-based systems and clinical medical records. These systems are typically inspected by hospital-based regulatory and accrediting organizations. Furthermore, Clinical Programs may not have the authority to direct validation studies on these systems. Any data system that does exist within the scope of control of the program is required to meet these standards.

Each Clinical Program must determine in advance whether the staff will depend on an electronic record or a paper record to perform a regulated activity. This determination should be documented for all records created and maintained by the facility.

Evidence:
Inspectors should assess the Clinical Program's list of critical electronic record systems to confirm it includes all electronic record systems used by the facility that meet the criteria in this standard. Additionally, a list that matches critical record types to specific record systems should be provided preinspection (e.g., electronic laboratory record versus paper eligibility record).

The inspector should determine the scope of electronic records used by the Clinical Program and any circumstances where the electronic record is used as a substitute for a paper record.

If electronic records are used in addition to paper records, the inspector should evaluate the electronic records to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.
- The system has limited access by authorized individuals.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.
- Documentation that the individuals performing the development, maintenance, or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- The electronic system is not the sole method for storing or retrieving needed records.

Example(s):
Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

If an electronic record of the location of a cellular therapy product in storage is printed for the chart and the information is verified by a signature or initials, and this printed record is then used by personnel to retrieve the product at the time of distribution, the electronic record is not considered to have been used as a substitute for a paper record.

If a computerized system (word processor) is used to generate SOPs, validation is not required since the quality and safety of a cellular therapy product would not be directly affected. However, if a computerized system is used to make a critical calculation (i.e., T cell dose, DMSO concentration, CD34 cell recovery) and the electronic calculation is the only calculation performed, validation is required to assure that the calculation is always performed correctly under any circumstances. However, if the computerized calculation is used to confirm a manual calculation, and the manual calculation is used for manufacturing purposes, the extent of validation need not be as extensive as in the previous example.

In the U.S., for electronic records used as a substitute for paper, the inspector should refer to the FDA document Part 11, Electronic Records; Electronic Signatures - Scope and Application, for guidance to assess the validation procedures (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072322.pdf), as well as the applicable requirements of HIPAA. In the European Union, the inspector should refer to the Model Requirements for Electronic Records and Document Management (MoReq) (http://ec.europa.eu/).

STANDARD:

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

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

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

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

B10.4.6 *For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation in the event that critical electronic record systems are not available. The alternative system shall be validated and Apheresis Collection Facility staff shall be trained in its use.*

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

B10.4.7.1 *A method shall be established or the system shall provide for review of data before final acceptance.*

Explanation:

The final review and acceptance of entered data does not require a second individual to verify the data. Nor does the identification of individuals responsible for record entries need to be automated. The intent of the standard is to be certain all data is verified to be correct and to maintain documentation of who has entered pieces of information.

STANDARD:

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

Example(s):
To identify individuals responsible for record entries, several options exist. Examples include using a sign-in sheet when using the system or using a worksheet to create an audit trail of each data element. More sophisticated systems usually have an automated system that tracks record entry based upon an individual's log-in credentials.

STANDARD:

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

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

Explanation:
Establishment of an electronic record keeping system requires validation. The extent of validation is somewhat dependent upon whether the computerized system was developed in-house, custom-built by an outside vendor/consultant, or developed from off-the-shelf software. More importantly, the extent of validation is dependent upon whether the electronic records are used as a substitute for paper records. When computers are used to generate paper printouts of electronic records, and the printouts are the "official" records used for the performance of further activities, the electronic records are not considered to be used as a substitute for paper records. If hard copies are scanned, there shall be a program that creates searchable documents to facilitate inspection and review.

The decision to validate a computerized system, and the extent of validation, should be determined by a documented risk assessment regarding the potential of the system to affect the quality and safety of a cellular therapy product and/or the integrity of a record. Finally, if hard copies are scanned, there shall be a program that creates searchable documents to facilitate inspection and review.

When electronic records are used as a substitute for paper, validation procedures include such things as:

- Documentation of development requirements and function.
- Verification that calculations are performed correctly.
- Evidence that records reproducibly contain the desired information.
- Tests of system functions under "worst case" scenarios such as system overloads (e.g., too many simultaneous users, too many simultaneous processes being performed [such as too many programs open on Windows desktop]), power failures, etc.
- A method for data verification before final entry.
- Internal consistency checks to verify that values are within defined ranges.
- Restricted entry of data to match predefined value limits.
- Required entry of data with field information limited with choices for data consistency.

- Source data is derived from pre-defined sources such as fixed forms. "Monitoring for data integrity" means establishing assurances that data has not been changed either by accident or by intent, and requires access to original documents whenever possible, along with a plan for verification of the electronic system data by comparison to original data. Evidence of a schedule of regular back-ups that include storage of back-up data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the back-up copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include all of the information entered into the database, acceptable sources of the entered data, and a description of system maintenance and development history.
- Formal and documented training in system use requirements for all personnel.
- Evidence of SOPs in place for computer record-keeping systems.
- Regular quality audit trails (especially when users are expected to create, modify, or delete regulated records during normal operation).
- A mechanism to report deviations to report and resolve problems.
- Evidence that changes to records do not obscure previous entries.
- Documentation that deleted electronic files have been converted to non-electronic media such as microfilm, microfiche, or paper in a manner that preserves the content and meaning of the record.

Any identifier generated by the system must be unique, and this process must be validated.

STANDARD:

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

Explanation:

Personnel must be trained to appropriately use all critical electronic record systems (including record entry, verification, and revision) and back-up processes when the critical systems are not available. This training must be continuous, including initial training and ongoing training as SOPs are revised and issues with the use of critical electronic record systems are identified.

STANDARD:

B10.4.9.2 Monitoring of data integrity.

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

B10.4.9.4 System assignment of unique identifiers.

STANDARD:

B10.5 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

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

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

Explanation:
Records need not be duplicated as part of the clinical record; however, the clinical record should allow tracing and tracking of relevant information to the correct source. It is expected that the Clinical Program will have an arrangement with a collection facility that meets FACT-JACIE Standards as the main source of cells. Cells may come from other places, and in those situations, it is the responsibility of the program to clearly outline what the other facilities' requirements are to help achieve the collection of quality cellular therapy products.

The clinical record should indicate where the donor selection records can be found. Generally, relevant and appropriate records will be maintained by the facility that performs the work. Maintenance of records must be specified in the SOPs and it must be clear who the responsible party is for maintaining records.

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

It is the responsibility of the Clinical Program to furnish to all other facilities involved in the collection or processing of the cellular therapy product outcome data so far as it concerns the safety, purity, and potency of the product involved.

Evidence:
If divided responsibility occurs regarding any aspect of the transplant process, a relevant patient file can be used to confirm that an appropriate mechanism is in place to track and trace the process from beginning to end and vice versa. A written SOP should describe specific responsibilities of each party of the divided responsibility.

There should be SOPs regarding dissemination of outcome data and the process must be in place accordingly.

Example(s):
Clinical Programs that consist of pediatric and adult services at different hospitals may perform cellular therapy product collections at one institution that are used for a patient at another institution. An example would be if a child received a haploidentical transplant from a parent and the donor cells were collected at the adult hospital and administered into the recipient at the pediatric hospital. Another example would be if a patient with non-Hodgkins Lymphoma had autologous peripheral blood stem cells collected in first remission at one hospital and subsequently had an autologous transplant at a second hospital.

MARROW COLLECTION FACILITY STANDARDS
PART CM

CM1 General

CM2 Marrow Collection Facility

CM3 Personnel

CM4 Quality Management

CM5 Policies and Standard Operating Procedures

CM6 Allogeneic and Autologous Donor Evaluation and Management

CM7 Coding and Labeling of Cellular Therapy Products

CM8 Process Controls

CM9 Cellular Therapy Product Storage

CM10 Cellular Therapy Product Transportation and Shipping

CM11 Records

CM12 Direct Distribution to Clinical Program

PART CM: MARROW COLLECTION FACILITY STANDARDS

CM1: GENERAL

STANDARD:

CM1.1 *These Standards apply to all collection, storage, and distribution activities performed in the Marrow Collection Facility on cellular therapy products obtained from living donors.*

Explanation:

Once a product has been collected, it is being stored until it is distributed from the Collection Facility. Distribution after collection may be directly to the Clinical Program, a third-party manufacturer, or to the Processing Facility for further processing and storage. The responsibilities that apply to distribution after collection are different from the responsibilities that apply to distribution to the recipient.

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

Explanation:

Stand-alone facilities such as donor centers that provide donor management or collection activities of cellular therapy products from living donors need to use cell processing facilities that meet the FACT-JACIE Standards in order to be eligible for accreditation. The Processing Facility is not required to be formally acknowledged as FACT or JACIE accredited; however, even if not pursuing accreditation, the facility must comply with the Standards.

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

- Evaluation of the autologous or allogeneic donor for suitability (medical fitness) to undergo the collection procedure.
- Evaluation of the allogeneic donor for donor eligibility (free of risks of transmission of infectious diseases).
- Collection of the cells at the Clinical Program's collection facility.
- Temporary storage of the product in the Processing Facility and distribution to the clinical unit.
- Thawing and other needed manipulations of the product before administration to the recipient.

Evidence:

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

Example(s):
Collection Facilities perform collection procedures for a variety of reasons. In addition to collecting cellular therapy products for transplantation, facilities may perform collection in support of research and/or products that require further manufacturing. Single instances of collection for these other purposes must be incorporated into the facility's QM Program. Facilities that collect only products for further manufacture may seek accreditation, in which case the collected product may not be released to a processing facility that meets the Standards. This is a restricted accreditation and any marketing must truthfully and completely disclose the limitations of the accreditation.

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

Explanation:
FACT and JACIE are voluntary inspection and accreditation programs sponsored by the American and European Societies for Blood and Marrow Transplantation and the International Society of Cellular Therapy. Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with the Standards does not guarantee compliance with all applicable laws and regulations. Governmental regulations must also be followed. It is the responsibility of the individual facility to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the Collection Facility may apply; for example, when a facility is sending or receiving cellular therapy products from outside of its immediate jurisdiction.

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

Evidence:
While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with applicable laws and regulations. Evidence of compliance with the Standards will require preinspection information identifying prevailing governmental authorities, and documentation of certificates, permits, or licenses.

Example(s):
In the Member States of the European Union (EU), both HPCs and T Cells fall under the European Directive 2004/23/EC on all tissues and cells, "Setting standards on quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells" and the implementing directives 2006/17/EC and 2006/86/EC. The 2001/83/EC directive regulates products that are classified as medicinal products (MP). This includes somatic cellular therapy MPs and gene therapy MPs. The TMP-Regulation 1394/2007 entered in force on December 30, 2008 to include tissue engineered products. The consequence of classification as an MP is that a GMP environment is required for the production of these cells. Furthermore, each Member State in the EU may add regulations to the directives, that also must be followed. Member State-specific regulations will not be detailed here.

STANDARD:

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

Explanation:
National or state laws and regulations may require registration or certification with the government or may require accreditation from professional organizations for the activities performed within the facility.

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

Example(s):
In the EU, the competent authorities in the Member States shall safeguard that all tissue establishments have been accredited, designated, authorized, or licensed and that these establishments have implemented the EU Directive and/or other national regulations.

Examples of verified compliance with regulations include hospital accreditation (such as the Joint Commission), state licensure, licensing of tissue establishments by the Member State in the EU, Clinical Laboratory Improvement Act (CLIA) certification, acceptable Occupational Safety and Health Administration (OSHA) inspections the College of American Pathologists (CAP), or any other applicable accreditation body.

STANDARD:

CM1.4 *The Marrow Collection Facility shall have a Marrow Collection 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 collections for at least twelve (12) months preceding initial accreditation.*

Evidence:
Current employee files and curriculum vitaes (CVs) should document evidence as to length of employment and experience with marrow collections.

STANDARD:

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

Explanation:
These standards refer specifically to the number of collection procedures, not the number of donors from whom HPC cells were collected, and may include allogeneic and/or autologous donors. Because of the risks to cellular therapy product integrity resulting from the many changes of product custody and risks to recipient safety related to administration, only procedures for therapeutic intent count towards the number of required procedures. This includes products that will be transplanted or distributed for further manufacture and ultimate administration. These products have increased requirements for teamwork, informed consent, and product handling. Marrow aspiration procedures for diagnostic purposes do not count towards the number of collection procedures.

A Collection Facility consists of one team of collectors, staff, and procedures. If a cellular therapy program applies for accreditation at two different collection sites, this minimum number of collection procedures applies to a single team. If there is little to no interaction between the sites, both sites must meet this minimum number.

This standard allows Collection Facilities to apply for accreditation prior to meeting the minimum volume, but this is intended for exceptional circumstances. In this scenario, there must be adequate Quality Management (QM) data to demonstrate compliance with the Standards, and the facility's team must be experienced (see CM3 Personnel). Accreditation will not be awarded until the minimum volume is met. The facility must decide if it is in a position to accept the risk of not meeting the minimum volume (and not becoming accredited) within the accreditation timeline.

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

Example(s):
FACT and JACIE will use the average number of collections per year over the accreditation cycle to determine if a Collection Facility meets the minimum collection volume. For example, if a FACT-accredited program performs three marrow collection procedures in the first year, one in the second, and then two in the third, the program will have performed an average of two procedures per year during the accreditation cycle and be considered to have met the standard.

Cellular therapy programs performing both adult and pediatric marrow collection may collect from adult donors in one facility and pediatric donors in another. If different individuals perform collection in each of the sites, then both sites must perform a minimum average of one collection per year within each accreditation cycle. Meeting this requirement at just one of the sites and not the other does not comply with the intent of the standard.

CM2: MARROW COLLECTION FACILITY

STANDARD:

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

Explanation:
Storage areas for cellular therapy products must be designated and controlled to prevent mix-ups and contamination regardless of the duration of the storage. Storage includes temporary holding of a product after collection and prior to transport or shipping to a processing facility. It is critical that the storage area be, at a minimum, secure and temperature-controlled and that the products be appropriately labeled and segregated, particularly for those products that may be held in the Collection Facility overnight and transported the following day.

Once received, supplies and reagents used for collection must be stored in a manner that preserves their function and sterility. Upon receipt of supplies, kits, and reagents, inspection for suitability must be documented. For items requiring storage at a specified temperature range, the temperature of the storage area must be monitored and documented.

There should be a mechanism to monitor the flow of supplies and reagents within the Collection Facility to prevent the use of outdated supplies and reagents. This system should also be able to identify the location of a given lot of a supply or reagent in the event that there is a manufacturing recall.

Evidence:
The inspector will tour the Collection Facility during the on-site inspection, including all locations where products are collected, stored, and distributed. Observation of the organization, design, location, and amount of space available in the facility can determine if it is adequate for the number and types of collections it performs, and if the collection environment is adequate to minimize the risk of contamination of the cellular therapy product.

The Standards may need to be applied differently between collection procedures performed in an operating room for hematopoietic reconstitution versus smaller outpatient collection environments for regenerative medicine in regards to risk to the donor, equipment, space for personnel, etc.

The inspector should observe storage areas and confirm that supplies and reagents are stored under the conditions specified by the manufacturer. When refrigerators are used to store cellular therapy products, supplies, and/or reagents, the inspector should look for evidence that each is appropriately labeled and adequately separated so as not to cause confusion or compromise the integrity or sterility of the contents. The inspector should also evaluate the inventory control system to determine if it is adequate to prevent the use of outdated or damaged supplies and reagents.

Operating rooms are often subject to other accreditation and facility management requirements. Documentation of compliance with other accreditation or governmental agencies (e.g., Centers for Medicare & Medicaid Services, The Joint Commission) may assist inspectors with verifying compliance with the Standards.

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

Example(s):
Adequate storage can be accomplished by storing products on a designated shelf that is appropriately labeled for that purpose, utilizing designated labeled compartments, or by other procedures. It is recommended that outdated products and reagents and those not intended for clinical use be stored in a separate unit from those designated for patient care if possible. When this is not possible, outdated and/or research material must be clearly separated from clinical material and appropriately labeled.

A first in, first out (FIFO) system is one that is most commonly encountered. This mechanism can be tracked on paper or via a computer program.

STANDARD:

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

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

Explanation:
There is no definition of adequate size; however, the size of the area should at least allow for safe practice and, in case of emergencies, allow for adequate room for resuscitation. The space used for collection and storage of cellular therapy products should be well-defined and adequate and there should be designated space for preparation and storage of reagents and equipment.

Evidence:
Collection Facilities submit a floor plan with preinspection documentation. Inspectors use these floor plans to gain a preliminary understanding of the designated areas and how processes and products flow throughout the facility.

A demonstration by personnel of where each of these activities is typically performed, how a cellular therapy product moves through the facility, and how products and associated paperwork are segregated in the unusual circumstance when there is more than one product present in the facility can demonstrate compliance or illustrate problems. Inspectors should note safeguards in place to prevent mislabeling, inappropriate product release, or mix-ups. The physical facility should be orderly and organized according to a defined workflow.

Although there is no standard for the amount of space necessary to provide a safe environment for collection, the inspector should evaluate this issue based on his/her own experience. The inspector should investigate what other activities are performed on the equipment and in the space.

STANDARD:

CM2.1.3 *There shall be suitable space for confidential donor examination and evaluation.*

CM2.2 *The Marrow Collection Facility shall provide adequate lighting, ventilation, and access to sinks to prevent the introduction, transmission, or spread of communicable disease.*

Evidence:
Collection Facilities must submit a floor plan of the facility prior to the on-site inspection. The inspector will tour the facility during the on-site inspection, including all locations where cellular therapy products are collected, stored, and distributed. The inspector should observe the design, lighting, ventilation in the facility as well as access to sinks for donors and staff to determine if the collection environment is adequate to minimize the risk of introduction, transmission, or spread of communicable disease.

STANDARD:
CM2.3 *Marrow Collection Facility parameters and environmental conditions shall be controlled to protect the safety and comfort of donors and personnel.*

CM2.4 *Critical Marrow Collection Facility parameters that may affect cellular therapy product viability, integrity, contamination, or cross-contamination during collection, including temperature and humidity at a minimum, shall be assessed for risk to the cellular therapy product.*

CM2.4.1 *Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.*

Explanation:
It is understood that cellular therapy programs have limited control over surgical departments and operating suites; however, the Collection Facility must establish a working relationship with those responsible for the operating rooms to protect the integrity of cellular therapy products. When collection is performed in a setting other than an operating room, parameters must be very carefully assessed.

The Collection facility must perform an assessment of conditions to determine if any parameters need to be controlled, monitored, and recorded. This includes parameters that may directly affect the cellular therapy product and also conditions that would diminish equipment or personnel performance, such as extreme humidity.

Methods to collect cellular therapy products that expose the products to greater risks of contamination or cross-contamination, such as open collection systems, warrant more stringent environmental controls. The Collection Facility must assess if temperature, humidity, ventilation, air quality, and surface contaminates must be controlled. There must be ongoing monitoring of any parameters that have been determined to be critical.

Environmental monitors for measures of air quality, such as particle counts and/or microbial colony counts, may be recommended, but applicable laws and regulations may not require specific air quality classification.

Evidence:
If no parameters are controlled, the Collection Facility is requested to provide documentation of its reasoning prior to the inspection. It is the inspector's responsibility to determine while on site if the facility parameters affecting cellular therapy product viability, integrity, contamination, sterility, or cross-contamination identified by the facility are appropriate. If the inspector believes a parameter not identified should be controlled, this will be indicated in the inspector's report and included for discussion by the FACT or JACIE Accreditation Committee.

Example(s):
On-site inspections have revealed instances when humidity did impact the safety of the cellular therapy product. For example, in one particularly humid climate, a Processing Facility's liquid nitrogen freezer lids defrosted enough to prevent them from completely closing.

Adverse temperatures and humidity levels may result in aborted collections and suboptimal personnel performance. Temperatures below freezing may damage products, and studies show a poorer survival of stem cells correlated with higher temperatures. High humidity can lead to the growth of mold or other organisms that could pose a threat to product sterility. However, this standard does not specifically require control of temperature and humidity. For example, the Collection Facility may reference facility management policies, such as the use of an air conditioning unit (which controls humidity in addition to temperature) that is maintained by the institution.

STANDARD:
CM2.5 The Marrow Collection Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.

Explanation:
The Collection Facility should follow local policies regarding cleaning and sanitation. These will usually be hospital policies covering the operating room.

Evidence:
Documentation of Joint Commission or similar agency accreditation may be used supportively to demonstrate the Collection Facility meets requirements for cleaning and sanitation; but, it is still incumbent on the inspector to fully observe and review the facility during the on-site inspection.

STANDARD:
CM2.6 There shall be adequate equipment and materials for the procedures performed.

Explanation:
The amount of relevant equipment in the Collection Facility should be appropriate for the type of collection performed, proportionate to the volume of work done, and should be conveniently located.

The Collection Facility should have policies and SOPs that address interruption in collection due to equipment failure such as for the handling and labeling of cellular therapy products, as well as policies and SOPs that prevent subsequent delay in collections, such as an additional machine for back up or arrangements with other collection agencies or centers.

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

STANDARD:
CM2.7 There shall be access to an intensive care unit or emergency services.

Explanation:
The Standards aim to protect donor safety in the rare emergency situation. The Collection Facility must have documentation that there is ready access to an ICU or equivalent coverage in an immediate fashion for its donors when appropriate. This requires the ability to provide multisystem support including assisted respiration.

Evidence:
The inspector should verify that personnel are appropriately trained to respond to emergency situations and that there is emergency equipment available and in working condition. A review of protocols for emergency response, personnel training and competency files, and a contract or a letter of understanding with local emergency services can be performed.

Example(s):
Examples of appropriate training and emergency equipment include an electrocardiograph, crash cart, code team (in the hospital), or ACLS- and/or CPR-trained individuals (in free standing Collection Facilities). If the only emergency response available to the Collection Facility is a community-based emergency service (911 in the U.S. or 112 in the EU), then the inspector should be able to verify that such an option is feasible and provides for a reasonably safe collection. Ideally, there should be documentation that there was at least one test of the emergency response system, particularly when community-based services are used.

STANDARD:
CM2.8 The Marrow Collection Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, donors, visitors, and volunteers.

CM2.9 The Marrow Collection Facility shall have a written safety manual that includes instructions for action in case of exposure, as applicable, to communicable disease and to chemical, biological, or radiological hazards.

Explanation:
These standards apply to all facilities involved in cellular therapy (Clinical Programs and Collection and Processing Facilities). Safety training, including universal precautions for handling blood, is a requirement of the occupational safety and health administrations in many countries.

The Collection Facility's policies and SOPs, including housekeeping and waste disposal, must document consistency with good biosafety SOPs, including adherence to universal precautions and to applicable laws and regulations regarding safety. Safety, infection control, or biohazard waste disposal SOPs that are unique to the facility must be covered in the facility's SOP Manual. The use of electronic training programs that cover safety and infection control is acceptable, but there must be evidence that the staff has completed all relevant training satisfactorily.

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

Evidence:
Ideally, the inspector should observe a marrow collection procedure to verify that personnel use appropriate protective clothing and observe other biosafety precautions. If there is no collection procedure underway, a mock procedure can be demonstrated. The inspector should examine how cellular therapy products are handled and discarded (e.g., incinerator, waste field) and compare his/her observations with the written protocols. The inspector should examine selected employee files for training in biological, chemical, and radiation safety (when appropriate). Compliance with state and federal regulations should be addressed by the facility and verified by the inspector. The inspector should also be alert during the tour for the presence of unused or inappropriately stored supplies or equipment that may contribute to an unsafe environment.

Example(s):
Safety training, including universal precautions, for handling blood is a requirement of OSHA in the U.S.

The safety manual may be an institution-wide document available by hard copy or electronically. Access to the institutional safety manual solely by computer is not acceptable without a written policy describing how to access the information in the event of a computer failure or down time.
The Collection Facility may keep a condensed or summarized hard copy of the institutional safety manual in the facility. In this case, there must be written documentation of how the condensed version is kept updated with institutional safety manual revisions. Such a document should focus on those hazards that are most likely to occur in the facility, such as needle sticks or handling donors with a known communicable disease.

STANDARD:

CM2.10 *All waste generated by the Marrow Collection Facility's activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable laws and regulations.*

Explanation:
Poor management of medical waste exposes personnel, waste holders, and the community to injuries, infections, and toxic effects. Hazardous waste generated by the facility's activities includes a broad range of materials, including used supplies, sharps, chemicals, radioactive material, viral vectors, genetically modified cells, and the cellular therapy products themselves. All medical waste shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste and in accordance with applicable governmental laws and regulations. Contaminated materials shall be placed in appropriate bags and containers marked with the international infectious substance symbol. Radioactive and chemical waste must be discarded using methods approved by appropriate governmental agencies. General waste that contains information that would constitute a breach of confidentiality if it became available to unauthorized persons, such as paper, CDs, disks etc., should be stored in a secured container before disposal and ultimately shredded or destroyed.

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

Example(s):
Contaminated materials may be typically discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, through the use of a sanitary landfill. Sharps like needles, blades, etc., whether or not they are infected, should be considered highly hazardous health care waste and placed for disposal in puncture proof containers. Chemicals such as cytostatic drugs, used in purging procedures, shall be discarded in accordance with applicable regulations.

STANDARD:
CM2.11 *Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.*

Explanation:
When handling potentially hazardous substances, personnel must use appropriate protective attire. To prevent the spread of hazardous substances, protective attire must be removed before leaving the workspace.

CM3: PERSONNEL

STANDARD:
CM3.1 *MARROW COLLECTION FACILITY MEDICAL DIRECTOR*

CM3.1.1 *There shall be a Marrow Collection Facility Medical Director who is a licensed physician with postgraduate certification, with training in cellular therapy product collection and transplantation.*

Explanation:
The Marrow Collection Facility Medical Director must be a physician licensed to practice medicine in the state, province, or country in which the Collection Facility is located and have postdoctoral training in fields such as blood and/or marrow collection and/or transplantation. The Medical Director need not be licensed in other jurisdictions in which satellite collection facilities are located.

Evidence:
To fulfill this standard, the Marrow Collection Facility Medical Director must provide a copy of his/her current state, provincial, or national license. Since documentation of the medical degree is required to obtain a medical license, the license will be considered to be documentation that the Medical Director is a physician. This documentation is submitted with the Collection Facility's application, and should be available to the inspector prior to the on-site inspection.

Example(s):
In the U.S., an active, dated state license can serve as evidence, as will an active, dated national licensure in other countries.

STANDARD:

CM3.1.2 The Marrow Collection Facility Medical Director or designee shall be responsible for the following elements:

CM3.1.2.1 All technical procedures.

CM3.1.2.2 Performance of the marrow collection procedure.

CM3.1.2.3 Supervision of staff.

CM3.1.2.4 Administrative operations.

CM3.1.2.5 The medical care of allogeneic and/or autologous donors undergoing marrow collection.

CM3.1.2.6 Pre-collection evaluation of allogeneic and/or autologous donors at the time of donation.

CM3.1.2.7 Care of any complications resulting from the collection procedure.

CM3.1.2.8 The Quality Management Program, including compliance with these Standards and other applicable laws and regulations.

Explanation:
The Marrow Collection Facility Medical Director is responsible for all administrative and technical aspects of the Collection Facility. This includes development and implementation of all SOPs, training of personnel, design and execution of validation studies and audits, development of and compliance with the QM Program, maintenance of all equipment, data analysis, reporting, and compliance of the facility with the Standards and applicable laws and regulations.

The Marrow Collection Facility Medical Director is directly responsible for the medical care of donors during the collection procedure, including the pre-collection evaluation of the prospective donor at the time of donation, performance of the collection procedure, training and supervision of assistants for the procedure, care of any complications resulting from the collection procedure, and compliance with the Standards. The Medical Director is not usually responsible for the initial selection of the donor or for the determination of donor eligibility. These are usually the responsibility of the clinical transplant team or donor registry.

The Marrow Collection Facility Medical Director may have other responsibilities, but he/she or a designee should be available at all times when the Collection Facility is operational. The Medical Director's responsibilities should be specifically documented.

Evidence:
The Marrow Collection Facility's organizational chart can be used to verify compliance with the standard in addition to the job description and areas of responsibilities as described in the QM Plan, SOPs, and other documents including who is/are the designee(s) and their responsibilities.

The inspector should review collection SOPs to verify compliance with the standard, that is, how pre-collection evaluation is performed and who is/are the designee(s) (e.g., residents) and what their responsibilities are.

Collection charts documenting the pre-collection evaluation of the prospective donor at the time of donation and care of any complications resulting from the collection procedure may also provide documentation of compliance.

STANDARD:

CM3.1.3 *The Marrow Collection Facility Medical Director shall have at least two (2) years experience in cellular therapy product collection procedures.*

CM3.1.4 *The Marrow Collection Facility Medical Director shall have performed or supervised ten (10) marrow collection procedures within his/her career at a minimum.*

Explanation:
The Marrow Collection Facility Medical Director must have at least one year of experience in the collection procedure for which accreditation is requested. The Medical Director shall have performed or supervised at least 10 marrow collection procedures within his/her career.

If there has been an extended time period since a collecting individual has performed collection, there should be a reassessment of training and competency.

Evidence:
The Marrow Collection Facility Medical Director is required to submit a CV that demonstrates training and/or experience prior to the on-site inspection. The inspector should review this information in advance, and request additional information if there are questions. Evidence of experience should be apparent. Documentation of the procedures performed or supervised should be available.

Example(s):
Experience can include training as part of a residency or fellowship program, specific training in another facility, and/or on-the-job training.

STANDARD:

CM3.1.5 The Marrow Collection Facility Medical Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

CM3.1.5.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:
The Marrow Collection Facility Medical Director must participate regularly in educational activities related to cellular therapy product collection and/or transplantation. The purpose of this requirement is for key personnel to keep up with current advancements in the field.

There are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use his/her judgment to determine whether or not a Marrow Collection Facility Director meets this standard. Recognized educational activities include both certified continuing education credits (preferable) and non-credit educational hours. Examples of acceptable forms of education are included in this Accreditation Manual, and may also include topics specific to cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Evidence:
To assess the appropriateness of the amount and type of continuing education in which the Marrow Collection Facility Medical Director participated, the following information must be submitted for each of the completed continuing education activities within the previous accreditation cycle:

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

To assess on-going activity in the field, the inspector may ask about membership in professional organizations, publications in peer-reviewed journals, and/or attendance at meetings and workshops. The inspector should verify that the hours were in activities relevant to cellular therapy product collection or transplantation.

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

Examples of appropriate continuing education activities include:

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

ASBMT offers an Online Learning center where recordings from BMT Tandem Meetings and the Clinical Education Conference and the ASBMT Online Seminars can be accessed.
These are available at
http://asbmt.org/professional-development/online-learning

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at: http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

CM3.2 QUALITY MANAGER

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

CM3.2.2 The Marrow Collection Facility Quality Manager should have a reporting structure independent of cellular therapy product manufacturing.

Explanation:

The Collection Facility must identify at least one person with responsibility for quality management (QM). This individual can be the Marrow Collection Facility Medical Director or a qualified designee. The Medical Director may assume the Quality Manager role as long as the role does not pose a conflict on proper implementation of a QM Plan for the Marrow Collection Facility. Delegation of a qualified designee must be documented, either in the QM Plan or in a SOP related to it. The title held by this individual may differ among facilities and is not relevant as long as the duties include those described in these Standards. The Quality Manager should be an individual with at least an undergraduate degree or equivalent in the field of health sciences or biological sciences with training, education, or experience with either QM or cellular therapy. Formal training may include practical work experience in a facility, fellowship, or certification program.

This person could be a member of another department, such as an institutional Quality Assessment and Improvement Department, who devotes some time to the QM activities of the Marrow Facility, or it could be a member of the program who has additional responsibilities within the facility.

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

STANDARD:

CM3.2.3 The Marrow Collection Facility Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy, cell collection, and quality management annually at a minimum.

CM3.2.3.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:

There are many ways to meet this standard, and the Standard is not meant to be prescriptive. A total of 10 hours in combination of these topics is required. Each topic does not need to be covered in 10 hours individually. The inspector should assess the documented number and content of the continuing education activities and use his/her judgment to determine whether or not a Quality Manager meets this standard.

Evidence:

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

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

The inspector may ask about membership in professional organizations and/or attendance at meetings, webinars, or other online training activities, publications, etc.

Example(s):

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

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

STANDARD:
CM3.3 STAFF

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

Explanation:
The Collection Facility must define how licensed health care professionals who are trained and competent in collection in accordance with laws and regulations are accessed. Appropriate licensed health care professional access will be evident in SOPs, agreements, or other institutional documents.

APPs may be trained and competent in marrow harvesting. In these cases, physicians still have ultimate responsibility for the procedure and well-being of the donor.

Example(s):
Examples of acceptable actions for programs that do not have a marrow collection service include: obtaining the product from the NMDP, contracting the service, or transferring the donor to a facility that performs marrow collection.

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

Explanation:
This standard requires that there be an adequate number of trained personnel available for the collection of cells relative to the workload. The number of staff available and other responsibilities of the staff will vary from institution to institution based on the size and scope of the facility, and no specific numbers of staff members are required by the Standards. There should be sufficient staff present to manage in the event of any donor emergency without neglecting ongoing collections. A designated back-up, trained individual is required, but this does not require the Collection Facility to hire an additional employee. There are many options to train personnel from other departments who are qualified to perform the necessary tasks should they be needed.

The Collection Facility Medical Director should indicate personnel responsible for specific activities in the Collection Facility and confirm that they are appropriately trained and competent to perform those activities, including confirmation that they have been trained in appropriate age-specific issues for the donor population they serve. Personnel should be retrained as necessary to remain up to date on current collection methods.

Evidence:
The inspector, as well as the applicant, will make a judgment of the adequacy of the staff support, including a review of the plan for staffing in the event of absences. The inspector should observe and inquire about the number of donors for whom one staff member is responsible at one time.

Documentation of initial training, continuing education, and periodic competency testing of all personnel is required. Documented training at the time of initial employment is expected of all new staff hired at the time of and following application for FACT or JACIE accreditation. Records of initial training may not be available for long-term employees of the facility; however, documentation of continued competency on a periodic basis should be available for all staff.

The inspector may request review of dated personnel records demonstrating competency and experience. The inspector should not request or be given confidential information such as the staff's medical records (e.g., vaccinations and health records).

Example(s):
Insufficient staffing may be indicated by excessive overtime, rapid turnover of personnel, incomplete record keeping, or an increase in adverse events.

Competency testing may include observation of performance of a procedure by a supervisor or coworker, oral or written examination of expected areas of performance, and/or participation in proficiency testing programs.

STANDARD:

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

Explanation:
Pediatric collections might require additional training and/or documented experience with this special population of donors. SOPs addressing special situations that apply to pediatrics should be in place with appropriate staff training and experience.

Evidence:
The inspector may request review of dated personnel records demonstrating training and competency in managing pediatric donors.

CM4: QUALITY MANAGEMENT

STANDARD:

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

Explanation:
Marrow Collection Facilities that are integrated with a Clinical Program are typically included in the Clinical Program's QM Program. However, some facilities operate independently of a program; these facilities must comply with the requirements in B4 to confirm their activities are regulated under a QM Program.

Evidence:
Records to demonstrate an active QM Program with oversight of the Marrow Collection Facility should be available to the inspector.

Example(s):
An example of a Marrow Collection Facility that operates independently of a Clinical Program is a facility that collects only for NMDP and/or other donor registries.

CM5: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

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

Explanation:
Each Collection Facility must have written policies and SOPs that comprehensively address all of the important aspects of the facility. The facility is not required to have an SOP titled for every item on the list, as long as each item is addressed somewhere within an appropriate SOP. The items listed include the minimum requirements; a facility may exceed these requirements, but may not omit any of these.

It is recognized that the practice of medicine requires some flexibility and the Collection Facility may choose to designate policies for some clinical care related to the collection procedure as practice guidelines.

Evidence:
A document(s) addressing the elements listed in CM5.1's substandards must be present. When multiple topics are covered by a single SOP, it will aid the inspection process if the Collection Facility prepares a crosswalk between the list of required SOPs in CM5.1 and the facility's own SOP Manual. A list of all SOPs, or a Table of Contents from the program's SOP manual, will be provided prior to the inspection (in addition to critical SOPs), to determine if in-depth review of other SOPs by the inspector is necessary.

The inspector should verify the procedure for development and review for all policies and SOPs is being followed and that the policies and SOPs are comprehensive and define all aspects of the Collection Facility function.

There will not be time for the inspector to read all policies and SOPs during the on-site inspection. The inspector will have received a copy of the Table of Contents for the SOP Manual with the pre-inspection material prior to the on-site inspection. The Table of Contents should be examined for evidence of the existence of SOPs addressing each item listed in the Standards before arriving at the inspection site. Prior confirmation that a specific SOP has been generated will reserve limited on-site inspection time for evidence of implementation of written SOPs and other activities that can only be verified in person at the inspection site.

Example(s):
The policies and SOPs can be generated within the Collection Facility or in collaboration with other entities within the institutional infrastructure. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and the emergency response to disasters. In cases where general institutional policies and SOPs are inadequate to meet standards or where there are issues that are specific to the Collection Facility, the Marow Collection Facility must develop its own policies and SOPs to supplement those of the institution. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for initial approval and review and approval of revisions every two years by the facility.

STANDARD:

CM5.1.1 *Donor and recipient confidentiality.*

CM5.1.2 *Donor consent.*

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

CM5.1.4 *Cellular therapy product collection.*

CM5.1.5 *Administration of blood products.*

CM5.1.6 *Prevention of mix-ups and cross-contamination.*

CM5.1.7 *Labeling (including associated forms and samples).*

CM5.1.8 *Cellular therapy product expiration dates.*

CM5.1.9 *Cellular therapy product storage.*

Explanation:
The Collection Facility must define the expiration dates and storage conditions (e.g., container, temperature) of all of its collected products, including those released to a Clinical Program and those released to another facility (commonly to a Processing Facility for processing and storage).

STANDARD:

CM5.1.10 *Release and exceptional release.*

Explanation:
Release is defined as the removal of a cellular therapy product from in-process status when it meets specified criteria. Marrow Collection Facilities must have release criteria for when a cellular therapy product can be distributed to the Processing Facility or Clinical Program. Release criteria are not only applicable to directly releasing a cellular therapy product for administration, but also to releasing a cellular therapy product to another facility (e.g., to a Processing Facility for processing and storage).

Each cellular therapy product must be verified to have met release criteria before being released. SOPs must outline how this verification takes place and who approves the release. There may be times when a cellular therapy product does not meet release criteria. If this product must still be used for urgent medical need, an SOP must define the process for exceptional release, outlining the steps to take for documentation and approval.

Evidence:
The inspector will review the SOP(s) describing the release criteria and the process for release of cellular therapy products that meet those criteria. The inspector will also verify existence of an SOP for exceptional release, including documentation and approval.

STANDARD:

CM5.1.11 *Transportation and shipping, including methods and conditions to be used for distribution to external facilities.*

CM5.1.12 *Critical equipment, reagent, and supply management including recalls and corrective actions in the event of failure.*

CM5.1.13 *Hygiene and use of personal protective equipment and attire.*

CM5.1.14 *Emergency and disaster plan related to the marrow collection procedure.*

Explanation:
Contingency planning for emergency and disaster events that may critically impact donor and/or recipient care must be included in Collection Facility SOPs. It is highly recommended that a facility that is part of a complete transplant program have a contingency plan in place in the event the Processing Facility and/or Clinical Program are unable to provide services as intended (e.g., significant personnel change or disaster).

Example(s):
For the emergency and disaster plan, the Collection Facility may use institutional policies for the general responses. However, specific SOPs relating to the chain of command and necessary SOPs to address the safety of donors and recipients is needed to augment the institutional policies (such as actions to take in response to an emergency or disaster occurring during a marrow collection or after a donor is prepared for a marrow collection, or an event that prevents collection for a recipient who has already undergone myeloablation). Examples of disasters include fires, hurricanes, floods, earthquakes, nuclear accidents, etc. Specific natural disaster policies may be more pertinent dependent on geographic location. In cases where institutional policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the facility, the facility must develop its own policies and SOPs. The article *Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program* (Wingard et all, 2006) provides a framework for disaster plans (available at http://asbmt.affiniscape.com/associations/11741/files/EmergencyPreparednessGuidelines.pdf).

The U.S. Food and Drug Administration offers information on its webpage titled, "The Impact of Severe Weather Conditions on Biological Products," at http://www.ncbi.nlm.nih.gov/pubmed/17085317.

STANDARD:

CM5.2 *The Marrow Collection Facility shall comply with B5.2 if it operates independently of a Clinical Program.*

Explanation:

Controlled documents must be maintained in an organized fashion so that all current documents can be found. Many Clinical Programs have adopted an electronic method of compiling its controlled documents.

Evidence:

The detailed list should be organized in such a manner that the inspector can ascertain that the controlled documents are comprehensive and define all aspects of the Clinical Program.

Example(s):

A Clinical Program may choose to have one detailed list of controlled documents, or divide controlled documents into several manuals by subject. A technical procedure manual in conjunction with a quality, a policy, and a database manual may serve to better organize information if the program chooses this format.

STANDARD:

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

CM5.3.1 *A clearly written description of the objectives.*

CM5.3.2 *A description of equipment and supplies used.*

CM5.3.3 *Acceptable end-points and the range of expected results.*

CM5.3.4 *A stepwise description of the procedure.*

CM5.3.5 *Age-specific issues where relevant.*

Explanation:

Depending on the age range of donors treated in the cellular therapy program, Collection Facilities should be able to demonstrate how processes are adjusted for age-specific issues. For example, a facility caring for teenage patients should demonstrate processes that accommodate the psychological, educational, family, and social needs of this age group, including routine peer group contact. Geriatric patients (greater than 65 years of age) should have appropriate access to rehabilitation and social support.

Collection of HPC and/or T Cells from pediatric donors requires specific policies and SOPs that address issues of age and size of the donor. Any program that collects a cellular therapy product from a minor donor must have appropriate SOPs that address at least issues of informed consent, donor size, and venous access.

Small donors undergoing marrow collection also have unique needs. Allogeneic blood may be needed if the recipient is significantly larger than the donor. Any cellular blood product administered to a donor prior to, during, or following a collection must be irradiated to prevent engraftment of these third-party cells in the transplant recipient if some are present as contaminants in the collected marrow. Technical aspects of the collection require attention because of the size of the iliac crests. Surgical considerations of temperature control and pain management also require pediatric expertise.

STANDARD:

CM5.3.6 *Reference to other Standard Operating Procedures or policies required to perform the procedure.*

CM5.3.7 *A reference section listing appropriate and current literature.*

CM5.3.8 *Reference to a current version of orders, worksheets, reports, labels, and forms.*

CM5.3.9 *The Marrow Collection Facility Director or designated physician shall approve, prior to implementation, new or revised controlled documents.*

Explanation:

The Collection Facility should establish a range of acceptable results, when appropriate, for each procedure. Examples include nucleated cell recovery, hematocrit, sterility, plasma volume, etc. The range for a given parameter can be determined within the Collection Facility by evaluating data from its own products.

Reference to relevant policies within an SOP requires some flexibility. Some Collection Facilities like to include it in the body of the SOP at the end of the relevant step, whereas others may include it at the very end of the procedure as a separate section that lists other required SOPs where the procedure identifier (minus the version) and name is listed. These decisions should be apparent in the "SOP for SOPs".

The Standards require documented review of each SOP by the Collection Facility Medical Director every two years. It is important that documentation clearly indicates the version of each SOP or policy that was reviewed. A single page in the manual with a signature and a date is not sufficient since SOPs may be revised throughout the year. Review of SOPs should include review of the applicable worksheets, forms, and attachments.

Current versions of worksheets, reports, labels, and forms, where applicable, must be identified in or be attached to each SOP. The purpose of this standard is to assure that these documents are easily accessible to a reader of the SOP and that it is clear what documents may be required for the performance of that SOP. It is acceptable to simply reference applicable worksheets, reports, labels, and forms for which a separate SOP exists describing their use.

Evidence:

The inspector should review the SOP manual and documentation of Collection Facility Medical Director review. A list of SOPs will be made available preinspection. The inspector must be given on-site access to any documented electronic approvals of procedural modifications.

Example(s):
In some programs, the actual "SOP" may be limited to minimal work instructions, and required elements such as a reference list may be found only in higher-level documents. Such variability is acceptable if all elements can be found within the quality documents.

It may be worthwhile to include a listing of the document identifiers and titles of worksheets, reports, labels, and forms needed for a given SOP in the proper SOP format. These forms need not necessarily be completed as an example, it may be prudent to attach one or more completed forms to illustrate possible real life scenarios.

For example, SOPs or policies for reporting adverse reactions to product administration or SOPs for reporting the results of microbial testing should be approved and reviewed by the Collection Facility Medical Director. A review signature on the document itself, or on a listing of the reviewed documents by name that includes the unique identifier and version, is acceptable. A validated electronic review system is also acceptable.

STANDARD:
CM5.4 *Controlled documents relevant to processes being performed shall be readily available to the facility staff.*

Explanation:
The written copy or electronic version (with provision of hardcopy as necessary) of the Collection Facility's SOP Manual must be immediately available to all relevant employees in their working environment. There must be only one source document created from which review occurs. Any copies of the policies and SOP manual must be identical to the source document and must not be used to alter, modify, extend, delete, or otherwise edit any SOP.

If an electronic manual is used, there must be a mechanism to obtain access to the manual at all times, even if the network is not available. For marrow harvests, the collection SOP must be readily available in the operating room.

Evidence:
The written copy or electronic version of the SOPs should be readily identifiable to the inspector. The inspector should expect to see the SOP manual or electronic access to SOPs in all performance areas of the Marrow Collection Facility.

Example(s):
The Collection Facility's SOPs are usually physically located in the management team member's office (e.g., Quality Manager). However, collection procedures are often performed outside of those locations (i.e. in the operating room). If the SOP manual is not physically present at locations in which the collection procedure is performed, there should be a process to access them in case they are needed and the staff should be familiar with that process.

STANDARD:

CM5.5 *Staff training and, if appropriate, competency shall be documented before performing a new or revised Standard Operating Procedure.*

Explanation:

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

Evidence:

Documentation that approved and implemented policies or SOPs are performed only after the individual staff member has reviewed and been trained on the new or revised procedure should be reviewed by the inspector.

Example(s):

It is recommended that there be a specific signoff sheet for every policy and SOP and associated revisions to document that each staff member required to review them has done so. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each procedure and to any major revision also facilitate documentation of appropriate training of staff.

Sometimes a revision to a policy or SOP is minor, such as an update to a referenced regulation or grammatical corrections. In these cases, full training may not be necessary. Review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

STANDARD:

CM5.6 *All personnel shall follow the Standard Operating Procedures related to their positions.*

Evidence:

Inspectors should observe procedures or question personnel regarding how they would perform a procedure compared to the written SOP or policy.

STANDARD:

CM5.7 *Planned deviations shall be pre-approved by the Marrow Collection Facility Medical Director, and reviewed by the Quality Manager.*

Explanation:

Planned deviations should be approved within a peer-review process (i.e., more than one individual), but approval from the Collection Facility Medical Director is required at a minimum. Processes set up for review of planned deviations are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately. Retrospective review must be performed in compliance with processes designed for deviations.

CM6: ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

STANDARD:

CM6.1 *There shall be written criteria for allogeneic and autologous donor evaluation and management by trained medical personnel.*

Explanation:

Standards in CM6 mirror those in B6, reflecting the fact that these responsibilities are usually the primary responsibility of the Clinical Program staff. Collection Facility staff are usually not responsible for donor selection. Cellular therapy program policies and SOPs must clearly define responsibility for all aspects of donor selection, evaluation, eligibility and suitability determination, and management. In situations in which the Collection Facility is primarily responsible for activities related to donor selection, the applicant and inspector must complete the corresponding sections in the Clinical Program inspection checklist.

These standards are intended to promote the safety of the donor and recipient as well as the safety and efficacy of the cellular therapy product. For allogeneic donors, additional requirements exist to achieve appropriate histocompatibility matching and to protect the recipient from the risks of transmissible disease.

Facilities should endeavor to obtain voluntary and unpaid donations of cells. Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation.

Donor eligibility and suitability should be differentiated as defined in A4, where, "eligibility" refers to a donor who meets all transmissible infectious disease screening and testing requirements, and "suitability" refers to issues that relate to the general health of the donor and the donor's medical fitness to undergo the collection procedure.

The Collection Facility must have in place written SOPs defining all aspects of donor identification, evaluation, selection, and management, including identification of the personnel responsible for each aspect. Facilities should consider requirements of applicable laws and regulations, professional organizations, associations or societies, and accrediting agencies when creating and reviewing these SOPs. For donors of cellular and tissue-based products, regulations on allogeneic donor eligibility determination require that donor evaluation include risk factor screening by health history questionnaires, review of medical records, physical examination, and testing for relevant communicable disease agents and diseases.

The allogeneic donor is determined to be eligible if he/she is:

- Free from risk factors for and clinical evidence of relevant communicable disease agents and diseases.
- Free from communicable disease risks associated with xenograft in the donor or in someone with whom the donor has had close contact.

- Tests negative or non-reactive for relevant communicable disease agents within the specified time frame for the product. It is the responsibility of the facility to document that donor evaluation procedures are in place to protect the recipient from the risk of disease transmission from the donor.

These standards also require that if allogeneic donors are ineligible according to applicable laws or regulations, or do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented. There must also be documentation in the recipient's medical record by the an attending physician of urgent medical need for the cellular therapy product. Urgent medical need means that no comparable stem cell or cellular product is available and the recipient is likely to suffer death or serious morbidity without the stem cells or cellular products. The product should be accompanied by a summary of records to the Processing Facility stating reasons the donor is ineligible, including results of health history screening, physical examination, and results of infectious disease testing.

In addition, this standard requires that the Collection Facility identify the institutional criteria for medical suitability of donors. This includes criteria for both related and unrelated donors. It also requires that each aspect of this process be performed according to written SOPs and that the results of the evaluation are to be documented. Donor acceptability should be documented within the medical record in the Clinical Program and be provided in writing to the Collection and Processing Facilities.

Evidence:
The inspector should verify that policies and SOPs for donor evaluation and management are written, clearly defined, and are unambiguous. Compliance with these SOPs can be verified by review of a specific donor evaluation. The inspector may also verify the rationale and informed consent for a specific donor who did not meet the institution's donor criteria as well as making sure that there is an SOP for urgent medical need documentation and labeling for allogeneic cellular therapy products.

Example(s):
Eligibility testing is only required for allogeneic donors; however, autologous donors must be tested if required by applicable laws and regulations. Autologous donors who are tested and have positive results for some infectious diseases (e.g., Hepatitis B, C, or HIV) are not necessarily excluded as a donor. It is helpful for programs to be aware of infectious disease status, but does not constitute a contraindication for autologous donation.

According to U.S FDA Final Guidance ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Product [HCT/Ps], August 2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This Guidance Document is available at:
http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf.

STANDARD:

CM6.2 ALLOGENEIC AND AUTOLOGOUS DONOR INFORMATION AND CONSENT FOR COLLECTION

CM6.2.1 The collection procedure shall be explained in terms the donor can understand, and shall include the following information at a minimum:

Explanation:

These standards apply to informed consent for the specific collection procedure. Clinical Programs typically obtain informed consent to donate; Collection Facilities must obtain informed consent to perform the specific procedure. It is acceptable to include both the consent to be a donor and the consent to the collection procedure in the same process and obtain both consents at the same time. The informed consent substance and process is determined by the law in the jurisdiction of the Collection Facility. The essential elements of informed consent are that the donor or recipient is told, in terms she or he can reasonably be expected to understand, the reasons for the proposed therapy or procedure, the risks associated with the treatment or procedure, and potential benefits. This requirement applies to both autologous and allogeneic donors. In addition, the donor or recipient should be given the opportunity to ask questions and to have these questions answered to his/her satisfaction. The discussion that ensues is the important part of the process of obtaining informed consent; however, it is the documentation of this process that can be easily audited. Informed consent is to be documented according to institutional standards and criteria.

The information must be given by a trained person able to transmit it in an appropriate and clear manner, using terms that are easily understood. The health professional must determine that the donor has a) understood the information provided, b) had an opportunity to ask questions and had been provided with satisfactory responses, and c) confirmed that all the information he/she has provided is true to the best of his/her knowledge and documented in the medical record.

Evidence:

Review of one or more completed donor consent forms to determine if all the required elements are in place along with review of the clinic note which details discussion of the protocol can verify compliance. The inspector may also ask to see each version of the consent form and/or clinic notes when a different process is used for pediatric patients and donors.

Example(s):

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

This process may take place over several visits. A preprinted consent form detailing all of the above elements is an easy method of documentation; however, informed consent does not specifically require such a form. In the absence of a form, the clinical notes detailing the consent discussion must be significantly detailed.

STANDARD:

CM6.2.1.1 The risks and benefits of the procedure.

CM6.2.1.2 Tests and procedures performed on the donor to protect the health of the donor and the recipient.

CM6.2.1.3 The rights of the donor or legally authorized representative to review the results of such tests according to applicable laws and regulations.

CM6.2.1.4 Protection of medical information and confidentiality.

CM6.2.2 Interpretation and translation shall be performed by individuals qualified to provide these services in the clinical setting.

CM6.2.3 Family members and legally authorized representatives should not serve as interpreters or translators.

CM6.2.4 The donor shall have an opportunity to ask questions.

CM6.2.5 The donor shall have the right to refuse to donate or withdraw consent.

CM6.2.5.1 The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal in the event that consent is withdrawn after the recipient has begun the preparative regimen.

Explanation:
This standard is not meant to be coercive, but to require full disclosure of the effects a donor's decisions has on a recipient. Donors shall be informed that the consequences to the recipient of the donor's refusal to donate are significantly different depending on the stage of transplant. If the potential donor declines prior to typing versus refusing after selection and the day before the administration, then the degree of risk incurred to the recipient will be very different.

STANDARD:

CM6.2.6 Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional familiar with the collection procedure.

CM6.2.6.1 Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

Explanation:
In the allogeneic setting, to prevent a conflict of interest that may exist when a physician or other healthcare provider cares for both the donor and the recipient, donors must be consented by a member of the team other than the primary healthcare professional of the intended recipient or a clinician who is not a member of the team but is knowledgeable with the collection procedures.

STANDARD:

CM6.2.7 *In the case of a donor who is a minor, informed consent shall be obtained from the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.*

Explanation:

Donors must be of legal age of consent (in the jurisdiction of the collection) or the informed consent for donation must be signed by the legally authorized representative. Specific consent is required for the use of growth factor in a minor, allogeneic donor. It is appropriate to discuss the donation procedure with the pediatric donor in terms he/she can understand. For minor donors, although consent is obtained from legally authorized representatives in accordance with local regulations, assent should also be obtained in an age-appropriate manner.

Example(s):

It may be helpful to include a child life specialist, a social worker, or another qualified individual in the consent process to make certain that the minor donor has age appropriate understanding.

STANDARD:

CM6.2.8 *The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician and/or the recipient.*

Explanation:

The purpose of this standard is to protect donor confidentiality regarding his or her health information. Donors should be aware of testing results so that they may decide whether or not to allow recipient access to information that may disclose lifestyle behaviors or prompt coercion to donate based on HLA typing results. The Collection Facility should have the consent available prior to the collection procedure. Release of health information is only required after donor selection.

Evidence:

Documentation that donor informed consent forms and recorded authorization to release relevant donor health information may document compliance. The date informed consent was obtained in relation to the date the release of the donor's health information occurred may be compared.

Example(s):

It is acceptable to obtain informed consent and authorization to release this information after donor screening and testing as long as it is obtained prior to sharing the results and prior to the collection. If a potential donor is screened but is deemed not to be suitable for collection, donor health information related to this decision does not need to be released to the potential recipient.

STANDARD:

CM6.2.9 *Documentation of consent shall be available to the Marrow Collection Facility staff prior to the collection procedure.*

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

CM6.3.1 There shall be criteria and evaluation policies and Standard Operating Procedures in place to protect the safety of donors during the process of cellular therapy product collection.

Explanation:
Donor suitability refers to issues related to the general health of the donor and protection of donor safety. The criteria and evaluation SOPs must account for the entire collection process from initial evaluation, mobilization where applicable, to collection, and post-collection care.

Example(s):
Vulnerable donors (e.g., children) and donors at increased medical risk from donation (e.g., those with cardiac disease) are examples for when donor suitability assessment is crucial.

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

STANDARD:

CM6.3.1.1 The Marrow Collection Facility shall confirm that clinically significant abnormal findings are reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

Explanation:
Abnormal findings in a donor, including but not limited to the testing results, may have important implications for the individual apart from his/her role as a donor. Appropriate care of the donor requires that clinically significant abnormalities be communicated and that recommendations be made to that donor for follow-up care (including transfer of care, if applicable). The Collection Facility must confirm these actions are documented in the donor's medical record.

Evidence:
The inspector should review documentation in the medical record that prospective donors were informed of the abnormal findings including recommendations for work-up, treatment, and follow-up (including transfer of care, if applicable). The inspector may need to specifically request a record of a prospective donor who had abnormal findings, since this may not be a common occurrence .

STANDARD:

CM6.3.1.2 Allogeneic donor suitability shall be evaluated by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.

Explanation:
An independent physician or health care professional must be utilized for evaluating donor suitability to reduce potential bias of the recipient's health care professional(s). This individual must not be the primary health care professional of the recipient and should have knowledge of the risks of the donation procedures.

Medical literature supports the idea that having the allogeneic donor evaluated by a physician or health care professional who is not the primary health care provider of the recipient decreases the potential conflict of interest with regard to the welfare of the recipient and the welfare of the donor (see "Family Donor Care Management: Principles and recommendations," (van Walraven et al, 2010). Furthermore, the American Academy of Pediatrics (AAP) and the American Society of Blood and Marrow Transplantation (ASBMT) recommend this practice for related donations.

For allogeneic donors, a physician other than the recipient's physician (e.g., a different physician in the program or a clinician who is not a member of the program but is knowledgeable with the collection procedures) must be utilized for evaluating donor suitability to reduce potential bias of the treating physician(s); for example, the donor's primary care physician, a general internal medicine clinic, or a clinic not directly associated with the program.

STANDARD:

CM6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

Explanation:
Communicable disease testing or screening of autologous donors in connection with cellular therapy product collection is no longer required by the Standards. However, in agreement with C1, testing required by applicable laws and regulations is required.

When testing for autologous donors, even if tests not approved for donor screening are used and the results are positive, the appropriate warning statements must be on the label.

STANDARD:

CM6.3.2 The risks of donation shall be evaluated and documented, including anesthesia for marrow collection.

Explanation:
The purpose of this standard is to evaluate the donor for potential risks associated with the collection, such as anesthesia for collection of HPC, Marrow. This evaluation is in general the responsibility of the Clinical Program, but the Collection Facility is responsible for verifying that appropriate testing and evaluation has been performed.

STANDARD:

CM6.3.3 The donor shall be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen, if utilized.

Explanation:
Hemoglobinopathy assessment is required since administration of mobilization agents such as G-CSF may pose a risk to the donor as it was associated with morbidity (e.g vaso-occlusive crisis) and mortality in donors with sickle cell disease (HbSS), HbSC, and also with compound hemoglobinopathies such as sickle-beta-thalassemia (S/β thal). Testing is not required, although it is an acceptable method.

Of note, donors with sickle trait were safely mobilized and collected. While the sickle trait donors did have higher symptom score than control donors, there were no symptoms suggestive of sickle crisis. Thus, in this group, the risk is limited.

References:
Granulocyte Colony-Stimulating Factor (G-CSF) Administration in Individuals with Sickle Cell Disease: Time for a Moratorium? Fitzhugh Cd et al ,Cytotherapy. 2009; 11(4): 464–471.

Granulocyte Colony-Stimulating Factor-Based Stem Cell Mobilization in Patients with Sickle Cell Disease. Rosenbaum C et al, Biology of Blood and Marrow Transplantation 2008; 14:719-723.

Mobilization, collection, and processing of peripheral blood stem cells in individuals with sickle cell trait. Kang et al, Blood 2002;99:850.

Evidence:
The inspector may look for the process or documentation of risk evaluation in the donor. For example, hemoglobinopathy risk evaluation might include a relevant question in the Donor History Questionnaire.

Example(s):
Hemoglobinopathy risk assessment may include testing for the detection of Hemoglobin S (e.g., Sickle Dex) or an Hb-electrophoresis test, but a test is not required. An assessment may be performed by looking at the donor's medical history.

STANDARD:

CM6.3.4 *A pregnancy test shall be performed for all female donors with childbearing potential within seven (7) days prior to starting the donor mobilization regimen (if mobilized donor is used), undergoing anesthesia, and, as applicable, within seven (7) days prior to the initiation of the recipient's preparative regimen.*

Explanation:
Pregnancy testing is required since the donation of marrow under anesthesia may pose a risk to the fetus. Child-bearing potential is meant to include all female donors from puberty through menopause, unless there is some definite medical indication that pregnancy is impossible (e.g., a past hysterectomy). The purpose of this standard is to prevent donor mobilization (although atypical prior to marrow collection), collection, and recipient conditioning from occurring before finding out that the donor is pregnant.

Evidence:
The inspector may look for the process or documentation of pregnancy testing of the donor.

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

If the recipient undergoes a preparative regimen for a long duration, a pregnancy test must be performed within seven days prior to beginning the regimen. The donor must be retested prior to collection to confirm there is no change in pregnancy status.

STANDARD:

CM6.3.5 *Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, or licensed in accordance with applicable laws and regulations.*

Explanation:
All laboratory tests must be performed by a laboratory accredited for the relevant tests. Testing may be performed at any time prior to the initiation of the recipient's preparative regimen except for infectious disease tests, which must be done within 30 days prior to collection of HPC and within seven days prior to or after collection of other cell products as required by United States FDA or as required by non-U.S. equivalent regulations.

Example(s):
Examples of relevant accreditation organizations include CLIA, CAP, ASHI, AABB, JCAHO, and others.

STANDARD:

CM6.3.6 *The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.*

CM6.3.7 *There shall be a written order from a physician specifying, at a minimum, anticipated date and goals of collection.*

CM6.3.8 *Collection from a donor who does not meet collection safety criteria shall require documentation of the rationale for his/her selection by the donor's physician. Collection staff shall document review of these donor safety issues.*

Explanation:
The decision to use a donor who does not meet donor safety criteria must be made by the donor's physician. However, a designee may actually document that decision. The Collection Facility must review this information on donor safety. These standards also require that if allogeneic donors selected for transplant do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented.

Evidence:
The inspector may ask for charts of nonconforming donors and documentation of selection rationale, safety issues, and communication.

STANDARD:

CM6.3.8.1 *There shall be written documentation of issues of donor health that pertain to the safety of the collection procedure available to the Marrow Collection Facility staff. Collection staff shall document review of these issues prior to collection.*

Explanation:
Safety documentation is performed by the staff members who conduct the donor health evaluation (in the Clinical Program or the Collection Facility). Responsibility should be defined in SOPs. Further, collection staff is required to document that donor health issues have been reviewed prior to collection.

STANDARD:

CM6.3.9 *There shall be a policy or Standard Operating Procedure for the management of collection-associated adverse events and follow-up of donors that includes routine management .*

Explanation:
There should be a policy that provides guidelines for the post-collection care of donors. All donors should be monitored closely following the collection procedure.

Example(s):
The guidelines for post-collection care of donors may include the following short- and long-term measures:

- A defined minimum duration of admission for observation and clear guidelines for discharge.
- Orders for donor monitoring during observation that may include frequency of vital sign monitoring, lab draws, frequency of clinical evaluations for adverse events, intravenous hydration, dressing of marrow harvest sites, pain medications, and iron supplementation.
- Discharge instructions that include a phone number to call when they experience symptoms and signs of adverse events such as prolonged fatigue, high fever, wound infection, etc.
- The donor should remain at the collection facility for an adequate time.
- Follow-up appointments usually within 1 – 4 weeks. If the donor leaves the immediate collection location and is unable to return to clinic for follow up, the donor should be instructed to have a CBC done approximately one to two weeks post-collection at their primary care office. A follow-up phone call may be made to the donor at 1 - 4 weeks after collection.
- Long-term follow-up guidelines beyond a few weeks after collection may be defined by the Collection Facility based on transplant type and medical need on a case by case basis.

The World Health Organization (WHO) guiding principles of Human Cell, Tissue and Organ Transplantation (guiding principle 10) recommends long-term follow-up of donors. These guiding principles can be found at
http://www.who.int/transplantation/Guiding_PrinciplesTransplantation_WHA63.22en.pdf.

STANDARD:

CM6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

CM6.4.1 A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated.

Explanation:

A donor advocate is an individual distinct from the transplant recipient's primary treating physician who confirms the donor is fully informed of the collection procedure and promotes the interests, well-being, and safety of the donor. According to Donor Registries for Bone Marrow Transplantation: Technology Assessment (NIH Office of Medical Applications of Research, 1985), the role of the advocate is to help ensure that the consent is made without time pressure and with full information, to enhance the personal attention given to the donor during all procedures, to help prevent unnecessary inefficiencies and discomfort, to mobilize official expressions of gratitude after the donation, and to aid in the resolution of subsequent problems.

For donors who are mentally incapacitated or not capable of full consent, including minors, a donor advocate must be utilized to appropriately counsel the donors and protect them from unsafe or futile donation procedures.

The donor advocacy role should be documented and should not be fulfilled by an individual involved in the recipient's care.

Evidence:

For centers using minor or mentally incapacitated donors, the inspector should ask for documentation that a donor advocate was involved in the donor selection process.

Example(s):

Examples of donor advocates include chaplains, patient advocates, social workers, etc. "Family Donor Care Management: Principles and recommendations," (van Walraven et al, 2010) provides recommendations for donor advocacy in the related transplant setting. When applicable laws and regulations define donor advocate and specific requirements, those must be followed.

STANDARD:

CM6.4.2 Allogeneic donor infectious disease testing shall be performed using donor screening tests approved or cleared by the governmental authority.

Evidence:

The inspector may look for Infectious disease markers testing results and verify they were performed according to applicable laws and regulations.

Example(s):

Agreements with the supplier for IDM testing and qualification of this supplier are examples**.**

STANDARD:

CM6.4.3 The Marrow Collection Facility shall comply with B6.4.6 through B6.4.6.8 when primarily responsible for donor screening for transmissible disease.

Explanation:

The Standards and the FDA require that all donors be screened by medical history and risk factors for human transmissible spongiform encephalopathy, Creutzfeldt-Jakob disease (CJD), and potential transmissible infectious disease agents through xenotransplantation as there are no screening tests for these agents. Travel history is essential for this screening. Information about areas of the world where CJD is a risk factor should be established using trusted sources (e.g., national or international health agencies' websites or publications).

In the setting of resistant disease or relapse/progressive disease, it may be medically necessary to administer donor lymphocytes or other cellular therapy products before availability of repeat transmissible disease testing. The recipient must be informed of this deviation and the discussion must be documented in the medical record.

Other risks may be associated with unlicensed vaccines, receipt of human-derived growth hormone or clotting factor concentrates, or hepatitis B immune globulin. Prospective donors should be questioned about these issues.

In some donors, other tests may be necessary based on the donor medical history. In the case of child donors born of mothers with HIV, hepatitis C, hepatitis B, or HTLV infection, the evaluation of risk of transmitting infection should include consideration of the age of the child, history of breastfeeding, and results of infectious disease marker testing; eligibility criteria must be in accordance with applicable governmental laws and regulations.

There are standard deferral times after immunization for allogeneic blood donation that can be used to determine the potential risk that may exist. Blood donors are typically deferred for four weeks after attenuated live virus vaccines such as oral polio, herpes zoster, and measles. In those cases in which a potential donor has recently been vaccinated, both the reason for the vaccination and the time interval should be evaluated to estimate the potential risk to a recipient. There should be specific SOPs in dealing with donors who had received smallpox vaccination. Donors must be screened for traveling to the area that would put them at risk for malaria, human transmissible spongiform encephalopathy, SARS (severe acute respiratory syndrome) during periods of world-wide prevalence, or rare strains of HIV, which may not be detected by current screening tests.

Cytomegalovirus (CMV) is not a relevant communicable agent or disease. However, allogeneic donors must be tested for evidence of infection with CMV, although the time frame for this testing is not restricted. A prospective donor who was previously positive for anti-CMV should be considered to be a seropositive donor. Use of CMV-seropositive donors is permissible; however, the Collection Facility (or transplant program, if applicable) should have a clearly defined policy or SOP that addresses the use of CMV-seropositive donors. Cellular therapy product labels from CMV-positive donors do not require the statements or biohazard label required for products positive for the agents listed in B6. However, there must be a SOP for communicating test results of donors who are positive or reactive for CMV antibody.

STANDARD:

CM6.4.4 The Marrow Collection Facility shall comply with B6.4.7 through B6.4.11 when primarily responsible for infectious and non-infectious disease testing of HPC donors.

Evidence:

Infectious disease testing is usually conducted by the Clinical Program during the donor selection process. However, if a facility conducts such testing for a program, this standard applies and the facility is responsible for completing the applicant portion of the inspection checklist for the referenced standards. For information regarding these standards, see the corresponding guidance sections.

STANDARD:

CM6.4.5 The Marrow Collection Facility shall comply with B6.4.3, B6.4.4, and B6.4.12 through B6.4.12.4 when primarily responsible for testing for the selection of allogeneic donors.

Evidence:

C6.4.5 only applies to Collection Facilities that are primarily responsible for testing allogeneic donors during the donor selection process. This testing is usually conducted by the Clinical Program. However, if a facility conducts such testing for a clinical program, this standard applies and the facility is responsible for completing the applicant portion of the inspection checklist for the standard.

CM7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

STANDARD:

CM7.1 ISBT 128 CODING AND LABELING

CM7.1.1 Cellular therapy products shall be identified according to ISBT 128 standard terminology or Eurocode.

Explanation:

ISBT 128 is the international information standard for transfusion and transplantation. Initially, ISBT 128 was developed for blood and blood component transfusion to increase the capacity for electronic data, to increase security and accuracy, and to permit unique unit identification globally. ISBT 128 has now been extended to include cellular therapy products and tissues. ICCBBA is the not-for-profit organization (www.iccbba.org) that is responsible for the development and maintenance of the ISBT 128 standard. ICCBBA maintains the databases for facility identification and product coding, assigns new product codes, and provides technical support. Several volunteer technical advisory groups support and inform ICCBBA. The Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) includes international representation from FACT, JACIE, ISCT, ASBMT, EBMT, NMDP, WMDA, ISBT, APBMT, and AABB. CTCLAG was formed to recommend standard definitions for cellular therapy products and rules for future assignment of cellular therapy product codes to draft labels and a labeling strategy for cellular therapy products, and to draft an implementation plan.

The two main pieces of the standard terminology to unambiguously describe a product are class and attributes. Classes are broad descriptions of products (such as HPC, Apheresis) and attributes are additional characteristics that uniquely define the product. A group of attributes, called Core Conditions, are required; these conditions include anticoagulant and/or additive, nominal collection volume, and storage temperature. There are also other characteristics called groups and variables that can be used to provide more information about the product. The intent is to capture relevant characteristics about the product from donor and collection through the final processing. It is not intended that products would be relabeled at the bedside, so attributes such as "thawed" would only be applied if that process occurred in the laboratory.

Cellular therapy products characterized in this standardized way can be labeled using common, well defined terms that are printed in eye-readable format. The eye-readable terminology may be in the native language of the country in which the product is collected. The language also adapts to machine readable technologies such as bar codes. In this way, the products will be universally understood and international transport and exchange will be facilitated.

The standard terminology is structured in a manner that allows revisions, additions, and deletions as necessary on a continuous basis. In this edition of Standards, the common major classes of products are defined as was current at the time of publication. No attributes were included because of their sheer number and complexity and also because this is a period of rapid growth in the use of ISBT 128 for cellular therapy. Modifications in definitions and additions will occur. As the responsible body for the database development and maintenance, ICCBBA is the appropriate authority for maintaining publications on current terminology. To prevent use of obsolete terminology, Marrow Collection Facilities are instructed to refer to Chapter Three, Cellular Therapy, of the ISBT 128 Standard Terminology document on www.iccbba.org for current terms and definitions related to cellular therapy.

If facilities have questions regarding ISBT 128 terminology, they can reference the Standards Terminology document, view the ICCBBA website at www.iccbba.org, or contact ICCBBA directly for additional information and assistance. The website also includes resources and tools for identifying and assigning standardized codes for cellular therapy products or requesting a code for a new unique product.

To utilize ISBT 128 to its full advantage by using its technical database in the unique identification of products worldwide and in the use of common language, facilities must register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each product's unique alphanumeric identifier. Facilities in or affiliated with hospitals may find that their Blood Bank has already registered and a unique facility code already exists. Stand-alone facilities can individually register and pay a nominal annual membership fee.

Eurocode International Blood Labeling Systems (IBLS) provides an international non-profit standard for labeling blood products and tissue to enhance security in blood transfusion and tissue transplantation.

The main benefits of Eurocode-IBLS are

- one bag - one number (unique product bag number worldwide)
- unique coding of product properties
- country codes following ISO 3166
- center codes according to national agreements

- matching enhanced space saving barcode systems
- charge-free access to all information via Internet

Eurocode IBLS assigns, publishes and maintains the databases for Eurocode facility identification (Center Codes) and product coding. Eurocode product codes also serve as part of the EU Single European Code for tissue (SEC).

Centers using Eurocode require a Eurocode membership. All resources such as Eurocode's technical specification, guidelines and the databases including all product and center codes can accessed freely on www.eurocode.org.

Eurocode product codes characterize each product by the product group it belongs to, supplemented by a set of properties laid out in up to 18 predefined categories such as anticoagulant used, storage temperature, donor/recipient relationship, intended use etc. These property categories are called "qualifiers".

Evidence:
Inspectors will inspect the Collection Facilities according to the current ISBT 128 terminology and definitions. Inspectors should review Chapter Three, Cellular Therapy, of the ISBT 128 Standard Terminology document at www.iccbba.org before conducting an inspection. It would be helpful to have the document available for reference during the inspection.

Example(s):
Facilities registered with ICCBBA who have fully implemented ISBT 128 labeling shall follow the ISBT 128 Standard. Labels that meet the appropriate information as defined by ISBT 128 comply with the Standards.

The appropriate product name for HPCs collected from marrow would be HPC, Marrow. The acronym HPC,(M), would be an abbreviation acceptable in documents, and possibly on partial labels. However, the U.S. FDA does not allow abbreviations on final product labels for licensed products.

Cellular therapy products with a biological license in the U.S. are subject to the bar code label requirements (21 CFR 201.25). The bar code, at a minimum, must contain the appropriate National Drug Code (NDC).

STANDARD:

CM7.1.2 Coding and labeling technologies shall be implemented using ISBT 128 or Eurocode.

Explanation:
The use of ISBT 128 or Eurocode for all cellular therapy products provides a uniform coding and labeling system worldwide. Such standardization is also beneficial to, and thus required for, autologous cellular therapy products.

In the sixth edition, active implementation for ISBT 128 coding and labeling within the Marrow Collection Facility was required. In the seventh edition, implementation of ISBT 128 or Eurocode is required. The implementation of coding and labeling are supported by FACT and JACIE and numerous

other organizations in the field for cellular therapy. On the ICCBBA website (http://www.iccbba.org), the most recent versions of the terminology are published, as well as resources to help centers implement ISBT 128. The Eurocode website (http://www.eurocode.org) includes guidelines, product codes, and other resources.

STANDARD:

CM7.2 LABELING OPERATIONS

CM7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products, product samples, and associated records.

Explanation:

The labeling SOPs should indicate that there are SOPs in place for each of the following:

- Ordering: initial orders and reorders.
- Receipt and quarantine.
- Verification of accuracy.
- Proper storage.
- Version control.
- Documented destruction of obsolete or unusable labels.

Evidence:

Label content (discussed below) will have been pre-reviewed by the FACT office (for FACT applicants) and by the JACIE inspectors (for JACIE applicants). Example labels will be available to the inspector prior to the inspection visit, and on-site, the inspector should verify that the labels submitted are in fact the labels in use at the facility. The inspector should focus more time on other aspects of the labeling process, specifically assessment of its adequacy to provide proper identification of products and product samples.

STANDARD:

CM7.2.1.1 Stocks of unused labels representing different products shall be stored in a controlled manner to prevent errors.

Explanation:

Labels must be stored in a designated area where access is limited to authorized personnel. Stocks of unused labels for representing different products must be stored separately to prevent errors. Labels should be organized physically or electronically so staff can readily identify the labels and be able to distinguish labels of different products from one another (e.g., by color-coding, size, or location). It is not acceptable to have labels of different types and for representing different types of products stored together with no separation. The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors.

Evidence:
The inspector should observe an organized storage area for the labels. There should be no obsolete version of labels available to staff, and labels in use must be the same as the approved labels.

Example(s):
Printed labels can be in containers to provide separation of each label type. Electronic labels can be in separate file folders for each label type.

STANDARD:

CM7.2.1.2 Obsolete labels shall be restricted from use.

Evidence:
The inspector should verify that the destruction process is documented and that there are no obsolete labels in the collection labeling/storage area.

STANDARD:

CM7.2.2 Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Marrow Collection Facility Medical Director or designee to confirm accuracy regarding identity, content, and conformity.

Explanation:
New labels must be placed in a quarantine area upon receipt. The new labels must be inspected for:

- Manufacturing or printing defects.
- Form or version number, if applicable.
- Legible and correct eye-readable information.
- Identity to source (original) label that has been approved for use by the Collection Facility Medical Director or designee.

Inspection must include comparison with a label approved by the Collection Facility Medical Director or designee.

The inspection of labels at receipt or after printing must be performed by one person and independently verified by a second person. The process and outcome must be documented prior to release of the labels from the quarantine area.

Evidence:
Validation studies of the print-on-demand labels must be evident for the inspector's review. Personnel confirmation that the correct label was printed must also be documented.

Example(s):
A form where superseded labels and new labels are attached to show the changes in the label content may be helpful. Approval of the Collection Facility Medical Director or designee can be documented on this form. The same form can be a used to document acceptability of the new label and inspection of content by two staff.

The Collection Facility might conduct a risk-assessment to determine if a label produced by the Processing Facility substantiates adherence with the approved labeling template.

STANDARD:

CM7.2.3 *Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Marrow Collection Facility Medical Director or designee.*

Explanation:
"On demand" means that the labels are printed just prior to the labeling process. Print-on-demand label systems must be validated against approved label templates. Each on-demand label does not need to be validated so long as the system by which they are printed has been validated to confirm accuracy regarding identity, content, and conformity to the templates. Personnel do, however, need to confirm that the correct label was printed.

The Collection Facility should first develop a validation protocol for implementation of "on-demand" computer software. Upon implementation of the process, the facility must confirm and document that the label printed meets the criteria of acceptability.

Evidence:
Validation studies of the print-on-demand labels must be evident for the inspector's review. Personnel confirmation that the correct label was printed must also be documented.

STANDARD:

CM7.2.4 *A system for label version control shall be employed.*

Explanation:
The document control system used for these various elements and what constitutes a label version must be defined by the Collection Facility. Any change in the label or label element that would change the interpretation of the label would constitute a version change. Only the current version of each label should be available for use in the collection area.

Evidence:
The inspector should verify that the versions of labels in the labeling/storage area are the current version.

Example(s):
Changes in the requirement for a uniform product proper name (i.e., from Hematopoietic Progenitor Cells-Marrow, to HPC, Marrow) or changes in the wording of required statements or warning statements would require a version change to that base label or label element.

A checklist where changes to a label's content are described is an example of how to document labeling changes. This could also include documentation of label content accuracy and destruction of obsolete labels. A master list of labels in use with version numbers helps with document control.

STANDARD:

CM7.2.4.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by applicable laws and regulations, whichever is longer.

Explanation:
Obsolete or unusable label stock should be defaced immediately to prevent their accidental use and then destroyed. However, as a controlled document, representative obsolete labels (or label templates) and their inclusive dates of service, must be archived minimally for 10 years.

Obsolete labels should be removed from inventory and discarded as soon as a new version is put in for use. The labels that are replaced by new versions must be archived.

STANDARD:

CM7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

CM7.2.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

Explanation:
Labels for re-packaged cellular therapy products must conform to the proper label content as described in Appendices II and III as applicable. Criteria for re-packaging of cellular and tracking mechanism should be included in SOPs.

Evidence:
If products are repackaged, the inspector should examine the labels on a repackaged product to ascertain whether there are mechanisms in place (either on the label itself or via accompanying paperwork) to track the product from its origin to the final disposition.

STANDARD:

CM7.2.5.2 A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.

Explanation:
This standard requires facilities to have a careful process for electronically transmitting information (such as with a bar code) and to double check the information rather than becoming solely dependent on the technology to work correctly.

For Collection Facilities that use automatic labeling systems that include computer-assisted label verification (such as a bar code scanner) of parts of the label, electronic verification must be part of the label system validation. Details regarding validation of electronic record systems are found in C11.

Evidence:
For systems using computer-assisted label verification to confirm label accuracy (such as bar-code scanning), SOPs and records should show how the automatic verification works.

STANDARD:

CM7.2.6 *When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.*

Explanation:
The cellular therapy container should not be covered wherein the contents cannot be viewed. Inspection of the content is essential in determining abnormal color of plasma that could be due to hemolysis, bacterial contamination that could affect the safety of the product, and clots that could reduce the efficacy of the product.

Evidence:
The inspector should examine labeled products on-site to verify that labels are firmly attached or affixed and that sufficient area of the product remains uncovered to allow examination of contents.

STANDARD:

CM7.2.7 *The information entered on a container label shall be verified by one (1) qualified staff member using a validated process or two (2) qualified staff members.*

Explanation:
One person who is trained in labeling using a validated process, or two people who are trained in labeling in accordance with institutional requirements and governmental regulations, must confirm that the manually entered information on the label is accurate. Verification of the information must be documented in the collection records. It is important for the collection staff to verify the accuracy of the donor/patient information and to confirm that all parts of the collection (product labels, tie tags, sample tubes, and associated forms) are labeled completely and legibly before removing them from the proximity of the donor.

In addition to confirming correct content, the label verification should include:

- The label is correctly affixed to the component (and/or tie tag).
- The correct label is positioned appropriately.
- The label is identical to the one specified in the SOP.
- Hand written information is written with indelible ink.
- All information is legible and accurate.
- The unique identifier is firmly affixed to the product bag and identical to the identifier on facility associated forms.
- The label is not damaged or defaced.

Evidence:
The inspector must verify the documentation in the collection records. Initials or signatures of staff as defined by the labeling process should be present in the collection records.

STANDARD:

CM7.2.8 Labeling elements required by applicable laws and regulations shall be present.

Explanation:
Label elements that are required by governmental regulation must be clearly visible. The Collection Facility should review applicable governmental requirements for labeling and format labels accordingly.

STANDARD:

CM7.2.9 All data fields on labels shall be completed.

Explanation:
All data fields on a label must be complete; fields for which information is not required must be filled as "NA".

Evidence:
The inspector should examine labeled products on-site to verify the presence of appropriate information on the label.

Example(s):
In some cases a base label is used, with stickers applied containing specific elements based on the product type or the modification that was performed. Also, many facilities apply biohazard labels and warning statements if applicable using tie tags.

STANDARD:

CM7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

Explanation:
Indelible ink must also be used to record any information entered manually on the label. Inks and labels must be resistant to alcohol wipes and sprays if they are likely to be subjected to such liquids at collection, in the Processing Facility, or on the ward. Validation of the labels should include the properties of the ink used.

Evidence:
Documentation of evidence that the inks and labels were demonstrated to be resistant to alcohol wipes and sprays should be available to the inspector.

STANDARD:

CM7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

Explanation:
Adhesives that are applied directly to the cellular therapy product bag have the potential to leach through the plastic into the product itself. Collection Facilities must use materials that meet criteria, if any, established by applicable regulatory authorities.

This standard does not apply to labels applied to a base label of a cellular therapy product bag.

Example(s):
Collection Facilities in the U.S. should contact the FDA regarding any labels affixed directly to the cellular therapy product bag to determine what data is needed to demonstrate that the labels meet FDA requirements. For further information, see the FDA document, "Guideline for the Uniform Labeling of Blood and Blood Components," (August 1985). This document is available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM080974.pdf.

STANDARD:

CM7.2.12 The label shall be validated as reliable for storage under the conditions in use.

Evidence:
Labels must have been validated to confirm they remain legible under the conditions in which they are used.

Example(s):
Validation of a label includes the properties of a label applied on the product and that the product is stored in its proper storage temperature.

STANDARD:

CM7.3 PRODUCT IDENTIFICATION

CM7.3.1 Each cellular therapy product collection shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.

CM7.3.1.1 The cellular therapy product, product samples, and concurrently collected samples shall be labeled with the same identifier.

CM7.3.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.

Explanation:
The product identifier must be unique. Unique is defined as not being used for any other purpose. Thus it is not acceptable to use only patient information (such as medical record number or social security number) or only the donor information (name, medical record number, or registry identifier) to identify the cellular therapy product. Generally, a unique identifier also implies that there is reasonable confidence that it will not be used for another purpose. Cellular therapy products collected from a

single donor at different times must be distinguished from each other by different unique product identifiers.

The essential point is that each cellular therapy product can be unambiguously traced from donor to recipient, and through all transport steps, processing steps, and storage locations. The label must clearly indicate the identity of the facility that assigned the product identifier, with the exception of cellular therapy products shipped by registries, where the source facility must remain confidential. In such cases, the records that accompany the product must allow tracing to the donor.

Each Collection Facility must have a SOP indicating how a unique identifier is assigned and tracked and include acceptable modifications that can be made to the product label or identifier. When a cellular therapy product from a single donor is divided into multiple containers, each container must be uniquely labeled. If products are being pooled, the pool number must allow tracing to the original products. Note that only products from a single donor may be pooled unless specifically allowed for a given protocol by the appropriate regulatory authority.

Product and donor samples collected at the time of cellular therapy product collection should be labeled so as to prevent misidentification. At a minimum, this must include the donor's name (except for the case of unrelated donors), identifier, and date of sample collection.

Evidence:
The inspector must review the SOP for labeling the product with the unique identifier and how the identifier is assigned. There should be evidence that the product identifier is not duplicated and this could be demonstrated with a product identifier log. The inspector should perform a review to determine that the product identifier can be traced to the records used from collection to distribution of the product. The SOP for collection and filtration shall be sufficiently detailed to permit the inspector to match the collection records to a uniquely identified final collected product and to the donor and recipient.

Example(s):
The donor or recipient registry number can be used by the local site as the sole or additional identifier if it is combined with other information that makes it unique, such as the collection date, so that each cellular therapy product can be uniquely identified.

Identification of products with multiple containers may occur by modifying the unique identifier on each container with a suffix (either letter or number) or by modifying the product label on each bag (such as Bag 1 of 2, etc.).

Marrow may be initially collected into two or more bags. In addition, following collection and filtration, the marrow may be transported to the processing laboratory or clinical unit in two or more bags. All bags resulting from a single harvest procedure should be linked to the harvest by a unique identifier.

STANDARD:

CM7.3.1.3 Supplementary identifiers shall not obscure the original identifier.

CM7.3.1.4 The facility associated with each identifier shall accompany the cellular therapy product.

Explanation:
The Collection Facility may assign additional identifier(s) to a product; however, it is recommended that no more than two unique product identifiers be affixed to a product container. The original identifier may not be obscured. If a supplemental unique identifier is replaced with another identifier, records must link the current unique identifier to the previous one.

Evidence:
The inspector will observe label SOPs if this function is being performed by the Collection Facility; if not, the inspector will verify that the supplemental labeling SOPs is in place and the content of the label is appropriate.

Example(s):
To prevent obscuring the original product identifier and other label information, the Collection Facility may record the supplemental identifier to a tie tag.

STANDARD:
CM7.4 LABEL CONTENT

CM7.4.1 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container shall bear the information in the Cellular Therapy Product Labeling table in Appendix II.

CM7.4.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information (COI) for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."

Explanation:
The required label content as specified in Appendix II represents minimum requirements, and must be present as indicated at the various stages of product collection, processing, and distribution.

While HPC, Marrow products may not be regulated by applicable health authorities, FACT and JACIE treat these products the same as HPC, Apheresis for purposes of label content. Therefore, HPC, Marrow product labels must include all label content as required by the information in Appendices II, III, and IV.

Accompanying paperwork should be packaged in a secondary bag with the product for transport to the processing facility or clinical site. It is not acceptable to transport multiple product bags, from different donors, using partial labels with all of the additional information on a single inventory sheet.

When labeling products after collection, it is important to include the time when collection of the product was completed, along with the time zone if different from the time zone of the anticipated processing facility, so that the Processing Facility will have an accurate determination of the age of the product and be able to apply the appropriate expiration date and time.

The Collection Facility address should be explicit enough to correctly identify the location and contact the facility if questions arise or an emergency occurs during processing and/or transportation. For

products distributed by an unrelated donor registry, a facility identifier that does not include the Collection Facility name and address should be used to protect donor privacy; however, this information should be part of the processing record or be available to the Processing Facility if needed.

A biohazard label must be attached or affixed to any cellular therapy product from which a donor sample has tested positive for a relevant communicable disease (excluding CMV) or when donor screening indicates a risk factor for a relevant communicable disease or disease agents. Table 2 of the inter-organizational Circular of Information for Cellular Therapy Products outlines when biohazard labels must be used. Biohazard labels can only be applied to products not required to be labeled biohazard when specific circumstances for their use are defined by facility or program policy. Biohazard labels must not be applied indiscriminately. These labels are meant to denote a greater hazard than that posed by any biological product. Using biohazard labels on all products without rationale that is documented in facility records is considered a deficiency.

Warning labels are required to be affixed or attached to the product when product testing or screening is positive for infectious disease risk or is incomplete (see Appendix II).

Communicable disease testing is not required for autologous donors, unless required by applicable laws, in conjunction with product collection nor is there a requirement for donor eligibility determination. However, if autologous donor testing and screening is not performed, or is incomplete, the product label must contain the statement "Not Evaluated for Infectious Substances." In addition if the autologous donor is tested or screened prior to collection and is found to be positive or at risk for a relevant communicable disease, the product label must bear a biohazard label and the appropriate warning statements. Since autologous recipients are not at risk of contracting a communicable disease from themselves (they already have the disease), the statement "Warning: Advise patient of communicable disease risk" is not required on autologous product labels even if donor testing results are positive, although a biohazard label is required.

If the complete allogeneic donor screening and testing is not performed, these products must be labeled with the statement "Not Evaluated for Infectious Substances." This statement must be also affixed or attached to the label of any product when either donor testing or donor screening for infectious disease risk has not been completed within the required 30-day period for HPC products or seven day period for other products (allogeneic and autologous products). The label of products for which donor testing is positive must also include the statement "Warning: Reactive test results for (name of disease agent or disease)" with the name of the disease agent or disease specified.

Once regulated products have reached the stage of licensure, the label or accompanying records must include the statement "Rx Only" indicating that the product may only be distributed by a prescription from the transplant physician. The physician order form required by the Standards may serve as the prescription. As of this writing, only cord blood has reached the level of licensure.

Evidence:
Prescreening of the labels by the FACT office or JACIE inspectors will be performed and every effort made to correct any deficiencies prior to the on-site inspection. Examples of all labels in use by the applicant facility will be provided to the inspector prior to the on-site inspection. For applicant programs performing both allogeneic and autologous transplants, examples of labels will include collection, processing, transport, and distribution labels for both types of transplant. In addition, labels illustrating each cellular therapy product source handled by the program should be included. Partial

labels, if used, should be included. Tie tags, instructions to the infusionist, biohazard, and warning labels should also be included. If any expected label is not included in the pre-inspection documents, the inspector should request it from the applicant Collection Facility or the FACT or JACIE office.

The inspector should review the labels prior to the on-site inspection and determine if deficiencies have been corrected. This will maximize the efficiency of the inspection by allowing the inspector to focus on elements that can only be verified on-site. However, when on-site, the inspector should verify that the labels currently in use are identical to those submitted prior to the on-site inspection and correspond to the labels in the SOP. If this is not the case, the inspector will need to resolve the discrepancies and verify that each label in use meets the requirements listed in Appendix II. The inspector should further verify that labels are available for every type of cellular therapy product collected, with suitable modifications. Examples of completed labels must not contain blank spaces. "N/A" or "none" or equivalent should be used as indicated.

Autologous product labels should be examined to confirm that "Not Evaluated for Infectious Substances" is present when the donor screening and testing does not contain all of the elements listed in B6. If the Collection Facility utilizes a partial label, the inspector must confirm that the SOP describes the use of the partial label, provides an example of the partial label, and includes the mechanism for providing the additional information that is not included on the partial label.

The inspector should ask to see the SOP that defines the conditions for using a biohazard label and determine if the facility's SOPs are adequate and appropriately safe to prevent transmission of infectious disease.

Example(s):
Testing and screening within 30 days for TC-T cell products as well as HPC products, and at the time of collection, are required under EU guidelines.

Products that are regulated under section 351 of the PHS Act in the U.S. must be labeled with the statement "Caution: New drug limited by federal law for investigational use." Currently HPC, Apheresis products and HPC, Cord Blood collected from unrelated donors for NMDP are regulated under an IND held by NMDP. Such products must contain this statement, attached or affixed to the label or accompanying the product.

Additional information may be attached to the product via a tie tag, or included in accompanying documentation, as detailed in FACT-JACIE Standards, Appendix II.

Note that residence in a country on the U.S. Department of Agriculture list as at risk of BSE is considered to constitute a risk identified by donor screening. Thus, allogeneic donor products require a biohazard label and the statement "Warning: Advise Patient of Communicable Disease risks."

The recommended storage temperature listed on the label may include ranges (e.g., 2-8° C, 20-26° C).

STANDARD:

CM7.4.3 *Labeling at the end of collection shall occur before the cellular therapy product bag is removed from the proximity of the donor.*

Explanation:
Collection product labels, tie tags, sample tubes, and associated forms must be labeled completely and legibly before removing them from the proximity of the donor to prevent mix-up.

Evidence:
The inspector should verify that labeling at the completion of the collection occurs before the product is removed from the proximity of the donor and contains all the information listed in Appendix II. The SOPs for collection and filtration shall be sufficiently detailed to permit the inspector to match the collection records to a uniquely identified final collected product and to the donor and recipient.

Example(s):
Proximity of the donor may be described as at bedside where the product collection occurs. Labeling of the product beside the donor will prevent mix-up when there is more than one donor being collected in a collection area.

STANDARD:

CM7.4.4 *Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix IV at the time of distribution.*

Explanation:
The FDA cGTP regulations have specific requirements regarding the information that must accompany a cellular therapy product at the time of distribution. Requirements for products from allogeneic donors are listed in Appendix IV. A statement is required attesting to donor eligibility (or ineligibility) based on the screening and testing that was performed, a summary of the records used to make the donor eligibility determination, and the identity and address of the facility that made that determination. This summary must include results of the donor screening for infectious disease risk and the communicable disease test results. The test and screening results must be listed with an interpretation of the values as positive or negative. There must also be a statement confirming that communicable disease testing was performed by a laboratory with the required qualifications. For products that are distributed for administration, the product administration form can be used for this purpose. For products that are distributed to another facility, this information must be included. If the Collection Facility is responsible for allogeneic donor eligibility determination, that facility is also responsible to distribute the above information to the Clinical Program and Cell Processing Facility. If the Clinical Program determines allogeneic donor eligibility, the Collection Facility must obtain the information from this group so that it may accompany the product.

According to FDA and non-U.S. regulations, as applicable, there are many statements, results, and documents that must "accompany" the cellular therapy product at all times after the determination of allogeneic donor eligibility has been documented (see 21 CFR 1271.55).

The FDA Final Guidance ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Product [HCT/Ps], August 2007) states that electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This Guidance Document is available at
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm.

Example(s):
It is permissible to have hard copies of each item physically accompany the product, and in some cases, that may be most appropriate, as when a product leaves the Collection Facility and is transported to another institution for processing, storage, and/or administration.

STANDARD:

CM7.4.5 *For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after the use of the product.*

Explanation:
If the Collection Facility participates in allogeneic donor eligibility determination, completion of this determination must be documented.

Evidence:
The inspector should review that the completion of determination documentation is completed within the timeframes outlined in the Collection Facility's SOPs.

Example(s):
Related documentation that allogeneic donor eligibility was completed during or after the use of the product should be in the donor's or recipient's records. Urgent medical need documentation to release the cellular therapy product should also be present.

STANDARD:

CM7.4.6 *Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "Not For Admin."*

CM8: PROCESS CONTROLS

STANDARD:

CM8.1 *Collection of cellular therapy products shall be performed according to written collection Standard Operating Procedures.*

Explanation:
To be considered complete, the collection SOP should include at least the following:

- Physical details of the collection procedure.
- Reagents and equipment to be used.
- The type of anticoagulants and/or solutions added to the cell collection container during the procedure.
- Requirements for monitoring the donor prior to, during, and after collection (as applicable).
- Recognition and treatment of adverse reactions.

- Expected results of the collection.
- Labeling of cell products.
- SOPs for storage and distribution of the cells.
- Methods for detection of clerical errors.
- SOPs for quality testing.
- Recording of date and time of each significant step.

Evidence:
The inspector should observe a portion of a collection procedure to determine whether or not the personnel follow applicable SOPs. If there is no collection procedure scheduled for the day of an on-site inspection, the inspector should ask the Collection Facility staff to perform a mock collection, including all parts of the donor interview and consent for which that facility is responsible, and all labeling and storage steps. In addition, inspectors should review collection records to verify that specific elements of the procedure were carried out according to the SOP. Deviations from the SOP may indicate inadequate training or out-of-date SOPs.

Questions may be asked to determine: Are cellular therapy products from different patients stored in the Collection Facility at the same time? Are products labeled at the donor's side prior to removal from the proximity of the donor? Are reagents identified as dedicated to a single collection procedure? Is there a record of the lot numbers and expiration dates for all reagents used in collection?

Example(s):
The Collection Facility may develop a document to record data that are captured according to the collection SOP. These data may include the items in the explanation section. The document should also identify the staff performing each step in the SOP.

STANDARD:

CM8.2 *There shall be a process for inventory control that encompasses equipment, supplies, reagents, and labels.*

CM8.2.1 *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.*

CM8.2.2 *Each supply and reagent used to collect cellular therapy products shall be visually examined at receipt and prior to use for damage or evidence of contamination.*

Explanation:
Cellular therapy product quality, as measured by adequate viability, integrity, lack of microbial contamination, and lack of cross-contamination, may be affected by the equipment, supplies, and reagents used for collection. Therefore, these items used in collection that might affect product quality must be identified and tracked. The identification and the tracking of supplies, reagents, and equipment used to collect cellular therapy products must be described in an SOP (see CM5.1). Supplies and reagents must be examined for contamination, breakage, discoloration, etc. at receipt. Records must be kept of the receipt and qualification of each supply or reagent and must include the type, manufacturer, lot number, dates of receipt, and expiration date. There must be a mechanism to link the supplies and reagents, lot numbers, and expiration dates to each product manufactured and, conversely, each

product collection record must include the identity of the supplies and reagents that were used. The reagents and supplies must also be visually inspected for contamination, breakage, and discoloration, immediately prior to use and procedure initiation; findings must be documented.

Generally, the cellular therapy product inventory and reagent and supply inventory are separately managed. Each product must be assigned a unique alphanumeric identifier that is part of the control system. Equipment, supplies, and reagents should be connected to the product through the unique identifier or through an alternative system. Testing laboratories may require that other identifiers be used. Any blood sample or tissue for testing must be accurately labeled to confirm identification with the donor and must include a record of the time and place the specimen was taken. The system must include documentation that materials under the inventory control system meet predefined facility requirements.

Evidence:
The inspector should confirm that there is a process in place to determine acceptability of all critical materials (reagents, supplies, labels, cellular therapy products, and product samples) before they are accepted into inventory and made available for use.

Description of acceptable criteria for reagents and supplies may be found in logs or relevant SOPs.

The inspector should review the inventory control process and documentation of supply and reagent examinations at receipt and prior to use to verify that the Collection Facility takes steps to be certain there is no obvious evidence of damage (e.g., leakage, damaged box).

Example(s):
The system in use may utilize an electronic system or a log book to enter all incoming supplies and materials.

Equipment identification can be achieved by using a pre-existing serial number, but may be better achieved by assigning a unique identifier that is visible on the piece of equipment. A more casual designation, such as "Brand X centrifuge," is less desirable since over the course of time more than one centrifuge might fit that description. It is possible to accomplish this by the use of serial numbers and records of dates of use; however, over time, this is more difficult to track reliably.

STANDARD:

CM8.2.3 *Supplies and reagents coming into contact with cellular therapy products during collection shall be sterile and of the appropriate grade for the intended use.*

Explanation:
Supplies and reagents that come into contact with cellular therapy products must be clinical or pharmaceutical grade, as appropriate, and free of microbial contamination. It is recognized that reagents not approved for human use were commonly used in the past (e.g., the use of various tissue culture media). However, Collection Facilities are expected to keep up to date on current collection techniques.

A Certificate of Analysis (COA) should be obtained if available from the manufacturer . Upon receipt of reagents and supplies, personnel should document review of package inserts to confirm that there are no changes in the intended use, and should retain the most current package insert for reference.

Evidence:
The inspector should request COAs of the reagents that are approved for human use or of pharmaceutical grade. Package inserts of reagents and supplies provide information regarding their intended use.

STANDARD:
CM8.3 *Equipment for the marrow collection procedure shall conform to applicable laws and regulations.*

Evidence:
The inspector should review the COA or CE of commercially available disposable sets used by the Collection Facility.

Example(s):
European Directive 2006/17/EC Annex IV 1.3.10 specifies that where possible, equipment that is compliant with the CE Marking Directive must be used for cellular therapy product collection. CE marking is a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation implementing certain directives. Staff using such equipment must have appropriate training. For additional guidelines regarding this requirement, see: http://ec.europa.eu/enterprise/newapproach/legislation/guide/.

STANDARD:
CM8.4 *Autologous or CMV-appropriate and irradiated blood components shall be available during the marrow collection procedure for all donors.*

CM8.4.1 *Allogeneic blood components administered to the donor during marrow collection shall be irradiated prior to transfusion.*

Explanation:
Donors may require a blood transfusion during the marrow collection procedure. Marrow Collection Facilities need to be prepared to provide appropriate blood products. Autologous units may be collected prior to the marrow harvest, or allogeneic CMV-appropriate and irradiated units may be used. The decision to use autologous or allogeneic blood depends on the benefits and risks to the donors, especially in the case of pediatric donors.

A special concern for the allogeneic donor is the fact that transfused allogeneic blood contains lymphocytes that can become part of the collected cellular therapy product. Therefore, these transfusions must be gamma-irradiated to prevent engraftment of third-party lymphocytes in the transplant recipient. Because of the occasional need for a second cellular therapy product collection, it is advisable to continue irradiating blood transfused to the donor in the postoperative period[1].

It is expected that normal sized, adult marrow donors would donate autologous blood and therefore not require allogeneic blood. However, in the situation of small marrow donors and large recipients, transfusion is expected. Many places have difficulty collecting autologous blood from donors <40 kilograms (kg). If the recipient is adult size and the donor is 25 kg (common in sibling transplants), transfusion is expected, frequently occurs during the collection, and the blood products must be irradiated. Additional information can be found in Transfusion Support of the Marrow Donor[2].

The use of irradiated blood components during the immediate post-operative period may be necessary if there is any consideration that the donor may need to donate a second product in that immediate timeframe. Under most circumstances, the requirements for irradiated blood products are during collection, but physicians might want to consider the use of irradiated blood components during the immediate post-operative period. For example, if children need to be harvested twice, or if the target yield was not achieved, a supplemental peripheral blood product from the donor may be necessary.

References cited:

1. Snyder El and Haley NR (eds): Cellular Therapy: A Physician's Handbook. Published by AABB, 2004:15.

2. Petz LD and Swisher SW, eds: CLINICAL PRACTICE OF TRANSFUSION MEDICINE, Second edition, 1981; Third edition 1996.

Evidence:

The inspector should verify the availability of irradiated, leukoreduced, and/or Cytomegalovirus (CMV) sero-negative cellular blood products and other blood components in case they are needed. A review of the process by which such products are ordered should provide adequate evidence.

STANDARD:

CM8.5 *Before cell collection is undertaken, there shall be a written order from a physician specifying, at a minimum, timing and goals of collection.*

Explanation:

The physician who evaluates the donor and makes the decision to proceed is not always the same one who actually collects the cells. The written order is required as a mechanism to be certain that there are no misunderstandings among team members regarding the specifics of the collection. The written order should include at least:

- Identity of the donor.
- Identity of the allogeneic recipient (if applicable).
- Timing of collection.
- Date and time the cells are needed by the recipient (as applicable)
- Cell type.
- Cell dose required.
- Appropriate authorized signatures.
- Blood group determination.
- Recipient weight.
- Donor weight and height.
- Pre- and post-collection laboratory results guidelines.

Pre- and post-collection laboratory results guidelines may include relevant hematologic and biochemical analyses. SOPs should outline how the Collection Facility will handle patients whose laboratory values are outside of the acceptable ranges.

Written orders will clarify the desired end result of a collection procedure. The information on the written order will help achieve the product cell dose needed for the recipient.

Evidence:
The inspector should confirm that the written order meets the criteria and, if there are any deviations, that they are approved.

STANDARD:
CM8.6 There shall be peripheral blood count criteria to proceed with collection.

Explanation:
Collection Facilities may set their own timeframes for performing testing on donors. Some registries may have specific requirements. Not only does the testing need to be performed, but facilities must have predetermined limits for when collection may or may not proceed.

STANDARD:
CM8.7 There shall be written documentation of an assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

Explanation:
Day-to-day management of the donor is the responsibility of the Collection Facility. It is incumbent on the collection team to safeguard the health of the donor at the time of collection. This does not require a complete history and physical examination by a physician for each collection procedure. Rather, the records from the initial evaluation (including consent for the procedure and documents regarding the goals of the collection procedure) must be immediately available to and reviewed by the collection team. A physician or registered nurse on the collection team must evaluate the donor before each collection procedure to determine if there have been changes in the health of the donor or changes in medications since the initial donor evaluation.

The interim evaluation should include a record of vital signs and a focused donor screening regarding changes in health, medications, or risk factors (e.g., tattoos, needle exposure) that are pertinent. Donors should also be assessed according to SOPs determined by the collecting facility, but at a minimum should include vital signs. The results of interim laboratory tests must be obtained to determine if the donor meets the minimal blood count criteria to proceed with the collection.

This evaluation must be documented as part of the permanent record of the donor. The evaluation must be performed by a qualified member of the transplant team competent in assessing the health status of the donor. Competency shall be defined in the program or facility SOP manual. The Collection Facility shall have a system in place to confirm donor identity so that all samples, labels, and records are appropriately and consistently completed.

Evidence:
The inspector should verify in the donor records that evaluation meets the minimal criteria prior to collection. The documentation of an approved planned deviation should be found if minimum criteria are not met.

STANDARD:

CM8.8 *General or regional anesthesia, if required, shall be performed or supervised by a licensed, specialist-certified anesthesiologist.*

CM8.9 *Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.*

Explanation:
Administration of hematopoietic cytokines such as G-CSF is not free of side effects. There are reports of serious morbidity and mortality among recipients of hematopoietic growth factors. A licensed health care professional who is trained in dealing with complications of G-CSF must supervise its administration. Supervision can be exercised either directly (especially during the first injection) or indirectly (e.g., via phone contact with nursing personnel) for the subsequent injections, especially if self-administration is considered. The interim assessment of donor symptoms related to G-CSF and relevant laboratory tests should be performed, and dose adjustments made accordingly.

When parameters have been set by the Clinical Program as to when not to administer mobilizing agents, the Collection Facility should have a mechanism in place to confirm all relevant personnel receive and follow these parameters.

Evidence:
The inspector should verify that the licensed health care professional supervising G-CSF administration is experienced in recognizing adverse reactions due to G-CSF. When appropriate, donor side effects potentially attributable to G-CSF should be reviewed by the inspector.

Example(s):
The patient record should show the doses of the mobilization agents to be administered and the person administering the agent.

STANDARD:

CM8.10 *The Marrow Collection Facility shall utilize a process for assessing the quality of cellular therapy products to confirm product safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.*

Explanation:
There is inherent variation among biological products that cannot be easily controlled. The consistent use of validated or qualified collection procedures and the use of testing to monitor collections can greatly reduce the inherent variability and result in high quality products. Quality monitors should be in place for tracking integrity, viability, contamination, sterility, or cross-contamination. SOPs are required that describe each collection procedure and its associated process control (see CM5).

STANDARD:

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

Explanation:
The Collection Facility Medical Director is responsible for defining release criteria for cellular therapy products distributed by the Collection Facility, identifying the tests to be performed, and testing intervals during collection. The release criteria may differ depending on whether the products are released to a processing facility for further manufacturing or directly to a clinical service for administration. This information must be clearly outlined in an SOP (see CM5.1). All test results that are available at release must be present in the collection record.

Evidence:
Documentation that the cellular therapy product met release criteria prior to distribution must be present. For products that did not meet release criteria, the required documentation for exceptional release should be present.

Example(s):
Additional release criteria that may be pertinent to a cellular therapy product being released to a processing facility include the following: the product is sealed completely without evidence of leakage, product labeling is complete and correct according to expected data, the product has been stored appropriately, expected product and/or donor samples are labeled and available to accompany the product, and allogeneic donor eligibility determination documentation is available.

STANDARD:

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

Explanation:
Methods of collection must be validated to result in acceptable cell viability, sterility, and recovery. This means that the methods, including reagents, anticoagulants, additives, equipment, and supplies used, and the environment of the collection, have been shown to consistently work in the past to result in a predictable and reliable product. The use of audits and reviews, as defined by the QM Program, are a means of continued validation of collection methods. Any new equipment or collection procedure must be qualified or validated (as applicable) prior to implementation and shown to result in acceptable cell, viability and recovery.

Evidence:
The inspector should verify the validation documentation prior to implementation of collection methods and periodic verification of indicators that show compliance with the predetermined release criteria.

Example(s):
Cell viability, sterility, and recovery data are routinely captured by the Processing Facility. The Collection Facility may request this information and use it for a retrospective validation of the method of collection.

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

Explanation:
This standard requires the use of aseptic technique as defined in A4 of the Standards. Harvested bone marrow must be transferred into sterile, commercially available bags approved for human use, or collected in a commercially available set approved for human use.

Evidence:
Aseptic techniques used during marrow collection can be verified by reviewing the sterility of the cellular therapy products collected.

Example(s):
Sterility data are routinely captured by the Processing Facility. The Collection Facility may request this information and use it for a retrospective validation of the method of collection.

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

Evidence:
The inspector should verify that the donor collection record reflects the appropriate parameters for pediatric donors as described in the Collection Facility's SOP.

Example(s):
Collection SOPs may reference the method applicable for pediatric donors, such as the need for the use of irradiated allogeneic red cell components if transfusion support is required when the age and weight of the pediatric donor prevents the application of autologous pre-donation techniques.

The written order for the product volume collection or cell type and dose from bone marrow should be appropriate for the age and size of the pediatric donor.

STANDARD:

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

Explanation:

Sterile transfer bags designed for cellular blood products are required for the collection of cells from bone marrow. Commercially available disposable sets are available. Ideally, the tubing connected to the bag should be heat-sealed or sealed with a grommet at the end of the collection prior to transport.

Evidence:

The inspector should observe the end of the collection procedure and verify that the collection container is sealed. Also verify the presence of heat sealers or grommets in the unit if applicable as indicated in the SOP.

Example(s):

Documentation of transfer bags' sterility from the manufacturer can be used as part of the qualification of the vendor. Inspection of collected cellular therapy products for a proper seal may be used as a product release criterion.

STANDARD:

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

Explanation:

Commercially available sets with at least in-line 500 and 200 micron filters are certified by the manufacturer and this certification should be retained for qualification of the supply.

Evidence:

The inspector should review the COA or CE of applicable commercially disposable sets used by the Collection Facility.

Example(s):

European Directive 2006/17/EC Annex IV 1.3.10 specifies that where possible, equipment that is compliant with the CE Marking Directive must be used for cellular therapy product collection. CE marking is a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation implementing certain directives. Staff using such equipment must have appropriate training. For additional guidelines regarding this requirement, see: http://ec.europa.eu/enterprise/newapproach/legislation/guide/.

STANDARD:

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

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

Explanation:
Records must be used during cellular therapy product collection and must be completed in real time as the procedure is performed. For collection procedures, it is acceptable to record the major steps of the collection in groups, such as sets of aspirations rather than every aspiration. Records must be accurate, indelible, and legible, and must identify the person performing the work and the dates of the various entries. Records of identification codes of personnel including methods to link the name and/or signature to the initials or other identification codes used in other documents and records must be maintained. These records should include dates of employment of the personnel.

In the event that an error or adverse event results during or as a consequence of collection, it is important to perform an investigation in a timely manner. From the appropriate record it must be possible to investigate each critical step, including identification of the individual responsible and the reagents and equipment utilized.

Evidence:
The inspector should review collection records to determine if they were completed in real time and are sufficiently detailed to trace all steps in the collection procedure. The inspector should verify that records of collection have the date of performance of the procedure and staff identification for the steps performed.

Example(s):
The Collection Facility may develop a collection record that will allow documentation of detailed collection steps in real time and identification of staff performing the procedure. Labeling and release of cellular therapy products may be included in such a collection record. Use of electronic records should have the concurrent documentation elements.

In the U.S., concurrent record keeping is required in 21 CFR 1271.270(a).

CM9: CELLULAR THERAPY PRODUCT STORAGE

STANDARD:

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

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

Explanation:
The Collection Facility shall establish a process to be certain that cellular therapy products are stored in a manner that maintains their integrity and potency, and that products are not released before all release criteria have been met.

The Collection Facility should define what constitutes storage. Any duration of time between the end of the collection and distribution to a Processing Facility or to a recipient for administration constitutes storage. Direct distribution to the Clinical Program is discouraged. Particular attention shall be paid to the security of the facility and control of temperature and humidity when cellular therapy products are stored in the facility for extended periods, such as overnight. Storage temperature and duration shall be defined by the facility and shall include conditions for fresh, cryopreserved, and thawed cellular therapy products. Generally, only fresh products are stored in the Collection Facility. Products that are awaiting release testing results (i.e., CD34 cell assessment by flow cytometry or the completion of donor eligibility determination) may be held in quarantine at one temperature (i.e., up to 4 hours at a facility defined room temperature) but stored for longer periods at another temperature (i.e., 2-8°C).

Temperature ranges and duration shall be determined for each type of product and should be based on the medical literature and/or on the facility's own data and validated methods. For liquid products, including thawed products, temperature ranges, storage duration, and product expiration date and time shall be established to prevent inadequate viability and to decrease the risk of contamination. Likewise, transport and shipping temperature both from the facility to the Processing Facility and at distribution to a Clinical Program shall be defined.

Evidence:
The inspector should review the Collection Facility's established storage criteria for all relevant products, and inspect the storage conditions and space to confirm adequacy of separation to prevent contamination and mix-ups. Storage temperatures on labeling may also serve as evidence.

Example(s):
EU Directive 2006/86/EC requires that the expiry date shall be part of the product information for all tissues and cells.

CM10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

STANDARD:

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

Explanation:
Cellular therapy products may be transported and/or shipped from the Collection Facility to a patient care unit or a Processing Facility within the same, adjacent, and/or remote buildings for immediate administration, processing, or storage. There shall be a prospective agreement in place between the relevant Collection Facility, Processing Facility, and Clinical Program regarding transport and/or shipping conditions and the responsibilities of each facility. SOPs for transportation and shipping shall be included in an SOP and shall address issues of packaging, labeling, temperature, identification, safety, product integrity, and handling for any length of transport.

STANDARD:

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

Explanation:

The cellular therapy product shall be packaged to protect it from potential harm during transit and to prevent exposure of individuals involved in its transport or shipping from potentially infectious agents. Exposure is a risk to individuals in environments where damage to a (usually) liquid product container might occur and normally would involve unanticipated spillage or splashing (e.g., dropped product, motor vehicular accident). When heat sealers are used on the tubing entering the primary container, a minimum of three (3) seals should be applied and the tubing disconnected by cutting through the middle seal to reduce the possibility of leakage.

Primary collection bags shall be placed in a secondary securely sealed container such as a zip-type bag. Human tissue, regardless of infectious disease testing, shall be considered potentially infectious. SOPs will vary depending on the distance, whether or not the courier and product leave a building, and the nature of the outside container.

STANDARD:

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

Explanation:

Procedures for transportation and shipping shall be included in an SOP and shall address issues of packaging, labeling, temperature, identification, safety, product integrity, and handling for any length of transit.

Example(s):

Distribution is any transportation or shipping and delivery of the cellular therapy product intended for human administration. The cellular therapy product has been determined to meet release criteria or urgent medical need requirements. Shipping is 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. For example, cryopreserved cord blood units are shipped in a vapor shipper from a cord blood bank to a tissue establishment (Processing Facility).

STANDARD:

CM10.3.1 *Cellular therapy products that are transported and/or shipped from the collection site to the Processing Facility shall be transported and/or shipped in an outer container made of material adequate to withstand leakage of contents, impact shocks, pressure changes, temperature changes, puncture, and other conditions incident to ordinary handling.*

Explanation:

These SOPs shall secure maintenance of the cellular therapy product components within a specified range of temperature during transportation or shipping. The product temperature during transit is dependent upon a number of variables, including: the transit time, ambient temperature ranges, initial

temperature, size of the product, and characteristics of the specific container system. The ideal transport temperature may range from 2-24°C. There shall be a prospective agreement among the collecting, processing, and receiving facilities regarding transport and/or shipping conditions. Most products should not be transported at temperatures above 24°C. Products not previously cryopreserved should never be allowed to cool to temperatures of or below freezing. Transport between facilities shall always consist of the use of an outer container that protects the product from adverse conditions encountered during transport (air pressure and temperature changes, rough handling, etc.), and has been validated to maintain the agreed upon transport temperature. For products transported between sites of a single cellular therapy program, the distance between the Collection Facility and the Processing Facility varies widely. For situations where transport from the Collection Facility to the Processing Facility requires only minutes, as long as the product is transported safely, a controlled temperature environment is optional.

Transport over longer distances, for more extended periods of time, or transport outside of a building may require that a controlled temperature environment be maintained using a shipping container and method validated for the temperature range specified.

For non-cryopreserved cellular therapy products requiring a controlled temperature, a validated thermally insulated container should be used with cold packs added as necessary to maintain the required temperature.

Containers for transport of cellular therapy products that are shipped from the Collection Facility or are transported on public roads shall be made of durable material and insulation that will withstand leakage of contents, shocks, pressure changes, and temperature extremes. The containers shall be validated prior to use to achieve proper performance for all expected extremes and maintenance of desired internal temperature. Subsequently, container performance should be verified at least twice yearly, during the warmest and coldest weather periods common for the area.

STANDARD:

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

Explanation:

If a patient has undergone high-dose marrow ablative treatment in preparation for transplant, the cellular therapy product is essential for the patient's survival since it may not be possible to obtain additional marrow or blood from the original donor or a second donor in time to prevent complications from aplasia. For this reason, it is important that the product be entrusted to a knowledgeable individual who accompanies it from the distributing facility to the receiving facility.

STANDARD:

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

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

Explanation:
Accompanying documentation shall include all documentation of allogeneic donor eligibility as defined in Appendix IV. It is not necessary that the records in their entirety accompany a cellular therapy product from the Collection Facility to the Processing Facility. Donor eligibility documents can be summarized. However, the entire document must be readily and easily accessible when needed.

Labeling requirements are defined in Appendix II and III.

CM11: RECORDS

STANDARD:

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

CM12: DIRECT DISTRIBUTION TO CLINICAL PROGRAM

STANDARD:

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

Explanation:
If the Collection Facility distributes cellular therapy products directly to a Clinical Program for administration or subsequent processing, aside from a few exceptions (see the following paragraph) the facility is responsible for the requirements defined in sections D7, D10, D11, and D13 (in these sections, wherever "processing" is referenced, "collection" shall be substituted).

A few exceptions exist to the Collection Facility assuming responsibility for sections D7, D10 and D11; examples of exceptions are as follows:

- Generally, Collection Facilities do not have the capability to re-inventory products and, thus, cannot accept products for return.
- Receipt of products does not apply to Collection Facilities.

Cellular therapy products may be collected for administration or for further manufacturing. The intent of referencing D7, D10, D11, D13, and the Appendices may be relevant to one or both purposes.

Evidence:
The inspector should examine distribution records to determine purposes of collection (administration or further manufacturing). Compliance with Sections D7, D10, D11, D13, and the Appendices can then be evaluated.

A Collection Facility that distributes cellular therapy products to a Clinical Program for administration, and/or to a Processing Facility for further manufacturing will provide an SOP, or other paper or electronic documentation, demonstrating compliance with clinical or further manufacturing standards in Sections D7, D10, D11, D13, and the Appendices.

See the guidance in the referenced sections for additional details.

APHERESIS COLLECTION FACILITY STANDARDS
PART C

C1 General

C2 Apheresis Collection Facility

C3 Personnel

C4 Quality Management

C5 Policies and Standard Operating Procedures

C6 Allogeneic and Autologous Donor Evaluation and Management

C7 Coding and Labeling of Cellular Therapy Products

C8 Process Controls

C9 Cellular Therapy Product Storage

C10 Cellular Therapy Product Transportation and Shipping

C11 Records

C12 Direct Distribution to Clinical Program

PART C: APHERESIS COLLECTION FACILITY STANDARDS

C1: GENERAL

STANDARD:

C1.1 *These Standards apply to all collection, storage, and distribution activities performed in the Apheresis Collection Facility on cellular therapy products obtained from living donors.*

Explanation:

Once a product has been collected, it is being stored until it is distributed from the Collection Facility. Distribution after collection may be directly to the Clinical Program, a third-party manufacturer, or to the Processing Facility for further processing and storage. The responsibilities that apply to distribution after collection are different from the responsibilities that apply to distribution to the recipient.

STANDARD:

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

Explanation:

Stand-alone facilities such as mobile apheresis services or donor centers that provide donor management or collection activities of cellular therapy products from living donors need to use cell processing facilities that meet the requirements of the Standards in order to be eligible for accreditation. The Processing Facility is not required to be formally acknowledged as FACT or JACIE accredited; however, even if not pursuing accreditation, the facility must comply with the Standards.

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

- Evaluation of the autologous or allogeneic donor for suitability (medical fitness) to undergo the collection procedure.
- Evaluation of the allogeneic donor for donor eligibility (free of risks of transmission of infectious diseases).
- Collection of the cells at the Clinical Program's collection facility.
- Temporary storage of the product in the Processing Facility and distribution to the clinical unit.
- Thawing and other needed manipulations of the product before administration to the recipient.

Evidence:

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

Example(s):
Collection Facilities perform collection procedures for a variety of reasons. In addition to collecting cellular therapy products for transplantation, facilities may perform collection in support of research and/or products that require further manufacturing. Single instances of collection for these other purposes must be incorporated into the facility's QM Program. Facilities that collect only products for further manufacture may seek accreditation, in which case the collected product may not be released to a processing facility that meets the Standards. This is a restricted accreditation and any marketing must truthfully and completely disclose the limitations of the accreditation.

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

Explanation:
FACT and JACIE are voluntary inspection and accreditation programs sponsored by the American and European Societies for Blood and Marrow Transplantation and the International Society of Cellular Therapy. Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with the Standards does not guarantee compliance with all applicable laws and regulations. Governmental regulations must also be followed. It is the responsibility of the individual Collection Facility to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the facility may apply; for example, when a facility is sending or receiving cellular therapy products from outside of its immediate jurisdiction.

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

Evidence:
While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with applicable laws and regulations. Evidence of compliance with the Standards will require preinspection information identifying prevailing governmental authorities, and documentation of certificates, permits, or licenses.

Example(s):
In the U.S., minimally manipulated cellular therapy products from first or second degree related donors are regulated under the 21 CFR 1271 GTP regulations and section 361 of the Public Health Service Act, with the exception of products collected from marrow. A cellular therapy product that is extensively manipulated, obtained from an unrelated donor, combined with a drug or device, or used for non-homologous use (does not perform the same function in the recipient as in the donor) is regulated as a drug, device, and/or biological product under section 351 of the Public Health Service Act and other applicable regulations in title 21 of the Code of Federal Regulations.

In the Member States of the European Union (EU), both HPCs and T Cells fall under the European Directive 2004/23/EC on all tissues and cells, "Setting standards on quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells" and the implementing directives 2006/17/EC and 2006/86/EC. The 2001/83/EC directive regulates products that are classified as medicinal products (MP). This includes somatic cellular therapy MPs and gene therapy MPs. The TMP-Regulation 1394/2007 entered in force on December 30, 2008 to include tissue-engineered products. The consequence of classification as an MP is that a GMP environment is required for the production of these cells. Furthermore, each Member State in the EU may add on additional regulations to the directives, that also must be followed. Member State-specific regulations will not be detailed here.

STANDARD:

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

Explanation:
National or state laws and regulations may require registration or certification with the government or may require accreditation from professional organizations for the activities performed within the facility.

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

Example(s):
Any facility that is involved with the recovery, screening, testing, packaging, processing, storage, labeling, or distribution of cellular therapy products in the U.S. is required to register with the FDA annually (21 CFR 207, 807, and 1271). This registration requires a listing of the activities in which the Collection Facility engages and a listing of each applicable type of cellular therapy product that is regulated under GTP or regulated as a medical device, drug, or biological drug (21 CFR 207 and 807). More information regarding the requirements and process for FDA registration can be found at http://www.fda.gov/cber/tissue/tisreg.htm. Note that each activity performed by the institution must be registered, regardless of who performs the activity. A Collection Facility that is within a larger institution such as a hospital or medical center may combine its registration with other services related to the same regulations. Activities that may be performed by a Collection Facility include the screening of donors for infectious disease risk to determine eligibility, temporary storage of products, and the apheresis collection procedure.

In the EU, the competent authorities in the Member States shall ensure that all tissue establishments have been accredited, designated, authorized, or licensed and that these establishments have implemented the EU Directive and/or other national regulations, where applicable.

Examples of verified compliance with regulations include acceptable FDA audits, state licensure, licensing of tissue establishments by the Member State in the EU, Clinical Laboratory Improvement Act (CLIA) certification, Occupational Safety and Health Administration (OSHA) inspections, or accreditation by the AABB, American Society for Histocompatibility and Immunogenetics/European Federation for Immunogenetics (ASHI/EFI), the College of American Pathologists (CAP), or any other applicable accreditation body.

STANDARD:

C1.4 *The Apheresis Collection Facility shall have an Apheresis Collection Facility Director, an Apheresis Collection 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 collections for at least twelve (12) months preceding initial accreditation.*

Explanation:

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

Evidence:

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

STANDARD:

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

Explanation:

These standards refer specifically to the number of apheresis collection procedures for cellular therapy products, not the number of patients from whom cells were collected, and may include both allogeneic and autologous donors. New facilities that want to gain the required experience needed for initial accreditation may conduct validation runs and use normal volunteers for collection of cellular therapy products that are never administered. These would count toward the goal of 10 cellular therapy products collected by apheresis; however, those types of collections (normal volunteers for products that are never administered) are not accepted for renewal accreditation.

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

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

Example(s):
FACT and JACIE will use the average number of collections per year over the accreditation cycle to determine if an Collection Facility meets the minimum collection volume. For example, if a FACT-accredited facility performs 6 apheresis collection procedures in the first year, 17 in the second, and then 7 in the third, the program will have performed an average of 10 procedures per year during the accreditation cycle and will have met the standard.

C2: APHERESIS COLLECTION FACILITY

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

Explanation:
Storage areas for cellular therapy products must be designated and controlled to prevent mix-ups and contamination regardless of the duration of the storage. Storage includes temporary holding of a product after collection and prior to transport to a processing facility. It is critical that the storage area be, at a minimum, secure and temperature-controlled and that the products be appropriately labeled and segregated, particularly for those products that may be held in the Collection Facility overnight and transported the following day.

Once received, supplies and reagents used for collection must be stored in a manner that preserves their function and sterility. Upon receipt of supplies, kits, and reagents, inspection for suitability must be documented. For items requiring storage at a specified temperature range, the temperature of the storage area must be monitored and documented.

There should be a mechanism to monitor the flow of supplies and reagents within the Collection Facility to prevent the use of outdated supplies and reagents. This system should also be able to identify the location of a given lot of a supply or reagent in the event that there is a manufacturing recall.

Evidence:
The inspector will tour the Collection Facility during the on-site inspection, including all locations where products are collected, stored, and distributed. Observation of the organization, design, location, and amount of space available in the facility can determine if it is adequate for the number and types of collections it performs, and if the collection environment is adequate to minimize the risk of contamination of the cellular therapy product.

If there are no collection procedures occurring on the day of the on-site inspection, the inspector should ask that a mock collection be demonstrated. This allows assessment of the adequacy of the environment as well as the procedural details and staff knowledge.

The inspector should also verify that the other procedures performed using the same instruments and space do not put recipients or donors at increased risk of disease transmission. An example would be an infusion room where patients with infectious diseases are treated.

The inspector should observe storage areas and confirm that supplies and reagents are stored under the conditions specified by the manufacturer. When refrigerators are used to store cellular therapy products, supplies, and/or reagents, the inspector should look for evidence that each is appropriately labeled and adequately separated so as not to cause confusion or compromise the integrity or sterility of the contents. The inspector should also evaluate the inventory control system to determine if it is adequate to prevent the use of outdated or damaged supplies and reagents.

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

Example(s):
Adequate storage can be accomplished by storing products on a designated shelf that is appropriately labeled for that purpose, utilizing designated labeled compartments, or by other procedures. It is recommended that outdated products and reagents and those not intended for clinical use be stored in a separate unit from those designated for patient care if possible. When this is not possible, outdated and/or research material must be clearly separated from clinical material and appropriately labeled.

A first in, first out (FIFO) system is one that is most commonly encountered. This mechanism can be tracked on paper or via a computer program.

STANDARD:

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

C2.1.2 *There shall be a designated area with appropriate location and adequate space and design to minimize the risk of airborne microbial contamination.*

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

Explanation:
There is no definition of adequate size; however, the size of the area should at least allow for safe practice and, in case of emergencies, allow for adequate room for resuscitation. The space used for collection and storage of cellular therapy products should be well-defined and adequate and there should be designated space for preparation and storage of reagents and equipment. It is appropriate to use the same space for other similar patients' activities such as therapeutic apheresis. However, apheresis of animals should not occur in the same area.

Evidence:
Collection Facilities submit a floor plan with preinspection documentation. Inspectors use these floor plans to gain a preliminary understanding of the designated areas and how processes and products flow throughout the facility.

A demonstration by personnel of where each of these activities is typically performed, how a product moves through the facility, and how products and associated paperwork are segregated if more than one product is present in the facility can demonstrate compliance. Inspectors should note safeguards in place to prevent mislabeling, inappropriate product release, or mix-ups. The physical facility should be orderly and organized according to a defined workflow.

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

STANDARD:

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

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

Evidence:
Collection Facilities must submit a floor plan of the facility prior to the on-site inspection. The inspector will tour the facility during the on-site inspection, including all locations where cellular therapy products are collected, stored, and distributed. The inspector should observe the design, lighting, and ventilation in the facility as well as access to sinks for donors and staff to determine if the collection environment is adequate to minimize the risk of introduction, transmission, or spread of communicable disease.

STANDARD:

C2.3 Apheresis Collection Facility parameters and 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 Apheresis Collection Facility parameters that may affect cellular therapy product viability, integrity, contamination, or cross-contamination during collection.

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

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

C2.5 *When using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled, monitored, and recorded, where appropriate, for air quality and surface* contaminants.

Explanation:
The Collection Facility must perform an assessment of conditions to determine if any parameters need to be controlled, monitored, and recorded. This includes parameters that may directly affect the cellular therapy product and also conditions that would diminish equipment or personnel performance, such as extreme humidity. Some equipment have operating limits but others do not.

Methods to collect cellular therapy products that expose the products to greater risks of contamination or cross-contamination, such as open collection systems, warrant more stringent environmental controls. If an Collection Facility uses collection methods that may result in contamination or cross-contamination, it must assess if temperature, humidity, ventilation, air quality, and surface contaminates must be controlled.

Environmental monitors for measures of air quality, such as particle counts and/or microbial colony counts, may be recommended, but applicable laws and regulations may not require specific air quality classification where collections are performed using closed systems.

Evidence:
If no parameters are controlled, the Collection Facility is requested to provide documentation of its reasoning prior to the inspection. It is the inspector's responsibility to determine while on site if the facility parameters affecting cellular therapy product viability, integrity, contamination, sterility, or cross-contamination identified by the facility are appropriate. If the inspector believes a parameter not identified should be controlled, this will be indicated in the inspector's report and included for discussion by the FACT or JACIE Accreditation Committee.

Example(s):
The typical Collection Facility operates with unclassified air, but may require control of temperature and humidity at a minimum to safeguard donor and personnel comfort in addition to cellular therapy product safety. Adverse temperatures and humidity levels may result in aborted collections and suboptimal personnel performance. Temperatures below freezing may damage products, and studies show a poorer survival of stem cells correlated with higher temperatures. High humidity can lead to the growth of mold or other organisms that could pose a threat to product sterility. However, this standard does not specifically require control of temperature and humidity. For example, the facility may verify acceptable humidity and temperature ranges with equipment manufacturers to set limits; if those limits are outside of usual conditions of the facility, it may choose not to control those parameters. The facility may also reference facility management policies, such as the use of an air conditioning unit (which controls humidity in addition to temperature) that is maintained by the institution. On-site inspections have revealed instances when humidity did impact the safety of the cellular therapy product. For example, in one particularly humid climate, a Processing Facility's liquid nitrogen freezer lids defrosted enough to prevent them from completely closing.

Contamination in the Collection Facility can be minimized through air filtration and by ensuring that the air pressure within the facility is positive to the surrounding areas (room pressure monitors should be used).

STANDARD:

C2.6 *The Apheresis Collection Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.*

Explanation:

Collection Facility cleaning and sanitation must be performed on a regular basis in order to prevent contamination and cross-contamination of products. There should be an approved method of cleaning of the facility and the equipment, and that cleaning should be documented. The methods used must be specified by an SOP (see C5.1). While the bench-top and equipment surfaces are most often cleaned and disinfected by facility personnel, other surfaces that may be cleaned by outside vendors such as floors, walls, and ceilings also fall under this standard. The facility, together with the cleaning services vendor, must establish SOPs for this activity.

For some specialized collection procedures, equipment or instruments that come into contact with the cellular therapy product may require cleaning and sterilization between uses. When this is the case, the Collection Facility must verify that the cleaning and sterilization methods used remove infectious agents.

Evidence:

Collection Facility cleaning must be documented and the records maintained for the period of time specified in institutional policies or applicable laws and regulations.

Example(s):

A checklist to document that facility cleaning and sanitation was performed according to SOPs can be left for the cleaning staff to complete when cleaning is performed afterhours.

STANDARD:

C2.7 *There shall be adequate equipment and materials for the procedures performed.*

Explanation:

The amount of relevant equipment in the Collection Facility should be appropriate for the type of collection performed, proportionate to the volume of work done, and should be conveniently located.

The Collection Facility should have policies and SOPs that address interruption in collection due to equipment failure such as for the handling and labeling of cellular therapy products, as well as policies and SOPs that prevent subsequent delay in collections, such as an additional machine for back up or arrangements with other collection agencies or centers.

Evidence:

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

STANDARD:

C2.8 *There shall be access to an intensive care unit or emergency services.*

Explanation:

The Standards aim to protect recipient and donor safety in the rare emergency situation. The Collection Facility must have documentation that there is ready access to an ICU or equivalent coverage in an immediate fashion for its recipients and donors when appropriate. This requires the ability to provide multisystem support including assisted respiration.

Evidence:

The inspector should verify that personnel are appropriately trained to respond to emergency situations and that there is emergency equipment available and in working condition. A review of protocols for emergency response, personnel training and competency files, and a contract or a letter of understanding with local emergency services can be performed.

Example(s):

Examples of appropriate training and emergency equipment include an electrocardiograph, crash cart, code team (in the hospital), or ACLS- and/or CPR-trained individuals (in freestanding Collection Facilities). If the only emergency response available to the Collection Facility is a community-based emergency service (such as 911 in the U.S. or 112 in the EU), the inspector should be able to verify that such an option is feasible and provides for a reasonably safe collection. Ideally, there should be documentation that there was at least one test of the emergency response system, particularly when community-based services are used.

STANDARD:

C2.9 *The Apheresis Collection Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, donors, visitors, and volunteers.*

C2.10 *The Apheresis Collection Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease and to chemical, biological, or radiological hazards.*

Explanation:

These standards apply to all facilities involved in cellular therapy (Clinical Programs and Collection and Processing Facilities). Safety training, including universal precautions for handling blood, is a requirement of the occupational safety and health administrations in many countries.

The Collection Facility policies and SOPs, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to applicable laws and regulations regarding safety. Safety, infection control, or biohazard waste disposal procedures that are unique to the facility must be covered in the facility's SOP manual. The use of electronic training programs that cover safety and infection control is acceptable, but there must be evidence that the staff has completed all relevant training satisfactorily.

Collection Facilities should post warning signs wherever radioactive materials are in use. All persons who may be exposed to blood or body fluids must utilize appropriate personal protective equipment.

This includes those exposed to cellular therapy products. The type of exposure that may be encountered will determine the appropriate protection. If aerosol exposure is likely, a mask, goggles, and gowns or aprons should be worn. Gloves must be worn whenever potential infectious exposure exists.

Evidence:
Ideally, the inspector should observe an apheresis collection to verify that personnel use appropriate protective clothing and observe other biosafety precautions. If there is no collection procedure underway, a mock procedure can be demonstrated. The inspector should examine how cellular therapy products are handled and discarded (e.g., incinerator, waste field) and compare his/her observations with the written protocols. The inspector should examine selected employee files for training in biological, chemical, and radiation safety (when appropriate). Compliance with state and federal regulations should be addressed by the Collection Facility and verified by the inspector. The inspector should also be alert during the tour for the presence of unused or inappropriately stored supplies or equipment that may contribute to an unsafe environment.

Example(s):
Safety training, including universal precautions, for handling blood is a requirement of OSHA in the U.S.

The safety manual may be an institution-wide document available by hard copy or electronically. Access to the institutional safety manual solely by computer is not acceptable without a written policy describing how to access the information in the event of a computer failure or down time.
The Collection Facility may keep a condensed or summarized hard copy of the institutional safety manual in the facility. In this case, there must be written documentation of how the condensed version is kept updated with institutional safety manual revisions. Such a document should focus on those hazards that are most likely to occur in the facility, such as needle sticks or handling recipients or donors with a known communicable disease.

STANDARD:
C2.11 *All waste generated by the Apheresis Collection Facility's activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable laws and regulations.*

Explanation:
Poor management of medical waste exposes personnel, waste holders, and the community to injuries, infections, and toxic effects. Hazardous waste generated by the Collection Facility's activities includes a broad range of materials, including used supplies, sharps, chemicals, radioactive material, viral vectors, genetically modified cells, and the cellular therapy products themselves. All medical waste shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste and in accordance with applicable governmental laws and regulations. Contaminated materials shall be placed in appropriate bags and containers marked with the international infectious substance symbol.

Radioactive and chemical waste must be discarded using methods approved by appropriate governmental agencies. General waste that contains information that would constitute a breach of confidentiality if it became available to unauthorized persons, such as paper, CDs, disks etc., should be stored in a secured container before disposal and ultimately shredded or destroyed.

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

Example(s):
Contaminated materials may be typically discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, through the use of a sanitary landfill. Sharps like needles, blades, etc., whether or not they are infected, should be considered highly hazardous health care waste and placed for disposal in puncture proof containers. Chemicals such as cytostatic drugs, used in purging procedures, shall be discarded in accordance with applicable regulations.

STANDARD:
C2.12 *Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.*

Explanation:
When handling potentially hazardous substances, personnel must use appropriate protective attire. To prevent the spread of hazardous substances, protective attire must be removed before leaving the workspace.

C3: PERSONNEL

STANDARD:
C3.1 *APHERESIS COLLECTION FACILITY DIRECTOR*

C3.1.1 *There shall be an Apheresis Collection Facility Director with a medical degree or degree in a relevant science, qualified by postgraduate training or experience for the scope of activities carried out in the Apheresis Collection Facility, and shall have two (2) years of training and experience in cellular therapy product collection procedures at a minimum. The Apheresis Collection Facility Director may also serve as the Apheresis Collection Facility Medical Director, if appropriately credentialed.*

Explanation:
The Apheresis Collection Facility Director should be an individual with a relevant degree. A Medical Doctor (M.D.) degree qualifies as a relevant doctoral degree; a non-physician director may hold a doctoral or baccalaureate degree (or international equivalent) in any of the biological sciences. A person with a diploma (such as nursing) can be the Director if he/she has considerable experience in directing a facility.

Evidence:
The inspector should review several pieces of documentation, such as the Apheresis Collection Facility Director's diploma(s), postgraduate training experience, or Curriculum Vitae (CV) for directing experience. This is a judgment call of the inspector and ultimately of the Accreditation Committee to decide if the directing experience is sufficient.

Example(s):
Documentation of evidence may include a medical school diploma, residency/fellowship certificates, and/or the Apheresis Collection Facility Director's CV indicating director experience. Examples of a relevant post-graduate (beyond baccalaureate) science degree could be in nursing, chemistry, biology, etc.

STANDARD:

C3.1.2 *The Apheresis Collection Facility Director shall be responsible for all Standard Operating Procedures, technical procedures, performance of the collection procedure, supervision of staff, administrative operations, and the Quality Management Program, including compliance with these Standards and applicable laws and regulations.*

Explanation:
The Apheresis Collection Facility Director is responsible for all administrative and technical aspects of the Collection Facility. This includes development and implementation of SOPs, training of personnel, design and execution of validation studies and audits, development of and compliance with the QM Program; maintenance of equipment, data analysis, and reporting; and compliance of the Collection Facility with the Standards and applicable laws and regulations.

The Apheresis Collection Facility Director may have other responsibilities, but he/she or a designee should be available at all times when the Collection Facility could be operational. The Collection Facility Director's responsibilities should be specifically documented.

Evidence:
The inspector should review the Collection Facility's organizational chart to verify compliance with the standard in addition to the job description and areas of responsibilities as described in SOPs, the QM Plan, etc., including who is/are the designee(s) and their responsibilities.

Example(s):
Documentation of evidence may include the Apheresis Collection Facility Director's signature for reviewing SOPs and the QM Plan.

STANDARD:

C3.1.3 *The Apheresis Collection Facility Director shall have performed or supervised a minimum of five (5) cellular therapy product apheresis collection procedures in the twelve (12) months preceding accreditation and a minimum average of five (5) cellular therapy product apheresis collection procedures per year within each accreditation cycle.*

C3.1.4 The Apheresis Collection Facility Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

C3.1.4.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:
The Apheresis Collection Facility Director should participate regularly in educational activities related to cellular therapy product collection and/or transplantation. The purpose of this requirement is for key personnel to keep up with current advancements in the field.

There are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use his/her judgment to determine whether or not an Apheresis Collection Facility Director meets this standard.

Evidence:
To assess the appropriateness of the amount and type of continuing education in which the Apheresis Collection Facility Director participated, the following information must be submitted for each of the completed continuing education activities within the previous accreditation cycle:

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

To assess on-going activity in the field, the inspector may ask about membership in professional organizations, publications in peer-reviewed journals, and/or attendance at meetings and workshops. The inspector should verify that the hours were in activities relevant to apheresis cellular therapy product collection and transplantation.

Example(s):
Evidence of compliance may include CME or Continuing Education certificates and either formal or informal study. Educational activities do not necessarily require large financial resources. The Collection Facility may choose to establish its own guidelines for the number of hours from each type of activity that can be counted toward the minimum requirement in this standard.

Examples of appropriate continuing education activities include:

- The annual meetings of several professional societies (such as those representing apheresis, transfusion medicine, cellular therapy, and scientific research) include information directly related to the field of apheresis cellular product collection and cellular therapy.
- Grand Rounds, if specifically related to cellular therapy or diseases for which cellular therapy is a therapeutic option. The CME log must include the title, subject, and date of the presentation.
- Presentation of CME/CPD lectures.
- Presentation of a paper at a scientific meeting.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or on-line tutorial.

- Review of an article in the medical literature related to cellular therapy; including those where the journal offers CME credits.
- Local or regional journal club, potentially including the preparation time.
- Morbidity and Mortality conferences.

ASBMT also offers an Online Learning center access recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning.

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at:
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

C3.2 APHERESIS COLLECTION FACILITY MEDICAL DIRECTOR

C3.2.1 There shall be an Apheresis Collection Facility Medical Director who is a licensed or certified physician with postgraduate certification, with training in cellular therapy product collection and transplantation.

Explanation:

The Apheresis Collection Facility Medical Director must be a physician licensed to practice medicine in the state, province, or country in which the Collection Facility is located and have postdoctoral training in fields such as blood and/or marrow collection and/or transplantation. The Medical Director need not be licensed in other jurisdictions in which satellite Apheresis Collection Facilities are located.

Evidence:

To fulfill this standard, the Medical Director must provide a photocopy of his/her current state, provincial, or national license. Since documentation of the medical degree is required to obtain a medical license, the license will be considered to be documentation that the Medical Director is a physician. This documentation is submitted with the Collection Facility's application, and should be available to the inspector prior to the on-site inspection.

STANDARD:

C3.2.2 The Apheresis Collection Facility Medical Director or designee shall be responsible for the medical care of donors undergoing apheresis, including the pre-collection evaluation of the donor at the time of donation and care of any complications resulting from the collection procedure.

Explanation:
The Apheresis Collection Facility Medical Director is directly responsible for the medical care of donors and recipients during the collection procedure, including the pre-collection evaluation of the prospective donor at the time of donation, performance of the collection procedure, care of any complications resulting from the collection procedure, and compliance with the Standards. The Medical Director is not usually responsible for the initial selection of the donor or for the determination of allogeneic donor eligibility. These are usually the responsibility of the clinical transplant team or donor registry.

The Apheresis Collection Facility Medical Director may have other responsibilities, but he/she or a designee should be available at all times when the Collection Facility is operational. The director's responsibilities should be specifically documented.

Evidence:
The inspector should review collection SOPs to verify compliance with the standard, that is, how pre-collection evaluation is performed and who is/are the designee(s) (e.g., residents) and what their responsibilities are.

Example(s):
Collection charts documenting the pre-collection evaluation of the prospective donor at the time of donation and care of any complications resulting from the collection procedure may provide documentation of compliance.

STANDARD:

C3.2.3 *The Apheresis Collection Facility Medical Director shall have at least two (2) years experience in performing and/or supervising cellular therapy product collection procedures.*

C3.2.4 *The Apheresis Collection Facility Medical Director shall have performed or supervised a minimum of five (5) cellular therapy product apheresis collection procedures in the twelve (12) months preceding accreditation and a minimum average of five (5) cellular therapy product apheresis collection procedures per year within each accreditation cycle.*

Explanation:
Collection of marrow and apheresis products is not necessarily the responsibility of the same individuals. Experience and training are expected only for the type of collection for which that individual is responsible. The Apheresis Collection Facility Medical Director shall have performed or supervised a minimum of five (5) collection procedures in the year preceding accreditation and shall have performed or supervised a minimum average of five (5) collection procedures per year within each accreditation cycle.

Evidence:
The Apheresis Collection Facility Medical Director is required to submit a CV that demonstrates training and/or experience prior to the on-site inspection. The inspector should review this information in advance, and request additional information if there are questions. Evidence of experience should be apparent. Documentation of the procedures performed or supervised should be available.

Example(s):
Experience can include training as part of a residency or fellowship program, specific training in another facility, and/or on-the-job training.

STANDARD:

C3.2.5 The Apheresis Collection Facility Medical Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

C3.2.5.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:
The Apheresis Collection Facility Medical Director must participate regularly in educational activities related to cellular therapy product collection. The purpose of this requirement is for key personnel to keep up with current advancements in the field.

Evidence:
To assess the appropriateness of the amount and type of continuing education in which the Apheresis Collection Facility Medical Director participated, the following information must be submitted for each of the completed continuing education activities within the previous accreditation cycle:

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

To assess on-going activity in the field, the inspector may ask about membership in professional organizations, publications in peer-reviewed journals, and/or attendance at meetings and workshops. The inspector should verify that the hours were in activities relevant to cellular therapy product collection.

Example(s):
There are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should assess the documented number and content of continuing education activities and use his/her judgment to determine whether or not an Apheresis Collection Facility Medical Director meets this standard.

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

Examples of appropriate continuing education activities include:

- The annual meeting of several professional societies.
- Grand Rounds, if specifically related to cellular therapy or diseases for which cellular therapy is a therapeutic option. The CME log must include the title, subject, and date of the presentation.
- Presentation of CME/CPD lectures.
- Presentation of a paper at a scientific meeting.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or on-line tutorial.
- Review of an article in the medical literature related to cellular therapy; including those where the journal offers CME credits.
- Local or regional journal club, potentially including the preparation time.
- Morbidity and Mortality conferences.

ASBMT also offers an Online Learning center where recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at:
http://www.ebmt.org/Contents/Education/Pages/Education.aspx

STANDARD:

C3.3 QUALITY MANAGER

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

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

Explanation:

The title held by this individual may differ among facilities and is not relevant as long as the duties include those described in the Standards. The Apheresis Collection Facility Quality Manager under ideal circumstances would be an individual with at least an undergraduate degree or equivalent in the field of health sciences or biological sciences and will have training in the field of cellular therapy product collection. However, individuals with education or experience with either QM or cellular therapy product collection may still be regarded as fulfilling the minimal qualifications for the job as long as the Apheresis Collection Facility Director can verify the proficiency of the individual to serve in this capacity. The Quality Manager may be shared with other portions of the cellular therapy program and/or the institution.

The Quality Manager must have an active role in preparing, reviewing, approving or implementing QM policies and SOPs and must confirm that the SOPs are in compliance with the Standards and all applicable laws and regulations before implementation. A key role of the Quality Manager is to develop systems for auditing Collection Facility activities to ascertain compliance with the written policies and SOPs.

The Collection Facility Director or other knowledgeable personnel may play a role in conducting or reviewing audits, especially audits that may include work performed by the Quality Manager. The director is ultimately responsible for the QM Plan and its proper implementation.

Evidence:
During inspection the inspector may want to inquire about SOPs in place to avoid bias when Quality Managers must review their own work.

Example(s):
Formal training may include documented practical work experience in a facility, fellowship, or a certification program.

The Standards do not prohibit the Quality Manager from participating in Collection Facility activities, as many facilities or institutions may not be large enough to support a free standing QM staff. However, the Quality Manager should not review or approve technical procedures for which he/she is solely responsible. In such cases, that review should be delegated to another staff member or to the Collection Facility Director or Collection Facility Medical Director. The Quality Manager can review SOPs where they have contributed to the activity following a reasonable time period to reduce the potential for bias. What constitutes a reasonable time lapse may vary based on the type of activity being reviewed. Audits most often will be performed weeks or months after the activity that is being audited was performed. The reasonable time period for specific activities to be reviewed should be defined by the facility's policies and SOPs.

The Collection Facility Director or Medical Director can also assume the Quality Manager role as long as the role does not pose a conflict on proper implementation of a QM Plan for the Collection Facility. Such a situation may occur more often in a small Collection Facility where technical responsibilities do not allow time for the activities of QM supervision.

STANDARD:

C3.3.3 *The Apheresis Collection Facility Quality Manager shall participate in ten (10) hours of educational activities related to cellular therapy, cell collection, and quality management annually at a minimum.*

C3.3.3.1 *Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.*

Explanation:
There are many ways to meet this standard, and the standard is not meant to be prescriptive. A total of 10 hours in combination of these topics is required. Each topic does not need to be covered in 10 hours individually. The inspector should assess the documented number and content of the continuing education activities and use his/her judgment to determine whether or not a QM Supervisor meets this standard.

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

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

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

Examples of appropriate continuing education activities include:

- The annual meeting of several professional societies.
- Grand Rounds, if specifically related to cellular therapy or diseases for which cellular therapy is a therapeutic option. The CME log must include the title, subject, and date of the presentation.
- Presentation of CME/CPD lectures.
- Presentation of a paper at a scientific meeting.
- Publication of a manuscript related to cellular therapy.
- Participation in a webinar or on-line tutorial.
- Review of an article in the medical literature related to cellular therapy; including those where the journal offers CME credits.
- Local or regional journal club, potentially including the preparation time.
- Morbidity and Mortality conferences.

ASBMT offers an Online Learning center where recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning.

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at:
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

C3.4 STAFF

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

Explanation:

This standard requires that there be an adequate number of trained personnel available for the collection of cells relative to the workload. The number of staff available and other responsibilities of the staff will vary from institution to institution based on the size and scope of the facility, and no specific numbers of staff members are required by the Standards. There should be sufficient staff present to manage in the event of any donor emergency without neglecting ongoing collections. A designated back-up, trained individual is required, but this does not require the Collection Facility to hire an additional employee. There are many options to train personnel from other departments who are qualified to perform the necessary tasks should they be needed.

The Collection Facility Director should indicate personnel responsible for specific activities in the Collection Facility and confirm that they are appropriately trained and competent to perform those activities, including confirmation that they have been trained in appropriate age-specific issues for the recipient and donor population they serve. Personnel should be retrained as necessary to remain up to date on current collection methods.

Evidence:

The inspector, as well as the applicant, will make a judgment of the adequacy of the staff support, including a review of the plan for staffing in the event of absences. The inspector should observe and inquire about the number of donors for whom one staff member is responsible at one time.

Documentation of initial training, continuing education, and periodic competency testing of all personnel is required. Documented training at the time of initial employment is expected of all new staff hired at the time of and following application for FACT or JACIE accreditation. Records of initial training may not be available for long-term employees of the facility; however, documentation of continued competency on a periodic basis should be available for all staff.

The inspector may request review of dated personnel records demonstrating competency and experience. The inspector should not request or be given confidential information such as staff medical records (e.g., vaccinations and health records).

Example(s):

Insufficient staffing may be indicated by excessive overtime, rapid turnover of personnel, incomplete record keeping, or an increase in adverse events.

Competency testing may include observation of performance of a procedure by a supervisor or coworker, oral or written examination of expected areas of performance, and/or participation in proficiency testing programs.

STANDARD:

C3.4.2 *For Apheresis Collection Facilities collecting cellular therapy products from pediatric donors, physicians and collection staff shall have documented training and experience on pediatric donors.*

Explanation:
Pediatric collections might require additional training and/or documented experience with this special population of donors. Other procedures involving pediatric patients performed by the Collection Facility, such as therapeutic apheresis and RBC exchange, might serve as experience.

SOPs addressing special situations that apply to pediatrics, such as RBC prime, should be in place with appropriate staff training and experience.

Evidence:
The inspector may request review of dated personnel records demonstrating competency in managing pediatric recipients and donors. The inspector might look for specific training applying to pediatrics.

C4: QUALITY MANAGEMENT

STANDARD:

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

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

Explanation:
The QM Program includes a description of the strategy (QM Plan) and the associated policies and SOPs that drive the operation of the QM Program. Development of a comprehensive QM Program is often the most challenging and time-consuming exercise that a Collection Facility encounters when preparing for FACT or JACIE accreditation.

Example(s):
The Collection Facility may choose to participate in an existing QM Program in its affiliated hospital, participate in the Clinical Program's QM Program, use portions of those QM Programs in its own, or have a stand-alone QM Program.

STANDARD:

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

Explanation:

The QM Plan is the written document that outlines how the QM Program (quality assurance, control, assessment, and improvement activities) is implemented.

The Standards have a broad scope of requirements for the QM Plan to comply with cGMP, cGTP, and other applicable international regulatory requirements.

The QM Plan must detail all key elements that affect the quality of recipient and donor care and cellular therapy products. The specific SOPs to be followed for each of these elements does not have to be fully described in the QM Plan, but must be referenced within the plan and linked to the appropriate document where the details are described.

The thoroughness and attention to detail of the written QM Plan is an indication of how QM is perceived and executed within the Collection Facility.

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

Evidence:

The written QM Plan for the Collection Facility will be provided to the inspector prior to the on-site inspection. If policies and SOPs are referenced in the QM Plan, they may be requested in advance to enable the inspector to review the details of the QM Program. The inspector is expected to evaluate implementation of the QM Plan at the facility and assess the understanding of QM by the staff.
An incomplete, too broad (i.e., a shared plan covering an entire Transfusion Medicine department), or poorly written QM Plan may be an indication that QM is not deemed an integral and important component of the facility. Under these circumstances, the inspector should pay particular attention to evaluating the QM efforts of the facility during the on-site inspection process. The inspector should specifically look for documentation of compliance for QM activities not directly performed by facility staff and seek evidence that QM activities link to the Clinical Program, Collection Facility, and Processing Facility.

STANDARD:

C4.2.1 *The Apheresis Collection Facility Director or designee shall be responsible for the Quality Management Plan as it pertains to the Apheresis Collection Facility.*

Explanation:
There shall be an individual (i.e., the Collection Facility Director or a qualified designee) at the Collection Facility in charge of the elements of the QM Plan that are directly related to the facility. A designee must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. Delegation to a qualified designee must be documented, either in the QM Plan or in SOPs related to it.

Evidence:
QM Plan review and approval should provide evidence of the Collection Facility Director's and designee's (if applicable) involvement.

Example(s):
A designee can be a member of another department, such as an institutional Quality Assessment and Improvement or Compliance Department, who devotes some time to the QM activities of the Collection Facility, or he/she could be a member of the facility's team. The same person may be responsible for QM of all components of the cellular therapy program or each individual area (clinical, collection, processing) may have a distinct individual responsibility for QM, as long as there is a mechanism for sharing of information to all participating entities.

STANDARD:

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

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

Explanation:
The organizational chart must include titles of key positions and the reporting structure for the Collection Facility and the QM Program.

The inspector will verify that the organization and daily function is as described. Organizational chart links must illustrate relationships to Clinical, Collection, and Processing Facilities that meet these standards.

The description of the operation of the QM Program should include the processes in place to accomplish its goals (e.g., meetings, participants, schedule, reporting, and documentation). Lines of responsibility and communication must be clearly defined in a way that is understood by all involved.

Evidence:
The organizational chart for the Collection Facility, will be provided to the inspector prior to the on-site inspection.

Example(s):
If a Collection Facility contracts services to or from an extended clinical or processing service, the organizational chart must include the contracted service(s) and summarize the reporting structure in the QM Plan.

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

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

Explanation:
The QM Plan, as approved by the Collection Facility Director, identifies the key personnel for whom documentation of training, competency, and continuing education is expected. These must include all individuals responsible for critical elements of the Collection Facility. Documentation of training for each individual must include all procedural skills routinely practiced. These requirements are detailed in C3.

Evidence:
The inspector should review training records to verify compliance with these regulations. Organization-specific issues and safety training are generally covered by orientation programs and continuing education programs, but inclusion of this content should be confirmed by the inspector. The inspector should review policies or SOPs describing the elements of staff training and continued competency as described in C4.4.

The inspector should review the records of one or more employees to determine if all of the required elements have been documented.

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

- Information sufficient for an understanding of the scientific/technical processes and principles relevant to their designated tasks.

- Information on the organizational framework, quality system, and health and safety rules of the establishment in which they work.
- Information concerning the broader ethical, legal, and regulatory context of their work.

Legal and regulatory context can be demonstrated by including training related to GTP, GMP, and the Standards.

STANDARD:

C4.4.1 A current job description for all staff.

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

C4.4.2.1 Initial qualifications.

Explanation:
Initial qualifications generally include minimal educational requirements, formal training that is either required or preferred, and licensing or certification.

STANDARD:

C4.4.2.2 New employee orientation.

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

Evidence:
Organization-specific issues are generally covered by institutional orientation programs, but this should be confirmed by the inspector.

STANDARD:

C4.4.2.3 Initial training and retraining when appropriate for all procedures performed.

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

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

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

STANDARD:

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

Explanation:
Competency is the ability to adequately perform a specific procedure or task according to direction. Collection Facilities must have a system for documenting competency for each critical function performed by a staff member (see Part A for the definition of "critical").

Example(s):
Competency may be assessed by observation, the use of written tests, successful completion of proficiency surveys, review of collection procedure end-points, or other ways as determined by the Collection Facility. Procedures for personnel training and competency assessment must be documented and reviewed.

Evidence:
The inspector should review records of employees' initial and annual competency.

STANDARD:

C4.4.2.5 Continuing education.

Explanation:
Staff should adhere to local and governmental continuing education requirements. The inspector should find evidence of suitable educational opportunities for staff related to their duties, such as quality-related meetings, webinars, and/or FACT or JACIE training sessions, if applicable.

Evidence:
The inspector should review policies or SOPs describing the elements of staff training and continued competency as described in C4.4.

The inspector will review the records of one or more employees to determine whether all of the required elements are documented.

STANDARD:

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

C4.5.1 There shall be a current listing of types of documents that are considered critical and shall comply with the document control system.

Explanation:
The QM Program must maintain a list of all active critical documents. For example, all SOPs required by these Standards must be considered to be critical documents, and must be controlled. Collection Facilities may call documents different names, and may identify additional types of documents as critical within the scope of the document control system.

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

STANDARD:

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

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

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

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

Example(s):
The process by which cellular therapy product collections are handled may require multiple SOPs, forms, and worksheets to be in place. This process might include a description of the product collection procedure, receipt, sampling, and labeling, among others.

STANDARD:

C4.5.3 The document control system shall include:

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

Explanation:
The Collection Facility should be consistent in the format or design of controlled documents.

Documents authored by the Collection Facility should follow the document control system, however departmental and institutional documents may differ.

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

STANDRD:

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

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

Evidence:
The inspector must verify that controlled documents are consistently versioned as defined in the document control system.

STANDARD:

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

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

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

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

STANDARD:

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

Explanation:
The methods of document distribution and storage should control or prevent unwanted or unauthorized document modification or duplication. Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software (to lock specific areas or a specific document to prevent printing) or having copies clearly printed with an expiration date or watermarked as copies. The intention is to make sure that only the currently approved document is available for use.

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

STANDARD:

C4.5.3.5 Controlled documents shall be reviewed every two years at a minimum.

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

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

The effective date of a controlled document is an assigned date following approval when the controlled document, such as an SOP, worksheet, form, or other document must be followed by trained personnel. For instance, a staff member may not perform a new or modified procedure until he/she has reviewed the SOP and completed required training and competency assessment. The amount and format of training and competency assessment may differ based on complexity of the changes. Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate person entered the signature.

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

STANDARD:

C4.5.3.7 Archived controlled documents, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

Explanation:

Documentation is especially important for the investigation of errors, accidents, suspected adverse events, biological product deviations, and complaints, since these investigations are frequently retrospective in nature. If outcomes change over time, one needs to be able to go back to previous versions of controlled documents to determine if an operational change is the cause.

Evidence:

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

Example(s):

The archival system may contain items such as date removed, version number, reason for removal, and identification of the person who performed removal.

STANDARD:

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

Example(s):

Collection Facilities may have forms, worksheets, etc., that are printed and distributed. There should be a system in place to recover these obsolete documents to prevent unintended use.

STANDARD:

C4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the establishment and maintenance of written agreements with external parties providing critical services that could affect the quality and safety of the cellular therapy product or welfare of the donor or recipient.

C4.6.1 Agreements shall be established with external parties providing critical services.

C4.6.2 *Agreements shall include the responsibility of the external party performing any step in collection, processing, testing, storage, distribution, or administration to comply with applicable laws and regulations, these Standards, and the standards of other required accreditation agencies.*

C4.6.3 *Agreements shall be dated and reviewed on a regular basis.*

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

The burden to determine compliance with the requirements of the accrediting organizations is on the Collection Facility, not on FACT or JACIE. Agreements must address other accreditations required by FACT.

Written agreements should clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements should be dated, reviewed, revised, and approved by both parties and legal if necessary, on a regular basis as defined by the program, and at least every two years. The policy or SOP for written agreements, or each individual agreement should describe the maintenance of records following termination of the agreement.

Programs should have an awareness of, and a review plan for, all agreements including those that the program does not control (i.e. does not develop or provide authorized signature), but which are relevant to the clinical care of the patient and/or donor or impact upon the cellular therapy product. A master list of written agreements and a checklist could assist with appropriate review and ensure that important elements are included, and a designee in the program is notified when changes are made.

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

Example(s):
It is recommended that a Collection Facility have a contingency plan in the event that it is unable to provide services as intended (e.g., significant personnel change or natural disaster). The contingency plan may require a written agreement with an external facility.

Examples of written agreements with external parties include memorandums of understanding, purchasing arrangements, service level agreements, contracts and preventive maintenance arrangements. Specific examples include written agreements with donor registries and external facilities used for the storage of cryopreserved cellular therapy products.

Such agreements may include, but are not limited to, donor qualification, determination of donor suitability and eligibility allogeneic donor only, collection of the cellular therapy product, donor or product testing, and long-term storage.

It is required that Collection Facilities will only use Processing Facilities that meet the Standards. An accredited Collection Facility may, however, collect products for one or more programs that are not FACT or JACIE accredited.

STANDARD:

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

Evidence:

The inspector should confirm documentation of all activities from definition of expected outcome to process improvement, when indicated. There must be evidence of ongoing analysis of data in addition to mere data collection. The inspector should ask to see the data and/or minutes of meetings, including the personnel in attendance and where data are presented.

STANDARD:

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

Explanation:

Outcome analysis involves the collection, evaluation, and distribution of patient outcome data.

Acceptable criteria for each cellular therapy product should be developed by the Collection Facility in conjunction with the clinical team, and this process defined in SOPs . Evaluation of patient outcome is required to confirm that the product that was manufactured and distributed met expected specifications. Any unexpected outcomes must be investigated, including risk assessment, and a corrective action and/or process improvement plan should be implemented. The facility personnel should evaluate all aspects of the collection procedure related to any unexpected outcome, including delayed or failed engraftment.

Product efficacy based on outcome may be more difficult to document for other cell products and that assessment will differ for each product type. Minimally the QM Plan must address the need for the development of an outcome analysis policy that is appropriate for each product type, and that adequately assesses that collection processes do not negatively impact outcome.

It is expected that criteria for which reasonable data can be obtained (product safety, product efficacy, and the clinical outcome) be determined and reviewed.

STANDARD:

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

Explanation:

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

Example(s):

This information can be obtained and analyzed directly by the Collection Facility or presented by another section of the cellular therapy program at a common quality management meeting where facility personnel are in attendance.

The Collection Facility may also consider the number of collections per patient, cell yield per collection, duration of each collection, and mobilization in its analysis.

STANDARD:

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

Explanation:

The responsibility for the collection and analysis of outcome data is an example of a QM requirement that may or may not be performed entirely within the Collection Facility. It is acceptable to share the same data between clinical, collection, and processing; however, the Collection Facility is responsible for ensuring it has access to clinical outcome data to enable it to adequately assess that its processes do not negatively impact outcome.

Timely engraftment of the HPC product in a recipient following a myeloablative regimen is directly related to the quality of that HPC product. Therefore, the Collection Facility personnel must be aware of the time to neutrophil and platelet engraftment for all recipients for whom they have supplied products. If delayed or failed engraftment occurs, it is important for the facility to be able to share results and trace back to the products source for information such as cell dose, cell type, sterility testing, viability, etc. It is not required for each section of the cellular therapy program to independently analyze engraftment, but it should be stipulated in the facility's policies or SOPs the responsibility each facility will assume, and the activity that will be undertaken by the Collection Facility.

STANDARD:

C4.8 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures, and a schedule for conducting, reviewing, and reporting audits of the Apheresis Collection Facility's activities to verify compliance with elements of the Quality Management Program and operational policies and Standard Operating Procedures, applicable laws or regulations, and these Standards.*

Explanation:

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

The audit process should occur throughout the year with reporting of audit results, corrective action, and follow-up on a regular schedule (at least once a year). A schedule of prospective audits is expected. There may be other audits required in response to specific events.

Evidence:

The Collection Facility should facilitate the on-site inspection with a concise presentation of recent audits, supported by policies and SOPs, and including documentation of corrective and preventive action and follow up. Examples of how results are trended and presented to relevant directors and staff are also helpful. The inspector should review audit results and schedule of planned audits, but it is not the intent to use a facility's audits to identify deficiencies during an inspection; the inspector shall maintain the confidentiality of the information.

Example(s):

Examples of audits in the Collection Facility include:

- Adherence to policies and SOPs (e.g., correct labeling procedures).
- Presence in the facility of written medical orders prior to collection of products.
- Equipment maintenance performed according to schedule.
- Identification of collection equipment used for each collection.
- Collection efficiency.
- Availability of complete records of allogeneic donor eligibility for each collection.
- Complete documentation that reagents and supplies were used prior to expiration.
- Cleaning and sanitation performed according to SOP and documented.
- Effectiveness checks or assessments on corrective action plans.

An audit process or report could include the following elements:

- Audit title.
- Audit type (e.g., Yearly Key Element, 2-Year Key Element, Focused, Follow-up).
- Clinical site or unit (e.g., pediatric, adult).
- Date audit is assigned, including name and title of staff who assigned the audit.
- Name and title of staff assigned to complete the audit.
- Audit period (date range).
- Audit parameter description.
- Date audit started and completed.
- Audit findings and recommendations.
- Timeline for follow up.
- Signatures and Comments.
    - Auditor signature and date.
    - Quality Manager signature, date, and comments.
    - Clinical Program Director signature, date, and comments.
    - BMT quality committee chair signature, date, and comments.
- Documented staff review and date of review.
- Quality meeting results presentation date, if required.

STANDARD:

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

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

The auditor must be knowledgeable in auditing techniques.

STANDARD:

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

Explanation:
There must be regular auditing of critical activities; frequency will depend on the importance of these activities, and to some extent on the results. Where there are published studies, these should be used to help assess audit results. For example, product yields may be expected to fall within a certain range based on national or international data. Although the yields continue to fall within that range, a trend downward to the lower end of the expected range may indicate a need to investigate the cause (e.g., new staff, a new piece of equipment, a reagent unexpectedly received from a different supplier.).

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

STANDARD:

C4.8.3 *Audits of critical processes shall be performed including the following annually at a minimum:*

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

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

STANDARD:

C4.8.3.2 Documentation of appropriate interim assessment of donor suitability and eligibility prior to the start of the collection procedure.

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

Example(s):

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

STANDARD:

C4.8.3.4 Management of cellular therapy products with positive microbial culture results.

Explanation:

The intent of this Standard is to only audit what is applicable to the Collection Facility's defined responsibilities.

STANDARD

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

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

C4.9.2 Investigation of cause.

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

C4.9.4 Reporting to regulatory agencies, if appropriate.

Explanation:
The cellular therapy program (i.e., Clinical Program and Collection and Processing Facilities) must develop an integrated approach to the management of cellular therapy products with positive microbial culture results that are identified before or after the products have been administered. Policies and SOPs are required across areas of an integrated cellular therapy program to manage the aspects for which the particular area of the program is responsible. This requirement may be satisfied with a single policy or SOP or there may be separate documents. For each topic, SOPs should detail what action is to be taken, who is responsible to take the action, and the expected timeframe of the actions. Different approaches to management may be acceptable if these approaches are consistently followed and meet regulatory requirements.

Policies and SOPs should cover investigation of the cause of the positive culture result, including at least evaluation of the collection and processing events for evidence of breach of sterility, determination if the donor had any evidence of sepsis at the time of collection, investigation of laboratory culture procedures to rule out a false positive result, contamination of the sample in the microbiology laboratory, or other causes that do not indicate compromise of the product. Collection Facility personnel are responsible for investigation of the relevant collection events.

Policies and SOPs must also be in place for the timely notification of clinical staff of the positive culture result, so that appropriate care can be delivered to the donor, and, if the product has already been administered, to the recipient.

In other cases, a positive result may only become known after the product has been administered. The Processing Facility is usually the first facility to be notified of a positive culture result. There should be timely notification of the Collection Facility, which should in turn investigate all records related to that collection to determine if anything in the collection process could have contributed to the positive culture result.

Evidence:
The inspector may ask to see the collection record of a cellular therapy product that was found to have a positive microbial culture and review how the Collection Facility managed the process.

Example(s):
Examples of evidence of compliance to this requirement may include:

- Policy and/or SOP on management of products with positive microbial culture results.
- QM meeting minutes containing a report on products with positive microbial results.
- Non-conformance reports for products with positive microbial results.

Each area in a cellular therapy program may have responsibilities that do not apply to another area. In this case, there may be an over-arching policy for the management of cellular therapy products with positive cultures.

An example of donor follow-up is a situation in which the investigation found that the donor was infected at the time of collection. The Clinical Program is responsible for following up with that donor to notify him/her of the infection and provide recommendations for care.

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

STANDARD:

C4.10 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for occurrences (errors, accidents, biological product deviations, adverse events, adverse reactions, and complaints). The following activities shall be included at a minimum:*

Evidence:

The inspector should expect to find a documented process for occurrences that includes detection, investigation, documentation, CAPA, and follow-up. This should be reviewed by the Apheresis Collection Facility Director and Quality Manager or designee. These occurrences and trends should be reported, as appropriate, to the Clinical Program Director, the Processing Facility, and appropriate governmental agencies.

STANDARD:

C4.10.1 *Detection.*

Explanation:

A goal of a QM Program is to continuously improve processes. Monitoring events and trends facilitates recognition of improvement opportunities. There must be a mechanism to detect, evaluate, document, and report occurrences in a timely fashion to key individuals, including the Apheresis Collection Facility Director, Medical Director and governmental agencies, as appropriate. The Collection Facility should define errors, accidents, deviations, adverse events , adverse reactions, and complaints in SOP along with when, how, by whom, and to whom each is reported. See the definitions of each of these types of occurrences in the Standards, Part A (Definitions). Management of each of these types of occurrences is slightly different, however, the same steps (detection, evaluation/investigation, documentation, determination of corrective and preventive action, and reporting) apply to all types.

It is recommended that Collection Facilities also define, document, investigate, implement corrective action, report, and track and trend less serious occurrences relating to the collection process, such as the occurrence of vasovagal episodes and citrate toxicity during collection. This practice may lead to significant process improvements within the cellular therapy program.

Cellular therapy products affected by biological product deviation(s) are released by the Collection Facility for use by the Clinical Program only when the benefit outweighs the risk to the patient and no alternative is available, although in some cases, the information is not known until after the administration of the cellular therapy product has occurred. The most common biological product deviations encountered involve products with a positive microbial culture or products from ineligible donors. Specific issues regarding products from ineligible donors are addressed in the guidance for Standard C6.

STANDARD:

C4.10.2 Investigation.

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

C4.10.3 Documentation.

C4.10.3.1 Documentation shall include a description of the occurrence, the involved individuals and cellular therapy product(s), when the occurrence occurred, when and to whom the occurrence was reported, and the immediate actions taken.

Explanation:

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

STANDARD:

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

C4.10.3.3 Cumulative files of occurrences shall be maintained.

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

Evidence:
The Collection Facility should be prepared to show examples of the cumulative files of occurrences that have occurred and been managed according to this process. If any occurrences have been reported to a governmental agency, the report(s) should be available for inspector review.

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

STANDARD:

C4.10.4 Reporting.

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

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

Explanation:
The FDA defines an adverse reaction as an adverse event involving the transmission of a communicable disease, cellular therapy product contamination, or failure of the product's function and integrity if the adverse reaction a) is fatal, b) is life-threatening, c) results in permanent impairment of a body function or permanent damage to body structure, or d) necessitates medical or surgical intervention. Adverse reactions may also include unexpected reactions to the graft that are designated as possibly, probably, or definitely related. For suspected adverse reactions to administration of products, the results of investigation and any follow-up activities must be documented.

Adverse reactions meeting the FDA definition of products regulated under GTP (allogeneic HPC, Apheresis and HPC, Cord Blood, T-Cells) or GMP (products produced under IND or IDE) must be reported to FDA within their specified guidelines. Reporting to other oversight organizations may also be necessary (e.g., accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees).

European Directive 2004/23/EU distinguishes between "serious adverse events," which are incidents, errors, etc. that have potential consequences, and "serious adverse reactions," which are actual reactions in a donor or recipient. Both must be documented and reported to the competent authorities. "Serious adverse event" is defined as any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life threatening, disabling, or incapacitating conditions for patients, or which might result in, or prolong, hospitalization or morbidity. "Serious adverse reaction" is defined as an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life threatening, disabling, incapacitating, or which results in or prolongs hospitalization or morbidity.

EU Commission Directives 2006/17/EC and 2006/86/EC include equivalent requirements for non-conforming products.

If an unexpected or serious adverse reaction occurs due to cellular therapy product collection or administration, for which there is a reasonable possibility that the response may have been caused by that product, the report of the adverse reaction and its outcome and investigation should be communicated to all facilities associated with collection, processing, and/or administration of infusing that product. This includes graft failure. Usually the Clinical Program is responsible for making the initial report; however, each involved facility must participate in the investigation and evaluation of the potential cause, particularly related to its own SOPs that were involved.

Examples:

The following are examples of adverse events that must may need to be reported:

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

STANDARD:

C4.10.5 Corrective and preventive action.

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

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

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

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

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

STANDARD:

C4.10.5.3 Investigations shall identify the root cause and a plan for short- and long-term corrective and preventive actions as warranted.

Explanation:
It is critical to investigate the cause(s) of events that pose significant risk or severity, and to establish and determine what corrective and preventive action will most likely be effective. The focus of the investigation should be to learn and improve, not to cast blame or be punitive. Often "systems" play a role in causation. Collection Facilities should be encouraged to stratify occurrences according to risk or severity, and invest more time and energy into management of the more critical issues. Only an understanding of cause allows creation and implementation of new or revised systems, or controlled documents that will correct the issue and may prevent the recurrence of an occurrence.

STANDARD:

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

Explanation:

The Collection Facility must document a policy or SOP for tracking and traceability of each cellular therapy product through all steps from collection to administration or final disposition. Documentation in the medical record should include the proper product name, unique product identifier (ISBT 128 donation identification number or DIN, or Single European Code or SEC), content of the cellular therapy product, identification of the donor including medical record numbers, unrelated donor registry identifiers including Global Registry Identifier for Donors (GRID), allogeneic donor eligibility status, and the unique identity of the intended recipient including registry identifiers, where appropriate. There must be a process, including the use of the ISBT128 barcode or other barcode or unique numbering system, to track and trace specimens removed from a cellular therapy product for testing at an external facility such as an HLA testing facility, transfusion service, or microbiology laboratory. This process must ensure linkage between the results of testing and the original product. There should also be a means, direct or indirect, that will allow outcome information to be related back to any other facilities involved in collection, processing, and distribution of the product. The final disposition of the product must be documented, whether the product was administered, destroyed, released, or used for research, remains in storage, or other disposition. The tracking and tracing system must comply with all applicable laws and regulations and the Standards.

Evidence:

Review of the following documents may show evidence of product trackability and traceability:

- Collection orders showing recipient and donor information, including unique identification.
- Product receipt and distribution records showing donor identity, recipient identity, and unique product identifier.

STANDARD:

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

Explanation:
Collection Facilities should be prepared for situations that may interrupt typical operations so that such interruptions do not adversely affect recipients, donors, or cellular therapy products. While a policy or SOP is required that addresses emergencies and disasters (see C5), the facility must also have a plan for the management of interruptions that do not rise to the disaster level. It's difficult to anticipate every possible situation that may occur. Therefore, the Standards do not require the facility to outline actions for specific events; rather, the facility is required to describe actions to take when an interruption presents, including who needs to be contacted, how to prioritize cases, key personnel to be involved in identifying alternative steps to continue functions, and notification of staff.

A contingency plan specific to the program would convey evidence that risk has been assessed for program-defined potential events of varying impact, such as a failure of the scheduling system, a water supply interruption, or shortage of a reagent. The plan should reflect differences between specific Collection Facility needs and general institutional needs, and complement the institutional plan.

As more and more of the Collection Facility's documents exist on an electronic platform, there is increasing risk of temporary or permanent document loss. The institutional Information Technology Department generally confirms that software in use is validated for its function, and that there is a regular schedule of back up to allow for retrieval of information when necessary. Freestanding facilities, as well as programs utilizing desktop storage, must have a plan to create a similar level of security. In either case, the program also needs a method to produce current versions of critical documents, such as preprinted orders, consent forms, SOPs, etc., when the electronic format is not available.

Policies, SOPs and associated worksheets and forms must be available to Collection Facility staff at all times. Arrangements must be made so that these documents are available in the event that the computer system goes down. Staff should have periodic training and review of alternate systems so they will be competent in the use of these systems should the need arise.

The Collection Facility should confirm that any electronic records in use meet other standards for validation and regularly scheduled back up of data. This may be in cooperation with the institutional information technology department if available. This standard covers the processes in place to obtain quality collections when the electronic records are unavailable.

This should include a mechanism to determine and document donor suitability and eligibility (allogeneic donors) prior to collection, including retrieval of critical laboratory values, consents, adequacy of line placement, or other procedural specifics. These records may be hard copies of reports from the system that are periodically produced to be used as a manual record. There may also be forms to be completed that mimic entry screens.

Evidence:
The inspector should review policies and forms to be used in case the electronic record system is unavailable.

Example(s):
Examples include malfunctioning electronic records systems, drug shortages, power outages, equipment failures, supply shortages, etc. A contingency procedure would identify alternative sources of supplies, alternative supplies, and/or alternative preparative regimens.

STANDARD:

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

Explanation:
Quality can be maintained only if there is control over critical manufactures, vendors, equipment, supplies, reagents, services, and the facility itself. The QM Plan must include a process to qualify reagents and supplies to safeguard their consistent function in validated procedures. This process must include the establishment of minimal standards for the acceptance of critical supplies and reagents and must document that those standards are met before they are made available for use. Even if supplies, reagents, and equipment are qualified, the manner in which they are used must also be qualified to prevent product mix-ups, contamination, or cross-contamination.

For further definitions and examples of qualification , see the JACIE *Quality Management Guide* (www.jacie.org/document-centre) or the FACT *Quality Handbook* (http://factwebsite.org/qm).

STANDARD:

C4.13.1 *Reagents that are not the appropriate grade shall undergo qualification for the intended use.*

C4.13.2 *Qualification plans shall include minimum acceptance criteria for performance.*

C4.13.3 *Qualification plans, results, and reports shall be reviewed and approved by the Quality Manager and Apheresis Collection Facility Director or designee.*

Explanation:
A plan for qualification must be reviewed and approved prior to performing a qualification. Qualification of critical items should include:

- Design Qualification (DQ).
- Installation Qualification (IQ).
- Operation Qualification (OQ).
- Performance Qualification (PQ).

The qualification plan should be reviewed after the qualification to determine if all acceptance criteria were met. This process must include the establishment of minimal standards for the acceptance and must document that those criteria are met before use.

Evidence:
The inspector should find evidence of qualification of manufacturers, vendors, supplies, equipment, facilities, services, and critical reagents . Qualification procedures should include instructions for requalification and under which circumstances qualification is required.

The Collection Facility must have a system in place that confirms that vendors provide materials in a timely and consistent manner that meets their acceptance criteria. Supplier qualification must also confirm that vendors are compliant with applicable governmental laws and regulations and that there is a system in place that is consistent with the Standards, such that they can demonstrate process control. Suppliers of infectious disease testing must also be qualified.

Example(s):
There are several ways to qualify a vendor of supplies, reagents, and services. The most effective is to perform an audit of the provider. Other, often more practical, methods may include one or more of the following:

- A review of third-party assessments by accrediting organizations such as FACT, JACIE, AABB, CAP or others.
- Remote audits by questionnaire.
- An ongoing dialog of resolution of service complaints or suggested process improvements.
- The sharing of internal audit findings and implemented corrective action plans from the provider back to the facility as evidence that deficiencies have been recognized and corrected.
- A documented review of the suppliers' past performance history.

Suppliers with pre-existing service agreements preceding the implementation of this standard can be qualified as meeting expectations by a retrospective review of the quality of service provided. Documentation, in the form of a brief written statement, that the service provider has met the Facility's requirements and worked with the facility to identify the cause of service failures and taken corrective actions in the past may serve as documentation of service provider qualification.

Critical reagents and supplies, that come into contact with donors, recipients, or cellular therapy products shall be sterile and approved for human use (appropriate grade for intended use).

Qualification of a readily used reagent in the field (e.g., ACD, NaCl, Plasmalyte) may consist of documented evidence of inspection of the reagent for discoloration and/or damage, use before the expiration date, and review of Certificates of Analysis prior to use.

Equipment qualification is performed to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. An example might be the qualification of a new blood warmer or heat sealing device.

Facility qualification is based on the level of manufacturing in the facility; and may range from a risk assessment to a full facility GMP qualification based on SOP and regulatory requirements.

STANDARD:

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

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

C4.14.2 Each validation shall include at a minimum:

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

C4.14.2.2 Acceptance criteria.

C4.14.2.3 Data collection.

C4.14.2.4 Evaluation of data.

C4.14.2.5 Summary of results.

C4.14.2.6 References, if applicable.

C4.14.2.7 Review and approval of the validation plan, validation report, and conclusion by the Quality Manager and the Apheresis Collection Facility Director or designee.

Explanation:

Validation is confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process (or SOP) is validated by establishing by objective evidence, that the process consistently produces an expected endpoint or result that meets predetermined acceptance criteria. Validations can be performed prospectively, concurrently or retrospectively.

Verification is the confirmation of the accuracy of something or that specified requirements have been fulfilled. Verification differs from validation in that validation determines that the process performs as expected whereas one verifies that the products of a process meet the required conditions.

Validation studies should be performed according to a validation SOP, utilizing a consistent format for approval of the validation plan, conducting of the studies, collection and documentation of results, data analysis, conclusions, and approval of the studies. A validation study performed because of a proposed change in a process or SOP shall include a documented assessment of the risk involved in the change to donor and recipient welfare and the quality and safety of cellular therapy products.

The design of the validation study should be adequate to determine if the process reproducibly achieves the purpose for which it is intended. The validation plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. Any change in the planned study that occurs during the study requires explanation. There should be an explanation, follow-up, and/or repeat of any test that fails to meet the expected outcome.

Validation should confirm acceptable endpoints can be achieved while maintaining purity, potency, and safety of the cellular therapy product. Examples of acceptable endpoints may include volume; collection efficiency; and contamination with red cells, granulocytes, and platelets.

In the Collection Facility, the following should be validated at a minimum:

- The apheresis device for the intended use. Each type of apheresis machine should be validated for the process and SOPs to be performed, including cellular therapy product and/or concurrent plasma. Subsequent machines of the same type may be qualified to document performance according to expected parameters, and a more limited validation of processes.
- The collection process. This validation should include all the variables used in the collection of each product, such as donor variables (e.g., WBC or CD34 cell count at initiation of collection, blood volume, or weight) and procedural variables (e.g., machine program chosen, blood volume processed, duration of collection). The validation study should demonstrate that the process reproducibly results in a product that is sterile, and is of a predetermined volume and nucleated cell content.
- Testing, if applicable.
- Labels and labeling. The validation of the label would demonstrate that the labels in use were checked against an approved template, were approved for use, maintain integrity during use, remain affixed or attached as required, are readable, do not contain any blank data points, and do include all of the required elements listed in Appendix II of the Standards. Validation of the labeling process should demonstrate completeness and correctness of each data point, and the accuracy of data as shown by traceability and trackability of the product from donor to recipient, or final disposition.

- Reagents, supplies, and disposables for intended use. Most Collection Facility reagents, supplies, and disposables are approved for human use. A manufacturer's certificate of analysis for each type of reagent should be available. If unapproved reagents are required for collection, these should be validated to work as expected, to cause no harm to the product, and to be sterile.
- Storage of the product prior to distribution.
- Distribution of the product. This may include packaging, temperature, and monitoring for products transported or shipped within or between facilities.
- Electronic records system, if applicable.

It is not the intent of the Standards to include hospital-based systems and clinical medical records. For further guidance see Standard C11.

Evidence:
The inspector should ask to see the SOPs for conducting validation studies and review a sample of validation studies. The inspector should note that studies are properly designed, objectively collect the required data, that outcome and intended actions are summarized, and that both the finalized plan and report are reviewed and approved by the Apheresis Collection Facility Director and Quality Manager.

Example(s):
A change of equipment used for collection would need to be validated, to verify product nucleated cell recovery, viability, sterility and potency are maintained at acceptable limits. The potential for adverse reactions and comparison of times to engraftment should also be examined.

In the case of collection of cells for a third-party manufacturer, the manufacturer may have data to validate the procedure. This is acceptable, though the collection procedure should at least be verified at the collection site to confirm it produces the expected results.

For further definitions and examples of validation, see the JACIE Quality Management Guide (www.jacie.org/document-centre) or the FACT Quality Handbook (http://factwebsite.org/qm).

STANDARD:

C4.15 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for inclusion of risk assessment in document control, change control, occurrence investigations, qualification, and validation.

C4.15.1 Changes to a process shall include evaluation of risk to confirm that the changes do not create an adverse impact or inherent risk elsewhere in the operation and shall be validated or verified as appropriate.

Explanation:
Risk assessment is a process to assess and document the risks involved in a change in a practice, process, SOP, or environment that has the potential to affect a critical procedure; direct patient care; and/or the cellular therapy product integrity, sterility, viability, and/or recovery. Risk assessment shall be completed for changes in processes to critical procedures including collection, labeling, and storage.

Risk assessment is a process that may be documented in a validation plan or exist as a separate document and should include:

- Identification of a risk.
- Context.
- Evaluation.
- Risk assessment and impact.
- Management response.

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

Example(s):
Identification of a risk can be made by providing a description of a potential or known risk. Establishing the context or scope means all the possible risks are identified and the possible ramifications or impact in all areas are analyzed thoroughly. Once the context or scope has been established successfully, the next step is identification and evaluation of potential risks either source or effect. During source analysis, the source of risks is analyzed and appropriate mitigation measures are put in place. This risk source could be either internal or external to the system. During problem analysis the effect rather than the cause of the risk is analyzed.

A general description of the issue and identity of the specific risk(s) should be included. After the risk(s) has been identified, it must be assessed on the potential of criticality or on their likelihood of occurrence and the potential impact including quantitative and qualitative evaluation. Risk prioritization is when the 'likelihood of occurrence × impact' is equal to risk.

There are many different approaches to calculating risk, and there are tools that can help assist in defining the probability of the effect occurring, the root cause, effects and magnitude of risk under different scenarios.

Once the risk assessment is established then a risk management plan can be developed and implemented. It comprises of the effective controls for mitigation of risk. Risk Management includes justification and rationale for accepting the risk and how to manage the impact if applicable. This can often be established in a simple one-page document for change with low impact and risk. An example might be a change in using another reagent or supply item of suitable grade.

Below is a risk assessment matrix that combines the concept of likelihood and severity. This may be useful for programs to utilize when assessing risk:

Risk Matrix		Probability (Likelihood of occurrence)		
		Occasional (Possible to occur in time, if not corrected)	**Likely** (Will probably occur in most circumstances)	**Frequent** (Expected to occur in most circumstances)
Severity of Incidence	**Minor** (low risk to the product or patient)	**Low (1)**	**Low (1)**	**Medium (2)**
	Moderate (Probable risk to product or patient)	**Medium (2)**	**Medium (2)**	**High (3)**
	Major (High risk to product or patient)	**High (3)**	**High (3)**	**High (3)**

STANDARD:

C4.16 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining feedback from donors or legally authorized representatives.

Explanation:

Feedback (including complaints) from donors, recipients, and legally authorized representatives may be obtained directly by the Collection Facility; however, it is also acceptable to use a hospital-wide system, such as patient satisfaction surveys, as long as the cellular therapy program is included and relevant issues can be readily identified.

STANDARD:

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

C4.17.1 Key performance data and review findings shall be reported to staff.

C4.17.2 The meetings should have defined attendees, documented minutes, and assigned actions.

Explanation:
QM activities shall be reported, at a minimum, quarterly to review the performance of the QM Program and its objectives. This is to determine whether the elements in the QM Plan are relevant and effective, and necessary actions are taken in a timely manner.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported with each audit while others may be retrospectively analyzed and reported at defined intervals. The data should be analyzed, assessed, and trended over time to identify improvement opportunities on a regular basis, such as at each QM meeting. Strategies to effect improvement should be identified and implemented. The results of these implemented strategies should be measured and the improvement strategies either continued or new alternatives developed depending on the results.

The minutes and attendance list of regularly scheduled QM meetings are effective ways to document QM activities and communication of quality assessments to key individuals within participating facilities in the cellular therapy program.

Evidence:
The inspector should ask to see evidence that the outcome of quality assessments is communicated to key individuals within all participating entities in the cellular therapy program. The inspector should ask to see the minutes of the QM meetings, which should document who was in attendance and what topics were covered. At a renewal inspection, it is particularly important to ask for QM meeting minutes that represent the time since the previous accreditation in order to determine that the QM Program is and has been ongoing. Minutes should summarize activities such as training performed, documents reviewed, audits performed, and SOPs introduced or revised.

STANDARD:

C4.17.3 *The Apheresis Collection Facility Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Apheresis Collection Facility.*

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

STANDARD:

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

C4.18.1 *The annual report and documentation of the review findings shall be made available to staff, the Clinical Program Director, and Processing Facility Director.*

Explanation:

The overall effectiveness of the QM Program must be reviewed and reported to staff on an annual basis. The annual report will provide a year-long view of the overall function of the QM Program, its effect on and interactions with the Clinical Program and Processing Facility, and provide clues on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated. If the Collection Facility is part of an integrated cellular therapy program, a single annual report is sufficient.

The annual report should also contain trending information related to key indicators that are monitored, patient outcomes, patient satisfaction, adverse events , and other important elements utilizing data from prior years.

Example(s):

Collection Facility Directors may wish to report on the effectiveness of the QM Program more frequently than once a year. If so, the report should utilize some data from the previous 12 months to provide a longitudinal perspective of how the QM Program is functioning over time. In addition to relevant measures addressed in B4.1.2, the Collection Facility may consider including the following measures:

- Collection efficiencies,
- Donor adverse events, and
- Other events such as complaints or deviations.

C5: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

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

Explanation:
Each Collection Facility must have written policies and SOPs that comprehensively address all important aspects of the facility. The facility is not required to have an SOP titled for every item on the list, as long as each item is addressed somewhere within an appropriate SOP. The items listed include the minimum requirements; a facility may exceed these requirements, but not omit any of these.

It is recognized that the practice of medicine requires some flexibility and the Collection Facility may choose to designate policies for some clinical care related to the collection procedure as practice guidelines.

Evidence:
When multiple topics are covered by a single SOP, it will aid the inspection process if the Collection Facility prepares a crosswalk between the list of required SOPs in C5.1 and the facility's own SOP Manual.

The inspector should verify the procedure for development and review for all policies and SOPs is being followed and that the policies and SOPs are comprehensive and define all aspects of the Collection Facility.

The inspector will have received a copy of the Table of Contents for the SOP Manual with the pre-inspection material prior to the on-site inspection. The Table of Contents should be examined for evidence of the existence of SOPs addressing each item listed in the Standards before arriving at the inspection site. Prior confirmation that a specific SOP has been generated will reserve limited on-site inspection time for evidence of implementation of written SOPs and other activities that can only be verified in person at the inspection site. Implementation may be verified by direct observation, by a mock up scenario, and/or verbal conveyance of the SOPs.

Example(s):
The policies and SOPs can be generated within the Collection Facility or in collaboration with other entities within the institutional infrastructure. This applies most often to SOPs addressing safety, infection control, biohazard disposal, radiation safety, and the emergency response to disasters. In cases where general institutional policies and SOPs are inadequate to meet standards or where there are issues that are specific to the facility, the facility must develop its own policies and SOPs to supplement those of the institution. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for initial approval and review and approval of revisions every two years by the facility.

STANDARD:

C5.1.1 *Donor and recipient confidentiality.*

C5.1.2 *Donor consent.*

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

C5.1.4 *Management of donors who require central venous access.*

C5.1.5 *Cellular therapy product collection.*

C5.1.6 Administration of blood products.

C5.1.7 Prevention of mix-ups and cross-contamination.

C5.1.8 Labeling (including associated forms and samples).

C5.1.9 Cellular therapy product expiration dates.

C5.1.10 Cellular therapy product storage.

Explanation:
The Collection Facility must define the expiration dates and storage conditions (e.g., container, temperature) of all of its collected products, including those released to a Clinical Program and those released to another facility.

STANDARD:
C5.1.11 Release and exceptional release.

Explanation:
Release is defined as the removal of a cellular therapy product from in-process status when it meets specified criteria. Collection Facilities must have release criteria for when a cellular therapy product can be distributed to the Processing Facility or Clinical Program. Release criteria are not only applicable to directly releasing a cellular therapy product for administration, but also to releasing a cellular therapy product to another facility (e.g., to a Processing Facility for processing and storage).

Each cellular therapy product must be verified to have met release criteria before being released. SOPs must outline how this verification takes place and who approves the release. There may be times when a cellular therapy product does not meet release criteria. If this product must still be used for urgent medical need, an SOP must define the process for exceptional release, outlining the steps to take for documentation and approval.

Evidence:
The inspector will review the SOP(s) describing the release criteria and the process for release of cellular therapy products that meet those criteria. The inspector will also verify existence of an SOP for exceptional release, including documentation and approval.

The inspector will review the SOP(s) describing the expiration dates and storage conditions for the cellular therapy products collected and the process for its performance.

Example(s):
Examples of release criteria include, but are not limited to:

- Correct labeling including storage temperature and expiration date.
- Sealed secondary container.
- Completed allogeneic donor eligibility documentation.

STANDARD:

C5.1.12 *Transportation and shipping, including methods and conditions to be used for distribution to external facilities.*

C5.1.13 *Critical reagent and supply management.*

C5.1.14 *Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.*

C5.1.15 *Recalls of equipment, supplies, and reagents.*

C5.1.16 *Cleaning and sanitation procedures including identification of the individuals responsible for the activities.*

C5.1.17 *Hygiene and use of personal protective equipment and attire.*

C5.1.18 *Disposal of medical and biohazard waste.*

C5.1.19 *Emergency and disaster plan, including the Apheresis Collection Facility response.*

Explanation:

SOPs addressing safety, infection control, biohazard disposal, radiation safety, and planned emergency response to disasters may be standardized throughout the institution. However, in cases such as an institutional disaster plan, such plans usually outline general actions to be taken. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for review and approval. Standard C5.1 requires that the Collection Facility have a disaster plan that is specific for the facility. This plan should include actions to be taken in case of a disaster (such as how to locate and use emergency power) and include specifics such as how to proceed if a donor is undergoing collection at the moment of the disaster or what to do if products need to be moved. Examples of disasters include fires, hurricanes, floods, earthquakes, nuclear accidents, etc. In cases where institutional policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the facility, the facility must develop its own policies and SOPs.

Evidence:

If an Collection Facility is operated out of a transfusion service and shares certain SOPs or policies with the transfusion service, then an index of the shared SOPs and policies should also be submitted.

The inspector will review the emergency and disaster plan, verifying that appropriate details are provided for collection personnel to follow.

Example(s):

The article *Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program* (Wingard et al, 2006) provides a framework for disaster plans that can be customized for specific facilities:
http://www.ncbi.nlm.nih.gov/pubmed/17085317.

The U.S. Food and Drug Administration offers information on its webpage titled, "The Impact of Severe Weather Conditions on Biological Products," at http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ProductSecurity/ucm147243.htm.

STANDARD:

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

Explanation:

The SOP Manual is a compilation of policies and SOPs containing written detailed instructions required to perform procedures. The purpose of the SOP Manual is to maintain the policies and SOPs in an organized fashion so that all current documents can be found. Many Collection Facilities have adopted an electronic method of compiling its policies and SOPs, which is acceptable. Hard-copy, bound manuals also meet the intent of the standard. The SOP Manual must include a list of all SOPs that are included in the manual to serve as a master index or table of contents from which personnel can determine which SOPs are included in the manual. SOPs must be under document control as outlined in C4.

Evidence:

Collection Facilities must submit the listing of the SOPs included in the SOP Manual(s) prior to the on-site inspection. The SOP Manual should be organized in such a manner for the inspector to ascertain that the policies and SOPs are comprehensive and define all aspects of the facility. The inspector should verify the procedure for development and review for all policies and SOPs is being followed.

Compliance to most of the standards in this section can be determined before the on-site inspection by review of the "SOP for SOPs" and the other submitted SOPs contained within the pre-inspection material, although one or more additional SOPs should be reviewed during the on-site inspection for compliance.

Example(s):

An Collection Facility may choose to have one SOP Manual or divide policies and SOPs into several manuals by subject. A technical procedure manual in conjunction with a quality, a policy, and a database manual may serve to better organize information if the facility chooses this format. Each SOP needs to follow the format outlined in the "SOP for SOPs." A format for creation of policies, worksheets, reports and forms needs to be in place and may be included in the "SOP for SOPs" if the facility desires.

STANDARD:

C5.3 *Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual Standard Operating Procedure shall include:*

Explanation:

This standard defines the minimum elements required in each SOP. SOPs are controlled documents and must comply with the requirements in B4.

Evidence:
Compliance with most of the standards in this section can be determined before the on-site inspection by review of the document control system and submitted SOPs contained within the pre-inspection material. However, additional SOPs should be reviewed during the inspection for compliance.

STANDARD:

C5.3.1 *A clearly written description of the objectives.*

C5.3.2 *A description of equipment and supplies used.*

C5.3.3 *Acceptable end-points and the range of expected results.*

C5.3.4 *A stepwise description of the procedure.*

C5.3.5 *Age-specific issues where relevant.*

Explanation:
Depending on the age range of donors treated in the cellular therapy program, Collection Facilities should be able to demonstrate how processes are adjusted for age-specific issues. For example, a facility caring for teenage donors should demonstrate processes that accommodate the psychological, educational, family, and social needs of this age group, including routine peer group contact. Geriatric donors (greater than 65 years of age) should have appropriate access to rehabilitation and social support.

Collection of HPC and/or T Cells from pediatric donors requires specific policies and SOPs that address issues of age and size of the donor. Any program that collects a cellular therapy product from a minor donor must have appropriate SOPs that address at least issues of informed consent, donor size, and venous access.

Collection of cells from small donors by apheresis requires several considerations, including at least extracorporeal volume, red cell depletion, and citrate toxicity. These issues are particularly important in donors under approximately 25 kg. Procedures should describe at least the priming of the extracorporeal circuit with irradiated red blood cells if the donor's blood volume or oxygen carrying capacity will be compromised during the procedure, and prophylactic calcium supplementation to prevent citrate toxicity. Alternative anticoagulants could also be considered.

Young children and other small donors may have inadequate peripheral vein size to accommodate apheresis needles. In these cases, there must be policies and SOPs for central venous access or provisions to collect with alternative methods, that include details of risk, consent, access to a competent physician to secure central venous access, documentation of adequate line placement, and other procedural details. There may be limitations based on applicable laws and regulations. Young children and small donors may be restricted from central venous catheters.

STANDARD:

C5.3.6 *Reference to other Standard Operating Procedures or policies required to perform the procedure.*

C5.3.7 *A reference section listing appropriate and current literature.*

C5.3.8 *Reference to a current version of orders, worksheets, reports, labels, and forms.*

C5.3.9 *The Apheresis Collection Facility Director or Medical Director shall approve, prior to implementation, new or revised controlled documents.*

Explanation:
The Collection Facility should establish a range of acceptable results, when appropriate, for each procedure. Examples include nucleated cell recovery, hematocrit, sterility, plasma volume, etc. The range for a given parameter can be determined within the facility by evaluating data from its own products.

Reference to relevant policies within an SOP requires some flexibility. Some Collection Facilities include it in the body of the SOP at the end of that relevant step, whereas others may include it at the very end of the procedure as a separate section that lists other required SOPs where the procedure identifier (minus the version) and name is listed.

The Standards require documented review of each SOP by the Collection Facility Director or by the Collection Facility Medical Director every two years. It is important that documentation clearly indicates the version of each SOP or policy that was reviewed. A single page in the manual with a signature and a date is not sufficient since SOPs may be revised throughout the year. Review of SOPs should include review of the applicable worksheets, forms, and attachments.

Current versions of worksheets, reports, labels, and forms, where applicable, must be identified in or be attached to each SOP. The purpose of this standard is to assure that these documents are easily accessible to a reader of the SOP and that it is clear what documents may be required for the performance of that SOP. It is acceptable to simply reference applicable worksheets, reports, labels, and forms for which a separate SOP exists describing their use. These documents must also be under document control in compliance with C4.

Evidence:
The inspector should review the SOP manual and documentation of Facility Collection Director and/or Medical Director review. The inspector must be given on-site access to the SOPs as well as documented electronic approvals of each procedural modification.

Example(s):
In some programs, the actual "SOP" may be limited to minimal work instructions, and required elements such as a reference list may be found only in higher-level documents. Such variability is acceptable if all elements can be found within the quality documents.

It may be worthwhile to include a listing of the document identifiers and titles of worksheets, reports, labels, and forms needed for a given SOP in the proper SOP format. These forms need not necessarily be completed as an example, but it may be prudent to attach one or more completed forms to illustrate possible real life scenarios.

For example, SOPs or policies for reporting adverse reactions to product administration or SOPs for reporting the results of microbial testing should be approved and reviewed by the Collection Facility Medical Director. A review signature on the document itself, or on a listing of the reviewed documents by name that includes the unique identifier, and version is acceptable. A validated electronic review system is also acceptable.

STANDARD:

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

Explanation:

The written copy or electronic version (with provision of hardcopy as necessary) of the SOP Manual must be immediately available to all relevant employees in their working environment. There must be only one source document created from which review occurs. Any copies of policies and SOPs must be identical to the source document and must not be used to alter, modify, extend, delete, or otherwise edit any SOP.

If an electronic manual is used, there must be a mechanism to access the manual at all times, even if the network is not available. If collections are performed in the patient room, the collection SOP must be readily available.

Evidence:

The written copy or electronic version of the SOPs should be readily identifiable to the inspector. The inspector should expect to see the SOP manual or electronic access to SOPs in all performance areas of the Collection Facility.

Example(s):

The SOP Manual is usually physically located in the facility or management team member office. However, collection procedures are often performed outside of those locations (i.e. at the bedside). If the SOP manual is not physically present at locations in which the collection procedure is performed, there should be a process to get access to them in case they are needed and the staff should be familiar with that process.

STANDARD:

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

Explanation:

The effective date of a controlled document is the date when all of the required individuals have officially approved the document. However, a staff member may not perform the new or modified SOP until they have undergone documented review and training. Collection Facilities are not required to train all staff members before implementing a new policy or procedure, but must document an individual's review and/or training before that person uses the revised policy or SOP.

Evidence:
Documentation that approved and implemented policies or SOPs are performed only after the individual staff member has reviewed and been trained on the new or revised procedure should be reviewed by the inspector.

Example(s):
It is recommended that there be a specific signoff sheet for every policy and SOP and associated revisions to document that each staff member required to review them has done so. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each SOP and to any major revision also facilitate documentation of appropriate training of staff.

Example(s):
Sometimes a revision to a policy or SOP is minor, such as an update to a referenced regulation or grammatical corrections. In these cases, full training may not be necessary. Review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

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

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

Explanation:
Planned deviations should be approved within a peer-review process (i.e., more than one individual), but approval from the Collection Facility or Medical Director is required at a minimum. Processes set up for review of planned deviations are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately. Retrospective review must be performed in compliance with processes designed for deviations.

C6: ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

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

Explanation:
Standards in C6 mirror those in B6, reflecting the fact that these responsibilities are usually the primary responsibility of the Clinical Program staff. Collection Facility staff are usually not responsible for donor selection. Cellular therapy program policies and SOPs must clearly define responsibility for all aspects of donor selection, evaluation, eligibility (allogeneic donors only) and suitability determination, and management.

In situations in which the Collection Facility is primarily responsible for activities related to donor selection, the applicant and inspector must complete the corresponding sections in the Clinical Program inspection checklist.

These standards are intended to optimize the safety of the donor and recipient as well as the safety and efficacy of the cellular therapy product. For allogeneic donors, additional requirements exist to achieve appropriate histocompatibility matching and to protect the recipient from the risks of transmissible disease.

Facilities should endeavor to obtain voluntary and unpaid donations of cells. Donors may receive compensation, which is strictly limited to making good the expenses and inconveniences related to the donation.

Donor eligibility and suitability should be differentiated as defined in A4, where, "eligibility" refers to a donor who meets all transmissible infectious disease screening and testing requirements, and "suitability" refers to issues that relate to the general health of the donor and the donor's medical fitness to undergo the collection procedure.

The Collection Facility must have in place written SOPs defining all aspects of donor identification, evaluation, selection, and management, including identification of the personnel responsible for each aspect. Facilities should consider requirements of the FDA, EU Directives, WMDA, and other regulatory authorities and accrediting agencies when creating and reviewing these SOPs. For donors of cellular and tissue-based products, applicable laws and regulations on allogeneic donor eligibility determination usually require that donor evaluation include risk factor screening by health history questionnaires, review of medical records, physical examination, and testing for relevant communicable disease agents and diseases. The allogeneic donor is determined to be eligible if he/she is:

- Free from risk factors for and clinical evidence of relevant communicable disease agents and diseases,
- Free from communicable disease risks associated with xenograft in the donor or in someone with whom the donor has had close contact, and
- Tests negative or non-reactive for relevant communicable disease agents within the specified time frame for the product. It is the responsibility of the facility to document that donor evaluation procedures are in place to protect the recipient from the risk of disease transmission from the donor.

These standards also require that if allogeneic donors are ineligible according to applicable laws and regulations, or do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented. There must also be documentation in the recipient's medical record by an attending physician of urgent medical need for the cellular therapy product. Urgent medical need means that no comparable cellular therapy product is available and the recipient is likely to suffer death or serious morbidity without the product. The product should be accompanied by a summary of records to the Collection and Processing Facilities stating reasons the donor is ineligible, including results of health history screening, physical examination, and results of infectious disease testing.

In addition, this standard requires that the Collection Facility identify the institutional criteria for medical suitability of donors. Written criteria should include criteria to determine the number of cellular therapy product donations permitted by a single donor. This includes criteria for both related and unrelated donors. It also requires that each aspect of this process be performed according to written SOPs and that the results of the evaluation are to be documented. Donor acceptability should be documented within the medical record in the Clinical Program and be provided in writing to the Collection and Processing Facilities.

Evidence:
The inspector should verify that policies and SOPs are written, clearly defined, and are unambiguous. The inspector may ask to verify compliance with these SOPs by reviewing a specific donor evaluation. The inspector may also verify the rationale and informed consent for a specific donor who did not meet the institution's donor criteria as well as making sure that there is an SOP for urgent medical need documentation and labeling for allogeneic products.

Example(s):
Eligibility testing is only required for allogeneic donors; however, autologous donors must be tested if required by applicable laws and regulations. Autologous donors who are tested and have positive results for some infectious diseases (e.g., Hepatitis B, C, or HIV), are not necessarily excluded as a donor. It is helpful for programs to be aware of infectious disease status, but does not constitute a contraindication for autologous donation.

According to U.S. FDA Final Guidance (Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Product [HCT/Ps], August 2007), electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This Guidance Document is available at:
http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM091345.pdf.

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

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

Explanation:
These standards apply to informed consent for the specific collection procedure. Clinical Programs typically obtain informed consent to donate; Collection Facilities must obtain informed consent to perform the specific procedure. The essential elements of informed consent are that the donor or recipient is told, in terms she or he can reasonably be expected to understand, the reasons for the proposed therapy or procedure, the risks associated with the treatment or procedure, and potential benefits. This applies to both autologous and allogeneic donors. In addition, the donor or recipient should be given the opportunity to ask questions and to have these questions answered to his/her satisfaction. The discussion that ensues is the important part of the process of obtaining informed consent; however, it is the documentation of this process that can be easily audited. Informed consent is to be documented according to institutional standards and criteria.

The information must be given by a trained person able to transmit it in an appropriate and clear manner, using terms that are easily understood. The health professional must be certain that the donor has a) understood the information provided, b) had an opportunity to ask questions and had been provided with satisfactory responses, and c) confirmed that all the information he/she has provided is true to the best of his/her knowledge and documented in the medical record.

Evidence:
Review of one or more completed donor consent forms to determine if all the required elements are in place along with a review of the clinic note which details discussion of the protocol. The inspector may also ask to see each version of the consent form and/or clinic notes when a different process is used for pediatric donors.

Example(s):
It is recommended that the consent process be documented in the clinic chart by the consenting physician. In addition, it is recommended that a signed copy of the informed consent, even outside of a research protocol, be provided to the donor and recipient.

This process may take place over several visits. A preprinted consent form detailing all of the above elements is an easy method of documentation; however, informed consent does not specifically require such a form. In the absence of a form, the clinical notes detailing the consent discussion must be significantly detailed.

STANDARD:

C6.2.1.1 The risks and benefits of the procedure.

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

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

C6.2.1.4 Protection of medical information and confidentiality.

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

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

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

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

C6.2.5.1 The allogeneic donor shall be informed of the potential consequences to the recipient of such refusal in the event that consent is withdrawn after the recipient has begun the preparative regimen.

Explanation:
This standard is not meant to be coercive, but to require full disclosure of the effects a donor's decisions has on a recipient. Donors shall be informed that the consequences to the recipient of the donor's refusal to donate are significantly different depending on the stage of transplant. If the potential donor declines prior to typing versus refusing after selection and the day before the administration, then the degree of risk incurred to the recipient will be very different.

STANDARD:

C6.2.6 *Donor informed consent for the cellular therapy product collection shall be obtained and documented by a licensed health care professional familiar with the collection procedure.*

C6.2.6.1 *Informed consent from the allogeneic donor shall be obtained by a licensed health care professional who is not the primary health care professional overseeing care of the recipient.*

Explanation:
In the allogeneic setting, to prevent conflict of interest that may exist when a physician or other healthcare provider cares for both the donor and the recipient, donors must be consented by a member of the team other than the primary healthcare professional of the intended recipient or a clinician who is not a member of the team but is knowledgeable with the collection procedures.

STANDARD:

C6.2.7 *In the case of a donor who is a minor, informed consent shall be obtained from the donor's legally authorized representative in accordance with applicable laws and regulations and shall be documented.*

Explanation:
Donors must be of legal age of consent (in the jurisdiction of the collection) or the informed consent for donation must be signed by the legally authorized representative. Specific consent is required for the use of growth factor, in a minor, allogeneic donor. It is appropriate to discuss the donation procedure with the pediatric donor in terms he/she can understand. For minor donors, although consent is obtained from legally authorized representatives in accordance with local regulations, assent should also be obtained in an age-appropriate manner.

Example(s):
It may be helpful to include a child life specialist, a social worker, or another qualified individual in the consent process to make certain that the minor donor has age appropriate understanding.

STANDARD:

C6.2.8 *The allogeneic donor shall give informed consent and authorization prior to release of the donor's health or other information to the recipient's physician and/or the recipient.*

Explanation:
The purpose of this standard is to protect donor confidentiality regarding his or her health information. The Collection Facility should have the consent available prior to the collection procedure. Release of health information to the recipient is only required after donor selection.

Evidence:
Documentation that donor informed consent forms and recorded authorization to release relevant donor health information may document compliance. The date informed consent was obtained in relation to the date the release of the donor's health information occurred will be compared.

Example(s):
It is acceptable to obtain informed consent and authorization to release this information after donor screening and testing as long as it is obtained prior to sharing the results and prior to the collection. If a potential donor is screened but is deemed not to be suitable for collection, donor health information related to this decision does not need to be released to the potential recipient.

STANDARD:

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

C6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

C6.3.1 There shall be criteria and evaluation policies and Standard Operating Procedures in place to protect the safety of donors during the process of cellular therapy product collection.

Explanation:
Donor suitability refers to issues that relate to the general health of the donor and protection of donor safety. The criteria and evaluation SOPs must account for the entire collection process from initial evaluation, mobilization where applicable, to collection, and post-collection care.

Example(s):
Vulnerable donors (e.g., children) and donors at increased medical risk from donation (e.g., those with cardiac disease) are examples for when donor suitability assessment is crucial.

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

STANDARD:

C6.3.1.1 The Apheresis Collection Facility shall confirm that clinically significant abnormal findings are reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

Explanation:
Abnormal findings in a donor, including but not limited to the testing results, may have important implications for the individual apart from his/her role as a donor. Appropriate care of the donor requires that clinically significant abnormalities be communicated to the donor and that recommendations be made to that donor for follow-up care (including transfer of care, if applicable). The Collection Facility must confirm these actions are documented in the donor's medical record.

Evidence:
The inspector should review documentation in the medical record that prospective donors were informed of the abnormal findings including recommendations for work-up, treatment, and follow-up (including transfer of care, if applicable). The inspector may need to specifically request a record of a prospective donor undergoing collection who had abnormal findings, since this may not be a common occurrence .

STANDARD:

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

Explanation:
An independent physician or health care professional must be utilized for evaluating donor suitability to reduce potential bias of the recipient's health care professional(s). This individual must not be the primary health care professional of the recipient and should have knowledge of the risks of the donation procedures.

Medical literature supports the idea that having the allogeneic donor evaluated by a physician or health care professional who is not the primary health care provider of the recipient decreases the potential conflict of interest with regard to the welfare of the recipient and the welfare of the donor (see "Family Donor Care Management: Principles and recommendations," (van Walraven et al, 2010). Furthermore, the American Academy of Pediatrics (AAP) and the American Society of Blood and Marrow Transplantation (ASBMT) recommend this practice for related donations.

For allogeneic donors, a physician other than the recipient's physician (e.g., a different physician in the program or a clinician who is not a member of the program but is knowledgeable with the collection procedures) must be utilized for evaluating donor suitability to reduce potential bias of the treating physician(s); for example, the donor's primary care physician, a general internal medicine clinic, or a clinic not directly associated with the program.

STANDARD:

C6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

Explanation:
When testing for autologous donors, even if tests not approved for donor screening are used and the results are positive, the appropriate warning statements must be on the label.

STANDARD:

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

Explanation:
The purpose of this standard is to evaluate the donor for potential risks associated with the collection.

There should be a mechanism for independent review of suitability for vulnerable donors (e.g., children) and for donors at increased medical risk from donation (e.g., those with cardiac disease). The rationale and medical necessity should be discussed with the donor and recipient and documented within both medical records.

STANDARD:

C6.3.2.1 Possible need for central venous access.

Explanation:
The appropriate and safe positioning and function of central venous catheters (CVCs) is critical to the performance of cellular therapy product collection by apheresis. A licensed, trained, and qualified health care provider (such as a physician or a nurse) is responsible for obtaining central venous access. Credentialing of health care providers for this activity is the responsibility of the individual institution.

It is ultimately the health care provider's responsibility to confirm the adequacy and safety of placement of a CVC by appropriate methods. Confirmation that the line is satisfactorily positioned and functioning prior to the collection episode must be provided. The methods should be appropriate for the site of placement (e.g., subclavian/jugular access – fluoroscopy or ultrasound) while femoral line placement could be confirmed by ultrasonography. The records describing the position and function of the catheter and that both are appropriate to proceed with the collection must be available to the collection team.

Prior to collection and use of a CVC, the Apheresis Collection Facility staff must receive the documentation of placement and its appropriateness for use. This step will allow the facility staff the assurance to use the CVC and include documentation of satisfactory venous access in the donor record. Appropriate care should be taken to protect donor safety when a CVC is inserted solely for a collection procedure and that collection extends over more than one day. Donors need to be assessed for the risks of CVCs, including significant complications such as hematomas, pneumothorax, hemothorax, and bacterial infections.

Evidence:
The inspector should inquire about the nature and frequency of CVC complications including significant hematomas, pneumothorax, hemothorax, and bacterial infections. These adverse events should also have been discussed during quality assurance meetings of the Apheresis Collection Facility.

The inspector should look at the documentation of central line placement by the Apheresis Collection Facility, including documentation of line position and function prior to collection.

Example(s):
The WMDA S(P)EAR Committee has provided recommendations for policies in response to reported adverse events (Document Reference: 0110824-CLWG-SEAR-August 2011):

- Stem cell donor registries should review their policies concerning the placement of CVCs.
- If a stem cell donor registry does not have a policy concerning CVC placement, one should be written.
- Insertion of a CVC for PBSC collection should only be used in exceptional circumstances, e.g., only when peripheral venous access is not deemed feasible after skilled assessment or cannot be obtained or has failed.
- The policy should cover, at a minimum, the need for the following:
    - Requirement for careful peripheral venous assessment at the time of donor medical evaluation.
    - Evidence that alternative methods of donation have been discussed if appropriate.
    - Written justification for placement of a CVC.
    - Consenting procedures (and counselling) for CVC insertion, including who should obtain informed consent.
    - Qualifications and expertise of the person(s) permitted to insert the CVC.
    - Permissible sites for CVC insertion.
    - The requirement for radiological guidance for all CVC inserted above the umbilicus, if locally available.
    - The need for care for all patients with CVCs, cared for by appropriately trained personnel.
    - The requirement for reporting SAE/AEs.

The National Health Service National Institute for Health and Clinical Excellence (NHS NICE) provides guidelines regarding the placement of CVCs. Visit http://guidance.nice.org.uk/TA49 to obtain these guidelines and additional information. The American Society of Anesthesiologists Task Force on Central Venous Access has also published guidelines available for review (Anesthesiology 2012; 116:539–73).

STANDARD:

C6.3.2.2 Mobilization for collection of HPC, Apheresis.

Explanation:
Mobilization therapy requires that evaluation occur for any medical condition that would expose the donor to risk for thrombotic events. This evaluation must be documented, including the pre-collection and collection time frames specific to growth factor administration.

Evidence:
The donor's medical records for pre-collection workup results will contain evidence of compliance.

STANDARD:

C6.3.3 The donor shall be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen.

Explanation:
Hemoglobinopathy assessment is required since administration of mobilization agents such as G-CSF may pose a risk to the donor as it was associated with morbidity (e.g vaso-occlusive crisis) and mortality in donors with sickle cell disease (HbSS), HbSC, and also with compound hemoglobinopathies such as sickle-beta-thalassemia (S/β thal). Testing is not required, although it is an acceptable method.

Of note, donors with sickle trait were safely mobilized and collected. While the sickle trait donors did have higher symptom score than control donors, there were no symptoms suggestive of sickle crisis. Thus, in this group, the risk is limited.

References:
Granulocyte Colony-Stimulating Factor (G-CSF) Administration in Individuals with Sickle Cell Disease: Time for a Moratorium? Fitzhugh Cd et al ,Cytotherapy. 2009; 11(4): 464–471.

Granulocyte Colony-Stimulating Factor-Based Stem Cell Mobilization in Patients with Sickle Cell Disease. Rosenbaum C et al, Biology of Blood and Marrow Transplantation 2008; 14:719-723.

Mobilization, collection, and processing of peripheral blood stem cells in individuals with sickle cell trait. Kang et al, Blood 2002;99:850.

Evidence:
The inspector may look for the process or documentation of risk evaluation in the donor. For example, hemoglobinopathy risk evaluation might include a relevant question in the Donor History Questionnaire.

Example(s):
Hemoglobinopathy risk assessment may include testing for the detection of Hemoglobin S (e.g., Sickle Dex) or an Hb-electrophoresis test, but a test is not required. An assessment may be performed by looking at the donor's medical history.

STANDARD:

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

Explanation:
Pregnancy testing is required since the donation of cells from peripheral blood may pose a risk to the fetus. Child-bearing potential is meant to include all female donors from puberty through menopause, unless there is some definite medical indication that pregnancy is impossible (e.g., past hysterectomy). The purpose of this standard is not to forbid collection during pregnancy but to prevent donor mobilization and recipient conditioning from occurring before finding out that the donor is pregnant.

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

If a cellular therapy product is collected from the donor and subsequently cryopreserved for administration weeks later, the donor does not have to be retested for pregnancy.

If the recipient undergoes a preparative regimen for a long duration, a pregnancy test must be performed within seven days prior to beginning the regimen. The donor must be retested prior to collection to confirm there is no change in pregnancy status.

STANDARD:

C6.3.5 *Laboratory testing of all donors shall be performed by a laboratory that is accredited, registered, or licensed in accordance with applicable laws and regulations.*

Explanation:
All laboratory tests must be performed by a laboratory accredited for the relevant tests. Testing may be performed at any time prior to the initiation of the recipient's preparative regimen except for infectious disease tests, which must be done within 30 days prior to collection of HPC and within seven days prior to or after collection of other cell products as required by United States FDA or as required by non-U.S. equivalent regulations.

Evidence:
The inspector may look for infectious disease markers testing results and verify they were performed according to applicable government authority laws and regulation.

Example(s):
Examples of relevant accreditation organizations include CLIA, CAP, ASHI, AABB, JCAHO, and others.

STANDARD:

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

C6.3.7 *There shall be a written order from a physician specifying, at a minimum, anticipated date and goals of collection.*

C6.3.8 *Collection from a donor who does not meet collection safety criteria shall require documentation of the rationale for his/her selection by the donor's physician. Collection staff shall document review of these donor safety issues.*

Explanation:
The decision to use a donor who does not meet Clinical Program donor safety criteria must be made by the donor's physician. However, a designee may actually document that decision. The Collection Facility must review this information on donor safety. These standards also require that if allogeneic donors selected for transplant do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented.

Evidence:
The inspector may ask for charts of nonconforming donors and documentation of selection rationale, safety issues, and communication.

STANDARD:

C6.3.8.1 *There shall be written documentation of issues of donor health that pertain to the safety of the collection procedure available to the Apheresis Collection Facility staff. Collection staff shall document review of these issues prior to collection.*

Explanation:
Safety documentation is performed by the staff who conduct the donor health evaluation (in the Clinical Program or the Collection Facility). Responsibility should be defined in SOPs. Further, collection staff is required to document that donor health issues have been reviewed prior to collection.

STANDARD:

C6.3.9 *There shall be a policy or Standard Operating Procedure for the management of collection-associated adverse events and follow-up of donors that includes routine management.*

Explanation:
There should be a policy that provides guidelines for the post-collection care of donors. All donors should be monitored closely following the collection procedure.

Example(s):
The guidelines for post-collection care of donors may include the following short and long-term measures:

- Upon completion of the collection, the donors should have a complete blood count and ionized calcium drawn and the physician caring for the donor should be notified of the results.
- If a temporary apheresis catheter was placed for the collection procedure, there should be a clear guideline for catheter removal prior to discharge. This may include minimum platelet count prior to removal of the catheter.
- Discharge instructions should be given.
- The donor should remain at the Collection Facility for an adequate time. A follow-up appointment in the facility or an appropriate facility post donation should be performed.
- The donor should be contacted in 1 - 4 weeks for follow-up post donation.
- Long-term follow up may be defined as recommended elsewhere (e.g. WHO, EBMT).

STANDARD:
C6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

C6.4.1 *A donor advocate shall be available to represent allogeneic donors who are minors or who are mentally incapacitated, as those terms are defined by applicable laws.*

Explanation:
A donor advocate is an individual distinct from the transplant recipient's primary treating physician whose primary obligation is to help the donor understand the risks and benefits of donation and promotes the interests, well-being, and safety of the donor. According to Donor Registries for Bone Marrow Transplantation: Technology Assessment (NIH Office of Medical Applications of Research, 1985), the role of the advocate is to help ensure that the consent is made without time pressure and with full information, to enhance the personal attention given to the donor during all procedures, to help prevent unnecessary inefficiencies and discomfort, to mobilize official expressions of gratitude after the donation, and to aid in the resolution of subsequent problems.

For donors who are mentally incapacitated or not capable of full consent, including minors, a donor advocate must be utilized to appropriately counsel the donors and protect them from unsafe or futile donation procedures.

The donor advocacy role should be documented and should not be fulfilled by an individual involved in the recipient's care.

Evidence:
For centers using minor or mentally incapacitated donors, the inspector should ask for documentation that a donor advocate was involved in the donor selection process.

Example(s):
Examples of donor advocates include chaplains, patient advocates, social workers, etc. "Family Donor Care Management: Principles and recommendations," (van Walraven et al, 2010) provides recommendations for donor advocacy in the related transplant setting. When applicable laws and regulations define donor advocate and specific requirements, those must be followed.

STANDARD:

C6.4.2 *Allogeneic donor infectious disease testing shall be performed using donor screening tests approved or cleared by the governmental authority.*

C6.4.3 *The Apheresis Collection Facility shall comply with B6.4.6 through B6.4.6.8 when primarily responsible for donor screening for transmissible disease.*

Explanation:
The Standards and the FDA require that all donors be screened by medical history and risk factors for human transmissible spongiform encephalopathy, Creutzfeldt-Jakob disease (CJD), and potential transmissible infectious disease agents through xenotransplantation as there are no screening tests for these agents. Travel history is essential for this screening. Information about areas of the world where CJD is a risk factor should be established using trusted sources (e.g., national or international health agencies' websites or publications).

In the setting of resistant disease or relapse/progressive disease, it may be medically necessary to administer donor lymphocytes or other cellular therapy products before availability of repeat transmissible disease testing. The recipient must be informed of this deviation and the discussion must be documented in the medical record.

Other risks may be associated with unlicensed vaccines, receipt of human-derived growth hormone or clotting factor concentrates, or hepatitis B immune globulin. Prospective donors should be questioned about these issues.

In some donors, other tests may be necessary based on the donor medical history. In the case of child donors born of mothers with HIV, hepatitis C, hepatitis B, or HTLV infection, the evaluation of risk of transmitting infection should include consideration of the age of the child, history of breastfeeding, and results of infectious disease marker testing; eligibility criteria must be in accordance with applicable governmental laws and regulations.

There are standard deferral times after immunization for allogeneic blood donation that can be used to determine the potential risk that may exist. Blood donors are typically deferred for four weeks after attenuated live virus vaccines such as oral polio, herpes zoster, and measles. In those cases in which a potential donor has recently been vaccinated, both the reason for the vaccination and the time interval should be evaluated to estimate the potential risk to a recipient. There should be specific SOPs in dealing with donors who had received smallpox vaccination. Donors must be screened for traveling to the area that would put them at risk for malaria, human transmissible spongiform encephalopathy, SARS (severe acute respiratory syndrome) during periods of world-wide prevalence, or rare strains of HIV, which may not be detected by current screening tests.

Cytomegalovirus (CMV) is not a relevant communicable agent or disease. However, allogeneic donors must be tested for evidence of infection with CMV, although the time frame for this testing is not restricted. A prospective donor who was previously positive for anti-CMV should be considered to be a seropositive donor. Use of CMV-seropositive donors is permissible; however, the Collection Facility (or transplant program, if applicable) should have a clearly defined policy or SOP that addresses the use of CMV-seropositive donors. Cellular therapy product labels from CMV-positive donors do not require the statements or biohazard label required for products positive for the agents listed in B6. However, there must be a SOP for communicating test results of donors who are positive or reactive for CMV antibody.

STANDARD:

C6.4.4 *The Apheresis Collection Facility shall comply with B6.4.7 through B6.4.11 when primarily responsible for infectious and non-infectious disease testing of HPC donors.*

Evidence:

Infectious disease testing is usually conducted by the Clinical Program during the donor selection process. However, if a facility conducts such testing for a program, this standard applies and the facility is responsible for completing the applicant portion of the inspection checklist for the referenced standards. For information regarding these standards, see the corresponding guidance sections.

STANDARD:

C6.4.5 *The Apheresis Collection Facility shall comply with B6.4.3, B6.4.4, and B6.4.12 through B6.4.12.4 when primarily responsible for testing for the selection of allogeneic donors.*

Evidence:
C6.4.5 only applies to Collection Facilities that are primarily responsible for testing allogeneic donors during the donor selection process. This testing is usually conducted by the Clinical Program. However, if a facility conducts such testing for a clinical program, this standard applies and the facility is responsible for completing the applicant portion of the inspection checklist for the standard.

STANDARD:

C6.4.6 *The Apheresis Collection Facility shall confirm that allogeneic donor eligibility, as defined by applicable laws and regulations, is determined by a physician after history, exam, medical record review, and testing before the donor begins the mobilization regimen.*

Explanation:
While donor suitability usually refers to issues related to the general health of the donor to protect donor safety, allogeneic donor eligibility is determined based on eligibility criteria set by government authorities and/or regulatory agencies and generally focus on protecting recipient safety (e.g., prevention of transmission of communicable disease).

Donor eligibility and suitability should be differentiated as defined in A4, where "eligibility" refers to a donor who meets all transmissible infectious disease screening and testing requirements, and "suitability" refers to issues that relate to the general health of the donor and the donor's medical fitness to undergo the collection procedure.

STANDARD:

C6.4.7 *Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.*

Example(s):
For products that are manufactured in or distributed for use in the U.S., FDA requires that an accompanying statement of authenticity be present for records translated into English.

STANDARD:

C6.4.8 *Collection of a cellular therapy product from an ineligible allogeneic donor, or from an allogeneic donor for whom donor eligibility determination is incomplete, shall require documentation of urgent medical need that includes the rationale for the selection and documentation of the informed consent of the donor and the recipient.*

Explanation:
These standards also require that if allogeneic donors are ineligible according to applicable laws and regulations, or non-U.S. equivalent, or do not meet the institutional medical criteria for donation, the rationale for use of that donor and the informed consent of both the donor and recipient must be documented. There must also be documentation in the medical record by the transplant physician of urgent medical need for the cellular therapy product. Urgent medical need means that no comparable stem cell or cellular product is available and the recipient is likely to suffer death or serious morbidity without the stem cells or cellular products.

The product should be accompanied by a summary of records to the Collection and Processing Facilities stating reasons the donor is ineligible, including results of health history screening, physical examination, and results of infectious disease testing.

STANDARD:

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

Explanation:

This standard is meant to require the Collection Facility Medical Director or designee to review all donor data prior to collection of cells, and to document in the record that the donor is eligible ("in writing" includes electronic documentation). The health care professional responsible for obtaining the health history must make certain that the donor has confirmed that all the information provided is true to the best of his/her knowledge.

STANDARD:

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

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

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

C6.5.3 Consent to donate.

C6.5.4 Results of laboratory testing.

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

Explanation:

There should be a written SOP covering the creation and retention of donor records. The policy should address the following:

- For each donor, there should be a record containing:
  - The donor identification (first name, family name, and date of birth).
  - Age, sex, and medical and behavioral history (the information collected must be sufficient to allow application of the exclusion criteria, where required), including donor eligibility information for allogeneic donors. If behavioral history is not performed (i.e., for autologous donors), it does not need to be included in the donor records.
  - Consent/authorization form(s), where applicable.
  - Clinical data, laboratory test results, and the results of other tests performed.
  - The donor's suitability must be documented, including the rationale for selecting the donor when he/she does not meet donor safety criteria. For unrelated donations, when the organization responsible for procurement has limited access to recipient data, the transplanting organization must be provided with relevant donor data.

- All the records should be clear and readable, protected from unauthorized amendment and retained and readily retrieved in this condition throughout their specified retention period in compliance with data protection legislation.
- Donor records required for full traceability must be kept for a minimum duration as dictated by institutional practice and/or governmental regulatory requirements.

C7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

STANDARD:

C7.1 ISBT 128 CODING AND LABELING

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

Explanation:

ISBT 128 is the international information standard for transfusion and transplantation. Initially, ISBT 128 was developed for blood and blood component transfusion to increase the capacity for electronic data, to increase security and accuracy, and to permit unique unit identification globally. ISBT 128 has now been extended to include cellular therapy products and tissues. ICCBBA is the not-for-profit organization (www.iccbba.org) that is responsible for the development and maintenance of the ISBT 128 standard. ICCBBA maintains the databases for facility identification and product coding, assigns new product codes, and provides technical support. Several volunteer technical advisory groups support and inform ICCBBA. The Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) includes international representation from FACT, JACIE, ISCT, ASBMT, EBMT, NMDP, WMDA, ISBT, APBMT, and AABB. CTCLAG was formed to recommend standard definitions for cellular therapy products and rules for future assignment of cellular therapy product codes, to draft labels and a labeling strategy for cellular therapy products, and to draft an implementation plan.

The two main pieces of the standard terminology to unambiguously describe a product are class and attributes. Classes are broad descriptions of products (such as HPC, Apheresis) and attributes are additional characteristics that uniquely define the product. A group of attributes, called Core Conditions, are required; these conditions include anticoagulant and/or additive, nominal collection volume, and storage temperature. There are also other characteristics called groups and variables that can be used to provide more information about the product. The intent is to capture relevant characteristics about the product from donor and collection through the final processing. It is not intended that products would be relabeled at the bedside, so attributes such as “thawed” would only be applied if that process occurred in the laboratory.

Cellular therapy products characterized in this standardized way can be labeled using common, well defined terms that are printed in eye-readable format. The eye-readable terminology may be in the native language of the country in which the product is collected. The language also adapts to machine readable technologies such as bar codes. In this way, the products will be universally understood and international transport and exchange will be facilitated.

The standard terminology is structured in a manner that allows revisions, additions, and deletions as necessary on a continuous basis. In this edition of Standards, the common major classes of products are defined as was current at the time of publication. No attributes were included because of their sheer number and complexity and also because this is a period of rapid growth in the use of ISBT 128 for cellular therapy. Modifications in definitions and additions will occur. As the responsible body for the database development and maintenance, ICCBBA is the appropriate authority for maintaining publications on current terminology. To prevent use of obsolete terminology, the Collection Facility is instructed to refer to the ICCBBA document *Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions*. Facilities should refer to Chapter Three, Cellular Therapy, for current terms and definitions related to cellular therapy.

If facilities have questions regarding ISBT 128 terminology, they can reference the ISBT 128 Standard Terminology document and view the ICCBBA website at www.iccbba.org or contact ICCBBA directly for additional information and assistance. The website also includes resources and tools for identifying and assigning standardized codes for cellular therapy products or requesting a code for a new unique product.

To utilize ISBT 128 to its full advantage by using its technical database in the unique identification of products worldwide and in the use of common language, facilities must register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each product's unique alphanumeric identifier. Facilities in or affiliated with hospitals may find that their blood bank has already registered and a unique facility code already exists. Stand-alone facilities can individually register and pay a nominal annual membership fee.

Eurocode International Blood Labeling Systems (IBLS) provides an international non-profit standard for labeling blood products and tissue to enhance security in blood transfusion and tissue transplantation.

The main benefits of Eurocode-IBLS are

- one bag - one number (unique product bag number worldwide)
- unique coding of product properties
- country codes following ISO 3166
- center codes according to national agreements
- matching enhanced space saving barcode systems
- charge-free access to all information via Internet

Eurocode IBLS assigns, publishes and maintains the databases for Eurocode facility identification (Center Codes) and product coding. Eurocode product codes also serve as part of the EU Single European Code for tissue (SEC).

Centers using Eurocode require a Eurocode membership. All resources such as Eurocode's technical specification, guidelines and the databases including all product and center codes can accessed freely on www.eurocode.org.

Eurocode product codes characterize each product by the product group it belongs to, supplemented by a set of properties laid out in up to 18 predefined categories such as anticoagulant used, storage temperature, donor/recipient relationship, intended use etc. These property categories are called "qualifiers".

Evidence:
Inspectors will inspect the Collection Facilities according to the current ISBT 128 terminology and definitions. Inspectors should review Chapter Three, Cellular Therapy of the ISBT 128 Standard Terminology document before conducting an inspection. It would be helpful to have the document available for reference during the inspection.

Example(s):
Facilities registered with ICCBBA who have fully implemented ISBT 128 labeling shall follow the ISBT 128 standard. Labels that meet the appropriate information as defined by ISBT 128 comply with the Standards.

The appropriate product name for HPC collected by apheresis would be HPC, Apheresis. The acronym HPC, A, would be an abbreviation acceptable in documents, and possibly on partial labels. However, the U.S. FDA does not allow abbreviations on final product labels for licensed products.

Cellular therapy products with a biological license in the U.S. are subject to the bar code label requirements (21 CFR 201.25). The bar code, at a minimum, must contain the appropriate National Drug Code (NDC).

STANDARD:

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

Explanation:
The use of ISBT 128 or Eurocode for all cellular therapy products provides a uniform coding and labeling system worldwide. Such standardization is even beneficial to, and thus required for, autologous cellular therapy products.

In the sixth edition, active implementation for ISBT 128 coding and labeling within the Marrow Collection Facility was required. In the seventh edition, implementation of ISBT 128 or Eurocode is required. The implementation of coding and labeling are supported by FACT and JACIE and numerous other organizations in the field for cellular therapy. On the ICCBBA website (http://www.iccbba.org), the most recent versions of the terminology are published, as well as resources to help centers implement ISBT 128. The Eurocode website (http://www.eurocode.org/index.html) includes guidelines, product codes, and other resources.

STANDARD:

C7.2 LABELING OPERATIONS

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

Explanation:
The labeling SOPs should indicate that there are SOPs in place for each of the following:

- Ordering: initial orders and reorders.
- Receipt and quarantine.
- Verification of accuracy.
- Proper storage.
- Version control.
- Documented destruction of obsolete or unusable labels.

STANDARD:

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

Explanation:
Labels must be stored in a designated area where access is limited to authorized personnel. Stocks of unused labels representing different products must be stored separately to prevent errors. Labels should be organized physically or electronically so staff can readily identify the labels and be able to distinguish labels of different products from one another (e.g., by color-coding, size, or location). It is not acceptable to have labels of different types and for representing different types of products stored together with no separation. The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors.

Evidence:
The inspector should observe that there is an organized storage area for the labels, and documentation of obsolete labels that have been destroyed. There should be no obsolete version of labels available to staff, and labels in use must be the same as the approved labels.

The inspector should verify that the destruction process is documented and that there are no obsolete labels in the collection labeling/storage area.

Example(s):
Printed labels can be in containers to provide separation of each label type. Electronic labels can be in separate file folders for each label type.

STANDARD:

C7.2.1.2 Obsolete labels shall be restricted from use.

Evidence:
The inspector should verify that the destruction process is documented and that there are no obsolete labels in the collection labeling/storage area.

STANDARD:

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

Explanation:

New labels must be placed in a quarantine area upon receipt. The new labels must be inspected for:

- Manufacturing or printing defects,
- Form or version number, if applicable,
- Legible and correct eye-readable information, and
- Identity to source (original) label that has been approved for use by the Facility Director or designee.

Inspection must include comparison with a label approved by the Collection Facility Director or designee.

The inspection of labels at receipt or after printing must be performed by one person and independently verified by a second person. The process and outcome must be documented prior to release of the labels from the quarantine area.

Evidence:

The inspector should review all relevant labeling SOPs (see C5.1). The inspector should review documentation of verification of accuracy.

Example(s):

A form where superseded labels and new labels are attached to show the changes in the label content may be helpful. Approval of the Collection Facility Director, Collection Facility Medical Director, or designee can be documented on this form. The same form can be a used to document acceptability of the new label and inspection of content by two staff.

The Collection Facility might conduct a risk-assessment to determine if a label produced by the Processing Facility substantiates adherence with the approved labeling template.

STANDARD:

C7.2.3 *Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Apheresis Collection Facility Director or designee.*

Explanation:

"On demand" means that the labels are printed just prior to the labeling process. Print-on-demand label systems must be validated against approved label templates. Each on-demand label does not need to be validated so long as the system by which they are printed has been validated to confirm accuracy regarding identity, content, and conformity to the templates. Personnel do, however, need to confirm that the correct label was printed.

The Collection Facility should first develop a validation protocol for implementation of "on-demand" computer software. Upon implementation of the process, the facility must confirm and document that the label printed meets the criteria of acceptability.

Evidence:
Validation studies of the print-on-demand labels must be evident for the inspector's review. Personnel confirmation that the correct label was printed must also be documented.

STANDARD:

C7.2.4 A system for label version control shall be employed.

Explanation:
The document control system used for these various elements and what constitutes a label version must be defined by the Collection Facility. Any change in the label or label element that would change the interpretation of the label would constitute a version change. Only the current version of each label should be available for use in the collection area.

Evidence:
The inspector should verify that the versions of labels in the labeling/storage area are the current version.

Example(s):
Changes in the requirement for a uniform product proper name or changes in the wording of required statements or warning statements would require a version change to that base label or label element.

STANDARD:

C7.2.4.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by applicable laws and regulations, whichever is longer.

Explanation:
Obsolete or unusable label stock should be defaced immediately to prevent their accidental use and then destroyed. However, as a controlled document, representative obsolete labels (or label templates) and their inclusive dates of service, must be archived minimally for 10 years after the last cellular therapy product was distributed, or as defined by applicable laws and regulations, whichever is longer.

Obsolete labels should be removed from inventory and discarded as soon as a new version is put in for use. The labels that are replaced by new versions must be archived.

STANDARD:

C7.2.5 A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.

C7.2.5.1 Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.

Explanation:
Labels for re-packaged cellular therapy products must conform to the proper label content as described in Appendices II and III as applicable. Criteria for re-packaging of cellular and tracking mechanism should be included in procedures.

Evidence:
If products are repackaged, the inspector should examine the labels on a repackaged product to ascertain whether there are mechanisms in place (either on the label itself or via accompanying paperwork) to track the product from its origin to the final disposition.

STANDARD:

C7.2.5.2 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.

Explanation:
This standard requires facilities to have a careful process for electronically transmitting information (such as with a bar code) and to double check the information rather than becoming solely dependent on the technology to work correctly.

For automatic labeling systems that include computer-assisted label verification (such as a bar code scanner) of parts of the label, electronic verification must be part of the label system validation. Details regarding validation of electronic record systems are found in C11.

Evidence:
For systems using computer-assisted label verification to confirm label accuracy (such as bar-code scanning), procedures and records should show how the automatic verification works.

STANDARD:

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.

Explanation:
The cellular therapy container should not be covered wherein the contents cannot be viewed. Inspection of the content is essential in determining abnormal color of plasma that could be due to hemolysis, bacterial contamination that could affect the safety of the product, and clots that could reduce the efficacy of the product.

Evidence:
The inspector should examine labeled products on-site to verify that labels are firmly attached or affixed and that sufficient area of the product remains uncovered to allow examination of contents.

STANDARD:

C7.2.7 The information entered on a container label shall be verified by one (1) qualified staff member using a validated process or two (2) qualified staff members.

Explanation:

One person who is trained in labeling using a validated process, or two people who are trained in labeling in accordance with institutional requirements and governmental regulations, must confirm that the manually entered information on the label is accurate. Verification of the information must be documented in the collection records. It is important for the collection staff to verify the accuracy of the donor/patient information and to confirm that all parts of the collection (product labels, tie tags, sample tubes and associated forms) are labeled completely and legibly before removing them from the donor.

In addition to confirming correct content, the label verification should include:

- The label is correctly affixed to the component (and/or tie tag).
- The correct label is positioned appropriately.
- The label is identical to the one specified in the SOP.
- Hand written information is written with indelible ink.
- All information is legible and accurate.
- The unique identifier is firmly affixed to the product bag and identical to the identifier on facility associated forms.
- The label is not damaged or defaced.

Evidence:

The inspector must verify the documentation in the collection records. Initials or signatures of staff as defined by the labeling process should be present in the collection records.

STANDARD:

C7.2.8 Labeling elements required by applicable laws and regulations shall be present.

Explanation:

Label elements that are required by governmental regulation must be clearly visible. The Collection Facility should review FDA, EU, and/or other applicable governmental requirements for labeling and format labels accordingly.

STANDARD:

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

Explanation:

All data fields on a label must be complete; fields for which information is not required must be filled as "NA."

Evidence:
The inspector should examine labeled products on-site to verify the presence of appropriate information on the label.

Example(s):
In some cases a base label is used, with stickers applied containing specific elements based on the product type or the modification that was performed. Also, many facilities apply biohazard labels and warning statements if applicable using tie tags.

STANDARD:

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

Explanation:
Indelible ink must also be used to record any information entered manually on the label. Inks and labels must be resistant to alcohol wipes and sprays if they are likely to be subjected to such liquids at collection, in the Processing Facility, or on the ward. Validation of the labels should include the properties of the ink used.

Evidence:
Documentation of evidence that the inks and labels were demonstrated to be resistant to alcohol wipes and spray, should be available to the inspector.

STANDARD:

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

Explanation:
Adhesives that are applied directly to the cellular therapy product bag have the potential to leach through the plastic into the product itself. Collection Facilities must use materials that meet criteria, if any, established by applicable regulatory authorities.

This standard does not apply to labels applied to a base label of a cellular therapy product bag.

Example(s):
Collection Facilities in the U.S. should contact the FDA regarding any labels affixed directly to the cellular therapy product bag to determine what data is needed to demonstrate that the labels meet FDA requirements. For further information, see the FDA document, "Guideline for the Uniform Labeling of Blood and Blood Components," (August 1985). This document is available at:
http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM080974.pdf

STANDARD:

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

Evidence:

Labels must have been validated to confirm they remain legible under the conditions in which they are used.

Example(s):

Validation of a label includes the properties of a label applied on the product and that the product is stored in its proper storage temperature.

STANDARD:

C7.3 PRODUCT IDENTIFICATION

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

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

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

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

Explanation:

The product identifier must be unique. Unique is defined as not being used for any other purpose. Thus it is not acceptable to use only patient information (such as medical record number or social security number) or only the donor information (name, medical record number, or registry identifier) to identify the cellular therapy product. Generally, a unique identifier also implies that there is reasonable confidence that it will not be used for another purpose. Cellular therapy products collected from a single donor at different times must be distinguished from each other by different unique product identifiers.

The essential point is that each cellular therapy product can be unambiguously traced from donor to recipient, and through all transport steps, processing steps, and storage locations. The label must clearly indicate the identity of the facility that assigned the product identifier, with the exception of cellular therapy products shipped by registries, where the source facility must remain confidential. In such cases, the records that accompany the product must allow tracing to the donor.

There must be a SOP indicating how a unique identifier is assigned and tracked and include acceptable modifications that can be made to the product label or identifier. When a cellular therapy product from a single donor is divided into multiple containers, each container must be uniquely labeled. If products are being pooled, the pool number must allow tracing to the original products. Note that only products from a single donor may be pooled unless specifically allowed for a given protocol by the appropriate regulatory authority.

Product and donor samples collected at the time of cellular therapy product collection should be labeled so as to prevent misidentification. At a minimum, this must include the donor's name (except for the case of unrelated donors), identifier, and date of sample collection.

Evidence:
The inspector must review the SOP for labeling the product with the unique identifier and how the identifier is assigned. There should be evidence that the product identifier is not duplicated and this could be demonstrated with a product identifier log. The inspector should perform a review to determine that the product identifier can be traced to the records used from collection to distribution of the product.

Example(s):
The donor or recipient registry number can be used by the local site as the sole or additional identifier if it is combined with other information that makes it unique, such as the collection date, so that each cellular therapy product can be uniquely identified.

Identification of products with multiple containers may occur by modifying the unique identifier on each container with a suffix (either letter or number) or by modifying the product label on each bag (such as Bag 1 of 2, etc.).

STANDARD:

C7.3.1.4 Supplementary identifiers shall not obscure the original identifier.

C7.3.1.5 The facility associated with each identifier shall accompany the cellular therapy product.

Explanation:
The Collection Facility may assign additional identifier(s) to a product; however, it is recommended that no more than two unique product identifiers be affixed to a product container. The original identifier may not be obscured. If a supplemental unique identifier is replaced with another identifier, records must link the current unique identifier to the previous one.

Evidence:
The inspector should observe label procedures if this function is being performed by the Collection Facility; if not, the inspector should verify that the supplemental labeling procedure is in place.

Example(s):
To prevent obscuring the original product identifier and other label information, the Collection Facility may record the supplemental identifier to a tie tag.

STANDARD:

C7.4 LABEL CONTENT

C7.4.1 At the end of the cellular therapy product collection, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix II.

C7.4.2 Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information (COI) for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."

Explanation:

The required label content as specified in Appendix II represents minimum requirements, and must be present as indicated at the various stages of product collection, processing, and distribution.

Accompanying paperwork should be packaged in a secondary bag with the product for transport to the processing facility or infusion site. It is not acceptable to transport multiple product bags, from different donors, using partial labels with all of the additional information on a single inventory sheet.

When labeling products after collection, it is important to include the time when collection of the product was completed, along with the time zone if different from the time zone of the anticipated processing facility, so that the Processing Facility will have an accurate determination of the age of the product and be able to apply the appropriate expiration date and time.

The Collection Facility address should be explicit enough to correctly identify the location and contact the facility if questions arise or an emergency occurs during processing and/or transportation. For products distributed by an unrelated donor registry, a facility identifier that does not include the facility name and address should be used to protect donor privacy; however, this information should be part of the processing record or be available to the Processing Facility if needed.

A biohazard label must be attached or affixed to any cellular therapy product from which a donor sample has tested positive for a relevant communicable disease (including tests for infectious agents listed in B6 and its substandards except CMV) or when donor screening indicates a risk factor for a relevant communicable disease or disease agents. Table 2 of the inter-organizational Circular of Information for Cellular Therapy Products outlines when biohazard labels must be used. Biohazard labels can only be applied to products not required to be labeled biohazard when specific circumstances for their use are defined by facility or program policy. Biohazard labels must not be applied indiscriminately. These labels are meant to denote a greater hazard than that posed by any biological product. Using biohazard labels on all products without rationale that is documented in facility records is considered a deficiency.

Warning labels are required to be affixed or attached to the product when product testing or screening is positive for infectious disease risk or is incomplete (see Appendix II).

Communicable disease testing is not required for autologous donors, unless required by applicable laws, in conjunction with product collection nor is there a requirement for donor eligibility determination. However, if autologous donor testing and screening is not performed, or is incomplete, the product label must contain the statement "Not Evaluated for Infectious Substances." In addition if the autologous donor is tested or screened prior to collection and is found to be positive or at risk for a relevant communicable disease, the product label must bear a biohazard label and the appropriate warning statements. Since autologous recipients are not at risk of contracting a communicable disease from themselves (they already have the disease), the statement "Warning: Advise patient of communicable disease risk" is not required on autologous product labels even if donor testing results are positive, although a biohazard label is required.

Once regulated products have reached the stage of licensure, the label or accompanying records must include the statement "Rx Only" indicating that the product may only be distributed by a prescription from the transplant physician. The physician order form required by the Standards may serve as the prescription. As of this writing, only cord blood has reached the level of licensure.

Evidence:
Prescreening of the labels by the FACT office or JACIE inspectors will be performed and every effort made to correct any deficiencies prior to the on-site inspection. Examples of all labels in use by the applicant facility will be provided to the inspector prior to the on-site inspection. For applicant programs performing both allogeneic and autologous cellular therapy, examples of labels will include collection, processing, transport, and distribution labels for both types. In addition, labels illustrating each cellular therapy product source handled by the program should be included. Partial labels, if used, should be included. Tie tags, instructions to the infusionist, biohazard labels, and warning labels should also be included. If any expected label is not included in the pre-inspection documents, the inspector should request it from the applicant Collection Facility or the FACT or JACIE office.

The inspector should review the labels prior to the on-site inspection and determine if deficiencies have been corrected. This will maximize the efficiency of the inspection by allowing the inspector to focus on elements that can only be verified on-site. However, when on-site, the inspector should verify that the labels currently in use are identical to those submitted prior to the on-site inspection and correspond to the labels in the SOP. If this is not the case, the inspector will need to resolve the discrepancies and verify that each label in use meets the requirements listed in Appendix II. The inspector should further verify that labels are available for every type of cellular therapy product collected, with suitable modifications. Examples of completed labels must not contain blank spaces. "N/A" or "none" should be used as indicated.

Autologous product labels should be examined to confirm that "Not Evaluated for Infectious Substances" is present when the donor screening and testing does not contain all of the elements listed in B6. If the Collection Facility utilizes a partial label, the inspector must confirm that the SOP describes the use of the partial label, provides an example of the partial label, and includes the mechanism for providing the additional information that is not included on the partial label.

The inspector should ask to see the SOP that defines the conditions for using a biohazard label and determine if the facility's procedures are adequate and appropriately safe to prevent transmission of infectious disease.

The inspector should review the labeling of products from NMDP-facilitated transplants to confirm this statement is used on the product or in the accompanying record (the infusion form or distribution record) issued with the product.

Example(s):
Additional information may be attached to the product via a tie tag, or included in accompanying documentation, as detailed in Appendix II.

Products that are regulated under section 351 of the PHS Act in the U.S. must be labeled with the statement "Caution: New drug limited by federal law for investigational use." Currently HPC, Apheresis products and HPC, Cord Blood collected from unrelated donors for NMDP are regulated under an IND held by NMDP. Such products must contain this statement, attached or affixed to the label or accompanying the product.

Note that residence in a country on the U.S. Department of Agriculture list as at risk of BSE is considered to constitute a risk identified by donor screening. Thus, allogeneic donor products require a biohazard label and the statement "Warning: Advise Patient of Communicable Disease risks."

Organizations that do not perform autologous donor testing must carefully establish processes that maintain compliance with FDA regulations for labeling. Autologous products must be labeled with "FOR AUTOLOGOUS USE ONLY" and other warning and biohazard labels for a variety of scenarios. The statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" must always be on the product if all donor eligibility requirements are not completed. For example, this statement must be on the following:

- A product not tested at all for relevant communicable disease agents and diseases.
- A product tested for only a subset of relevant communicable disease agents and diseases.
- A product screened and tested for all relevant communicable disease agents and diseases but using diagnostic tests rather than donor screening tests.
- A product screened and tested for all relevant communicable disease agents and diseases using approved donor screening test, but for which no official donor eligibility determination was made.

The use of the biohazard legend and the statement "WARNING: Reactive test results for (name of disease agent or disease)" is different. Any autologous product with the presence of risk factors for or clinical evidence of relevant communicable disease agents or diseases must have these two labels, whether or not the regulations for donor eligibility determination were completely followed. If all donor eligibility requirements are not met, but the product is reactive for a relevant communicable disease, the product must be labeled with two warning statements: "WARNING: Reactive test results for (name of disease agent or disease)" and "NOT EVALUATED FOR INFECTIOUS SUBSTANCES".

STANDARD:

C7.4.3 *Labeling at the end of collection shall occur before the cellular therapy product bag is disconnected from the donor.*

Explanation:
Collection product labels, tie tags, sample tubes and associated forms must be labeled completely and legibly before disconnecting the cellular therapy product from the donor. Labeling of the product before disconnecting it from the donor will prevent mix-up when there is more than one donor undergoing collection.

If confidentiality is a concern, partial labels may be used until the product is disconnected from the donor.

STANDARD:

C7.4.4 *Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix IV at the time of distribution.*

Explanation:
The FDA cGTP regulations have specific requirements regarding the information that must accompany a cellular therapy product at the time of distribution. Requirements for products from allogeneic donors are listed in Appendix IV. A statement is required attesting to donor eligibility (or ineligibility) based on the screening and testing that was performed, a summary of the records used to make the donor eligibility determination, and the identity and address of the facility that made that determination. This summary must include results of the donor screening for infectious disease risk and the communicable disease test results. The test and screening results must be listed with an interpretation of the values as positive or negative. There must also be a statement confirming that communicable disease testing was performed by a laboratory with the required qualifications. For products that are distributed for administration, the product administration form can be used for this purpose. For products that are distributed to another facility, this information must be included. If the Collection Facility is responsible for allogeneic donor eligibility determination, that facility is also responsible for distributing the above information to the Clinical Program and Cell Processing Facility. If the Clinical Program determines allogeneic donor eligibility, the Collection Facility must obtain the information from the program so that it may accompany the product.

According to FDA and non-U.S. regulations, as applicable, there are many statements, results, and documents that must "accompany" the cellular therapy product at all times after the determination of allogeneic donor eligibility has been documented (see 21 CFR 1271.55).

The FDA Final Guidance ("Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Product [HCT/Ps], August 2007) states that electronic access to accompanying records within a facility would satisfy regulatory requirements listed in 21 CFR 1271.55. This Guidance Document is available at:
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm.

Example(s):
It is permissible to have hard copies of each item physically accompany the product, and in some cases, that may be most appropriate, as when a product leaves the Collection Facility and is transported to another institution for processing, storage, and/or administration.

STANDARD:

C7.4.5 *For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after the use of the product.*

Explanation:
If the Collection Facility participates in donor eligibility determination, completion of this determination must be documented.

Evidence:
The inspector should review that the completion of determination documentation is completed within the timeframes outlined in the Collection Facility's SOPs.

Example(s):
Related documentation that allogeneic donor eligibility was completed during or after the use of the product should be in the donor's or recipient's records. Urgent medical need documentation to release the cellular therapy product should also be present.

STANDARD:

C7.4.6 *Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "Not For Admin."*

C8: PROCESS CONTROLS

STANDARD:

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

Explanation:
To be considered complete, the collection SOP should include at least the following:

- Physical details of the collection procedure.
- Reagents and equipment to be used.
- The type of anticoagulants and/or solutions added to the cell collection container during the procedure.
- Requirements for monitoring the donor prior to, during, and after collection (as applicable).
- Recognition and treatment of adverse reactions.
- Expected results of the collection.
- Labeling of cell products.
- SOPs for storage, distribution, transport and/or shipping of the cells.
- Methods for detection of clerical errors.
- SOPs for quality testing.
- Recording of date and time of each significant step.

Evidence:
The inspector should observe a portion of a collection procedure to determine whether or not the personnel follow applicable SOPs. If there is no collection procedure scheduled for the day of an on-site inspection, the inspector should ask the Collection Facility staff to perform a mock collection, including all parts of the donor interview and consent for which that facility is responsible, and all labeling and storage steps. In addition, inspectors should review collection records to verify that specific elements of the procedure were carried out according to the SOP. Deviations from the SOP may indicate inadequate training or out-of-date SOPs.

Questions may be asked to determine: Are cellular therapy products from different donors stored in the Collection Facility at the same time? Are products labeled at the donor's side prior to disconnecting from the apheresis line to avoid misidentification? Are reagents identified as dedicated to a single collection procedure? Is there a record of the lot numbers and expiration dates for all reagents used in collection? Is the specific apheresis machine used in each collection identified? How is cleaning and disinfection performed between collection procedures?

Example(s):
The Collection Facility may develop a document to record data that are captured according to the collection SOP. These data may include the items in the explanation section. The document should also identify the staff performing each step in the SOP.

STANDARD:

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

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

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

Explanation:
Cellular therapy product quality, as measured by adequate viability, integrity, lack of microbial contamination, and lack of cross-contamination, may be affected by the supplies, reagents, and equipment used for collection. Therefore, these items used in collection that might affect product quality must be identified and tracked. For this purpose, there must be a system by which the critical equipment can be uniquely identified.

The identification and the tracking of supplies, reagents, and equipment used to collect cellular therapy products must be described in an SOP. Critical materials must be defined by the Collection Facility and tracked and traced. Supplies and reagents must be examined for contamination, breakage, discoloration, etc., at receipt. Records must be kept of the receipt and qualification of each supply or reagent and must include the type, manufacturer, lot number, dates of receipt, and expiration date. There must be a mechanism to link the supplies and reagents, lot numbers, and expiration dates to each product manufactured and, conversely, each product collection record must include the identity of the supplies and reagents that were used. The reagents and supplies must also be visually inspected for contamination, breakage, and discoloration, immediately prior to use and procedure initiation; findings must be documented.

Generally, the cellular therapy product inventory and reagent and supply inventory are separately managed. Each product must be assigned a unique alphanumeric identifier that is part of the control system. Equipment, supplies, and reagents should be connected to the product through the unique identifier or through an alternative system so that a link to the product can be made. Testing laboratories may require that other identifiers be used. Any blood sample or tissue for testing must be accurately labeled to confirm identification of the donor and must include a record of the time and place the specimen was taken. The system must include documentation that materials under the inventory control system meet predefined facility requirements.

Evidence:
The inspector should confirm that there is a process in place to determine acceptability of all critical materials (reagents, supplies, labels, cellular therapy products, and product samples) before they are accepted into inventory and prior to use.

Description of acceptable criteria for reagents and supplies may be found in logs or relevant SOPs.

The inspector should review the inventory control process and documentation of supply and reagent examinations at receipt and prior to use to verify that the Collection Facility takes steps to confirm there is no obvious evidence of damage (e.g., leakage, damaged box).

Example(s):
The system in use may utilize an electronic system or a log book to enter all incoming supplies and materials.

Equipment identification can be achieved by using a pre-existing serial number, but may be better achieved by assigning a unique identifier that is visible on the piece of equipment. A more casual designation, such as "Brand X centrifuge," is less desirable since over the course of time more than one centrifuge might fit that description. It is possible to accomplish this by the use of serial numbers and records of dates of use; however, over time, this is more difficult to track reliably.

STANDARD:

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

Explanation:
Supplies and reagents that come into contact with cellular therapy products must be clinical or pharmaceutical grade, as appropriate, and free of microbial contamination. It is recognized that reagents not approved for human use were commonly used in the past, for example, the use of various tissue culture media. However, Collection Facilities are expected to keep up to date on current collection techniques.

A Certificate of Analysis (COA) should be obtained if available from the manufacturer . Upon receipt of reagents and supplies, personnel should document review of package inserts to confirm that there are no changes in the intended use, and should retain the most current package insert for reference.

Evidence:
The inspector should request COAs of the reagents that are approved for human use or of pharmaceutical grade. Package inserts of reagents and supplies provide information regarding their intended use.

STANDARD:

C8.3 *Equipment shall be inspected for cleanliness prior to each use and verified to be in compliance with the maintenance schedule daily prior to use. Equipment shall also be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.*

C8.3.1 *All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.*

C8.3.2 *When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products collected since the last calibration.*

Explanation:
Equipment used for collection or product testing must be maintained, calibrated, cleaned, and, if applicable, sterilized. Equipment SOPs must also describe how the equipment is operated or refer to relevant operations manuals that are available within the Collection Facility. The SOPs should also provide instruction in the event of failure of any device. Maintenance and calibration are required to detect malfunctions and defects and to safeguard that the critical parameters are maintained within acceptable limits at all times. There must be a schedule for equipment maintenance and quality control. Schedules may vary based on frequency of use, performance stability, or recommendations from the manufacturer.

Specified critical equipment must be calibrated by a qualified technician. A calibration report from the qualified technician must be provided to the Collection Facility and be available during the inspection. Critical equipment with the condition of calibration solely by the manufacturer must be identified in the facility SOP.

Mobile donor centers must have SOPs that demonstrate compliance with the Standards. A description of critical equipment movement shall be included in the SOP in accordance with industry guidance.

Tags or stickers should be visible on the equipment indicating that quality control (QC) parameters have been met, the date QC testing was performed, and when such testing is next due. Where applicable, calibration SOPs should include limits for accuracy and precision. Equipment with a critical measuring function (e.g., time, temperature, speed) should be calibrated against a traceable standard, if available.

Note that if critical equipment used in collection is located outside of the Collection Facility, such as sterilization equipment, it is the facility's responsibility to safeguard that equipment is properly assembled for function, maintained, and calibrated. Such records should be available to the inspector.

It is also important to maintain a schedule of equipment cleaning, sterilization, sanitation, and disinfection that is described by an SOP (see C5.1), and documented. This is important to prevent microbial contamination of products, as well as to prevent transmission of infectious disease and cross-contamination.

Evidence:
On-site, the inspector should see a sampling of such records. The inspector should look for SOP(s) describing the corrective action to be taken when precision and accuracy limits are not met, and written instructions to be followed if the equipment fails (see C5.1). This should include an investigation of potential adverse effects on manufactured cellular therapy products using the equipment tracking system.

The inspector should confirm by visual inspection that equipment can be easily accessed for cleaning and maintenance.

Example(s):
It is recommended that recent records of regularly scheduled maintenance and quality control be readily available for each piece of equipment. Calibration on at least an annual basis is also recommended.

For U.S. programs, 21 CFR 1271.200 provides additional details on calibration. GMP regulations also provide details. Note that these are only required for 351 products; however, may be helpful in any case. See also 21 CFR 211.63-72.

STANDARD:
C8.4 Equipment shall conform to applicable laws and regulations.

Example(s):
European Directive 2006/17/EC Annex IV 1.3.10 specifies that where possible, equipment that is compliant with the CE Marking Directive must be used for cellular therapy product collection. CE marking is a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation implementing certain directives. Staff using such equipment must have appropriate training. For additional guidelines regarding this requirement, see:
http://ec.europa.eu/.

STANDARD:

C8.5 *Autologous or CMV-appropriate and irradiated blood components shall be available during the apheresis collection procedure for all donors.*

C8.5.1 Allogeneic blood components administered to the donor during apheresis collection shall be irradiated prior to transfusion.

Explanation:

Donors may require a blood transfusion during the apheresis collection procedure. Collection Facilities need to be prepared to provide appropriate blood products. Autologous units may be collected prior to apheresis, or allogeneic CMV-appropriate and irradiated units may be used. The decision to use autologous or allogeneic blood depends on the benefits and risks to the donors, especially in the case of pediatric donors.

A special concern for the allogeneic donor is the fact that transfused allogeneic blood contains lymphocytes that can become part of the collected cellular therapy product. Therefore, these transfusions must be gamma-irradiated to prevent engraftment of third-party lymphocytes in the transplant recipient. Because of the occasional need for a second cellular therapy product collection, it is advisable to continue irradiating blood transfused to the donor in the postoperative period[1].

It is expected that normal sized, adult marrow donors would donate autologous blood and therefore not require allogeneic blood. However, in the situation of small marrow donors and large recipients, transfusion is expected. Many places have difficulty collecting autologous blood from donors <40 kilograms (kg). If the recipient is adult size and the donor is 25 kg (common in sibling transplants), transfusion is expected, frequently occurs during the collection, and the blood products must be irradiated. Additional information can be found in Transfusion Support of the Marrow Donor[2].

The use of irradiated blood components during the immediate post-operative period may be necessary if there is any consideration that the donor may need to donate a second product in that immediate timeframe. Under most circumstances, the requirements for irradiated blood products are during collection, but physicians might want to consider the use of irradiated blood components during the immediate post-operative period. For example, if children need to be harvested twice, or if the target yield was not achieved, a supplemental peripheral blood product from the donor may be necessary.

References cited:

1. Snyder El and Haley NR (eds): Cellular Therapy: A Physician's Handbook. Published by AABB, 2004:15.

2. Petz LD and Swisher SW, eds: CLINICAL PRACTICE OF TRANSFUSION MEDICINE, Second edition, 1981; Third edition 1996.

Evidence:
The inspector should verify the availability of irradiated, leukoreduced, and/or Cytomegalovirus (CMV) sero-negative cellular blood products and other blood components in case they are needed. A review of the process by which such products are ordered should provide adequate evidence.

STANDARD:
C8.6 *Before cell collection is undertaken, there shall be a written order from a physician specifying, at a minimum, timing and goals of collection.*

Explanation:
The physician who evaluates the donor and makes the decision to proceed is not always the same one who actually collects the cells. The written order is required as a mechanism to safeguard that there are no misunderstandings among team members regarding the specifics of the collection. The written order should include at least:

- Identity of the donor.
- Identity of the allogeneic recipient (if applicable).
- Timing of collection.
- Date and time the cells are needed by the recipient (as applicable).
- Cell type.
- Cell dose required.
- Total blood volume to process (if apheresis) or number of collections according to standard SOPs.
- Appropriate authorized signatures.
- Blood group determination.
- Recipient weight.
- Donor weight and height.
- Pre- and post-collection laboratory results guidelines.

Collection timing may include a timeframe driven by CD34 analysis or specific date(s) and time(s). Pre- and post-collection laboratory results guidelines may include relevant hematologic and biochemical analyses. SOPs should outline how the Collection Facility will handle donors whose laboratory values are outside of the acceptable ranges.

Evidence:
The inspector should confirm that the written order meets the criteria and, if there are deviations, that they were approved.

STANDARD:
C8.7 *A complete blood count, including platelet count, shall be performed within 24 hours prior to each subsequent cellular therapy product collection by apheresis.*

Explanation:
The Standards require peripheral blood count criteria for proceeding with collection; however, testing within 24 hours is only required for collection procedures after the first one is completed. Normal donors are unlikely to have sudden changes in counts; however, the apheresis procedure itself may cause changes that could put donors at increased risk during subsequent collections.

Collection Facilities may set their own timeframes for performing testing on donors in advance of the first collection. Some registries may have specific requirements. Not only does the testing need to be performed, but facilities must have predetermined limits for when collection may or may not proceed.

STANDARD:
C8.8 *There shall be peripheral blood count criteria to proceed with collection.*

C8.9 *There shall be written documentation of an assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.*

Explanation:
Day-to-day management of the donor is the responsibility of the Collection Facility. It is incumbent on the collection team to confirm the health of the donor at the time of collection. This does not require a complete history and physical examination by a physician for each collection procedure. Rather, the records from the initial evaluation (including consent for the procedure and documents regarding the goals of the collection procedure) must be immediately available to and reviewed by the collection team. A physician or registered nurse on the collection team must evaluate the donor before each collection procedure to determine if there have been changes in the health of the donor or changes in medications since the last donation.

The interim evaluation should include a record of vital signs and a focused donor screening regarding changes in health, medications, or risk factors (e.g., tattoos, needle exposure) that are pertinent. Donors should also be assessed according to SOPs determined by the collecting facility, but at a minimum should include vital signs. The results of interim laboratory tests must be obtained to determine if the donor meets the minimal blood count criteria to proceed with the collection.

This evaluation must be documented as part of the permanent record of the donor. The evaluation must be performed by a qualified member of the transplant team competent in assessing the health status of the donor. Competency shall be defined in the program or facility SOP manual. The Collection Facility shall have a system in place to confirm donor identity so that all samples, labels, and records are appropriately and consistently completed.

Evidence:
The inspector should verify in the donor records that evaluation meets the minimal criteria prior to collection. Documentation of an approved planned deviation should be found if minimum criteria are not met.

STANDARD:
C8.10 *If required, central venous catheters shall be placed by a licensed health care professional qualified to perform the procedure.*

C8.10.1 Adequacy of central line placement shall be verified by the Apheresis Collection Facility prior to initiating the collection procedure.

Explanation:
Appropriate and safe positioning and function of central venous catheters is critical to the performance of cellular therapy product collection by apheresis. A licensed, trained, and qualified health care provider (such as a physician or a nurse) is responsible for obtaining central venous access. Credentialing of health care providers for this activity is the responsibility of the individual institution.

It is ultimately the health care provider's responsibility to confirm the adequacy and safety of placement of a central venous line by appropriate methods. Confirmation that the line is satisfactorily positioned and functioning prior to the collection episode must be provided. The methods should be appropriate for the site of placement (i.e., subclavian/jugular access – fluoroscopy, ultrasound) while femoral line placement could be confirmed by ultrasonography. Imaging should be used for central venous line placements due to known risks (e.g., death due to hemothorax). The records describing the position and function of the catheter and that both are appropriate to proceed with the collection must be available to the collection team. The Collection Facility staff must document satisfactory venous access in the donor record.

Prior to cell collection and use of a catheter, the Collection Facility staff must receive the documentation of placement of the central venous catheters and its appropriateness for use. This step will allow the facility staff the assurance to use the central venous catheter and include documentation of satisfactory venous access in the donor record. Appropriate care should be taken to protect donor safety when a CVC is inserted solely for a collection procedure and that collection extends over more than one day.

Evidence:
The inspector should inquire about the nature and frequency of complications including significant hematomas, pneumothorax, hemothorax, and bacterial infections. These adverse events should also have been discussed during quality assurance meetings of the Collection Facility.

The inspector may look at the documentation of central line placement by the Collection Facility, including documentation of imaging used to confirm line position and function prior to collection.

Example(s):
The National Health Service National Institute for Health and Clinical Excellence (NHS NICE) provides guidelines regarding the placement of central venous catheters. Visit http://guidance.nice.org.uk/TA49 to obtain these guidelines and additional information. The American Society of Anesthesiologists Task Force on Central Venous Access has also provided guidelines available for review (Anesthesiology 2012; 116:539–73).

A Report of Serious (Product) Events and Adverse Reactions [S(P)EAR Alert] was submitted to the World Marrow Donor Association (WMDA) dated August 2011 informing the committee of a donor death due to a tension haemo/pneumothorax related to the insertion of a central venous catheter. The event is noted in this guidance as a warning to transplant programs of the critical importance of compliance with this standard. S(P)EAR Document Reference: 20110824-CLWG-SEAR-August 2011.

STANDARD:

C8.11 *Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.*

Explanation:

Administration of hematopoietic cytokines such as G-CSF is not free from side effects. There are reports of serious morbidity and mortality among recipients of hematopoietic growth factors. A licensed health care professional who is trained in dealing with complications of G-CSF must supervise its administration. Supervision can be exercised either directly (especially during the first injection) or indirectly (e.g., via phone contact with nursing personnel) for the subsequent injections, especially if self-administration is considered. The interim assessment of donor symptoms related to G-CSF and relevant laboratory tests should be performed, and dose adjustments made accordingly.

When parameters have been set by the Clinical Program as to when not to administer mobilizing agents, the Collection Facility should have a mechanism in place to be certain all relevant personnel receive and follow these parameters.

Evidence:

The inspector should verify that the licensed health care professional supervising G-CSF administration is experienced in recognizing adverse reactions due to G-CSF. When appropriate, donor side effects potentially attributable to G-CSF should be reviewed by the inspector.

Example(s):

The patient record should show the doses of the mobilization agents to be administered and the person administering the agent.

STANDARD:

C8.12 *The Apheresis Collection Facility shall utilize a process for assessing the quality of cellular therapy products to confirm product safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such assessments shall become part of the permanent record of the product collected.*

Explanation:

Since cellular therapy products are biological, there is inherent variation among products that cannot be easily controlled. The consistent use of validated or qualified collection SOPs and the use of testing to monitor collections can greatly reduce the inherent variability and result in high quality products. Quality monitors should be in place for tracking integrity, viability, contamination, sterility or cross-contamination. SOPs are required that describe each collection procedure and its associated process control (see C5.1).

STANDARD:

C8.12.1 *Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to confirm products meet predetermined release specifications.*

Explanation:
The Collection Facility Director is responsible for defining release criteria for cellular therapy products distributed by the Collection Facility, identifying the tests to be performed, and testing intervals during collection. The release criteria may differ depending on whether the products are released to a processing facility for further manufacturing or directly to a clinical service for administration. This information must be clearly outlined in an SOP (see C5.1). All test results that are available at release must be present in the collection record.

Evidence:
Documentation that the cellular therapy product met release criteria prior to distribution must be present. For products that did not meet release criteria, the required documentation for exceptional release should be present.

Example(s):
Release criteria that may be pertinent to a cellular therapy product being released to a processing facility include the following: the product is sealed completely without evidence of leakage, the product labeling is complete and correct according to expected data, the product has been stored appropriately, the product and/or donor samples are labeled and available to accompany the product, and allogeneic donor eligibility determination documentation is available.

STANDARD:

C8.12.2 *Methods for collection shall employ procedures validated to result in acceptable cell viability, sterility, and recovery.*

Explanation:
Methods of collection must be validated to result in acceptable cell viability, sterility, and recovery. This means that the methods, including reagents, anticoagulants, additives, equipment, and supplies used, and the environment of the collection, have been shown to consistently work in the past to result in a predictable and reliable product. The use of audits and reviews, as defined by the QM Program, are a means of continued validation of collection methods. Any new equipment or collection procedure must be validated prior to implementation and shown to be consistent with or superior to the previous method and result in acceptable cell viability sterility, and recovery.

Evidence:
The inspector should verify the validation documentation prior to implementation of collection methods and periodic verification of indicators that show compliance with the predetermined release criteria.

Example(s):
Cell viability, sterility, and recovery data may be routinely captured by the Processing Facility. The Collection Facility should request this information and use it for a retrospective validation of the method of collection.

STANDARD:

C8.13 *Collection methods shall employ aseptic technique so that cellular therapy products do not become contaminated during collection.*

Explanation:

This standard requires the use of aseptic technique as defined in A4 of the Standards. Cells collected by apheresis procedures must utilize commercially-obtained disposable sets with sterile transfer bags approved for human use.

Evidence:

The inspector should verify the use of such items by the Collection Facility. Peripheral blood access and venous catheter access aseptic technique can be verified by monitoring sterility of the cellular therapy products collected, or by monitoring the performance of the arm cleansing method used prior to insertion of peripheral blood access devices, and the aseptic techniques used to access venous catheters.

Example(s):

Sterility data are routinely captured by the Processing Facility. The Collection Facility may request this information and use it for a retrospective validation of the method of collection.

STANDARD:

C8.14 *Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures.*

Evidence:

The inspector should verify that the donor collection record reflects the appropriate parameters for pediatric donors as described in the Collection Facility's SOP.

Example(s):

Collection SOPs may reference the method applicable for pediatric donors, such as the use of blood prime.

The written order for the product collection volume or cell dose of the HPC or MNC from peripheral blood should be appropriate for the age and size of the pediatric donor.

STANDARD:

C8.15 *Cellular therapy products shall be packaged in a closed sterile transfer pack appropriate for blood products.*

Explanation:

Sterile transfer bags designed for cellular blood products are required for the collection of cells by apheresis. Commercially available disposable sets are available and should be used for collection. Ideally, the tubing connected to the bag should be heat-sealed or sealed with a grommet at the end of the collection prior to transport.

Evidence:
The inspector should observe the end of the collection procedure and verify that the collection container is sealed. The inspector should also verify the presence of heat sealers or grommets in the unit if applicable as indicated in the SOP.

Example(s):
Documentation of transfer bags' sterility from the manufacturer can be used as part of the qualification of the vendor. Inspection of collected cellular therapy products for a proper seal may be used as a product release criterion.

STANDARD:
C8.16 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

C8.16.1 Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.

Explanation:
Records must be used during cellular therapy product collection and must be completed in real time as the procedure is performed. Records must be accurate, indelible, and legible, and must identify the person performing the work and the dates of the various entries. Records of identification codes of personnel including methods to link the name and/or signature to the initials or other identification codes used in other documents and records must be maintained. These records should include dates of employment of the personnel.

In the event that an error or adverse event results during or as a consequence of collection, it is important to perform an investigation in a timely manner. From the appropriate record it must be possible to investigate each critical step, including identification of the individual responsible and the reagents and equipment utilized.

Evidence:
The inspector should review collection records to determine if they were completed in real time and are sufficiently detailed to trace all steps in the collection procedure. The inspector should verify that records of collection have the date of performance of the procedure and staff identification for the steps performed.

Example(s):
The Collection Facility may develop a collection record that will allow documentation of detailed collection steps in real time and identification of staff performing the procedure. Labeling and release of cellular therapy products may be included in such a collection record. Use of electronic records should have the concurrent documentation elements.

In the U.S., concurrent record keeping is required in 21 CFR 1271.270(a).

STANDARD:
C8.17 There shall be a policy addressing safe administration of ECP.

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

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

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

Explanation:
ECP is a leukapheresis-based immunomodulatory therapy used in the treatment of acute and chronic graft versus host disease (GVHD), along with other non-transplant indications involving the separation of leukocytes by apheresis followed by addition of a psoralen, usually 8-methoxypsoralen (8-MOP) and exposure to UVA light. It is probable that inspectors will increasingly encounter the use of ECP within and associated with transplant programs undergoing inspection, both within and outside of clinical trials.

There are different methodologies for ECP that include both closed and open circuits. In the former which is the most common, collected leukocytes remain integral to the circuit of the cell separator, while with minority of ECP procedures, the leukapheresis product is detached at some point (e.g., for addition of psoralen and/or UV irradiation). It is possible for patients requiring ECP to attend another hospital that may be at a distance from the transplant unit and have no other relationship aside from provision of ECP. No specific methodology or technology is required or recommended by the Standards.

The transplant physician will provide an order specifying at a minimum the patient's diagnosis and indication for ECP. There shall be documented agreement prior to ECP administration between the transplant physician and the apheresis physician regarding the proposed regimen, timing of the procedure, and any other factors affecting safe administration. Documentation of all elements (i.e., diagnosis, indication, regimen, timing) applies in cases where the transplant physician and apheresis physician are the same individual.

If ECP is a part of therapy for GVHD or other indications for transplant recipients within a Clinical Program or Collection Facility applying for FACT or JACIE accreditation, the activities must meet the Standards as they apply. If the Collection Facility is independent from the Clinical Program, there should be a written agreement between these facilities.

Upon completion of the series of administration of ECP, a final report of the details of the treatment is provided to the Clinical Program. This may be used in the assessment of the response of the patient to the treatment.

Outcomes and adverse events can be monitored according to the Collection Facility or Clinical Program quality activities management.

Evidence:
The inspector should confirm evidence of patient consent, a therapy plan, procedure details, and a final report. The inspector should verify that there is patient education material about ECP and that consultation has occurred prior to therapy. Documentation of the administration of ECP should be available to the inspector.

Example(s):
The following publications may be used as references when establishing processes for ECP:

- Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, Ayuk F, Kiani A, Schwerdtfeger R, Vogelsang GB, Kobbe G, Gramatzki M, Lawitschka A, Mohty M, Pavletic SZ, Greinix H, Holler E. Biol Blood Marrow Transplant. 2011 Jan;17(1):1-17.
- Extracorporeal photopheresis for the treatment of acute and chronic graft-versus-host disease in adults and children: best practice recommendations from an Italian Society of Hemapheresis and Cell Manipulation (SIdEM) and Italian Group for Bone Marrow Transplantation (GITMO) consensus process. Pierelli L, Perseghin P, Marchetti M, Messina C, Perotti C, Mazzoni A, Bacigalupo A, Locatelli F, Carlier P, Bosi A; Società Italiana di Emaferesi and Manipolazione Cellulare (SIdEM); Gruppo Italiano Trapianto Midollo Osseo (GITMO). Transfusion. 2013 Oct;53(10):2340-52.
- Extracorporeal photopheresis for treatment of adults and children with acute GVHD: UK consensus statement and review of published literature. Das-Gupta E, Dignan F, Shaw B, Raj K, Malladi R, Gennery A, Bonney D, Taylor P, Scarisbrick J. Bone Marrow Transplant. 2014 Jun 2.
- Diagnosis and management of chronic graft-versus-host disease. Dignan FL, Amrolia P, Clark A, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Shaw BE, Potter MN; Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. Br J Haematol. 2012 Jul;158(1):46-61
- Diagnosis and management of acute graft-versus-host disease. Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Hadzic N, Shaw BE, Potter MN; Haemato-oncology Task Force of British Committee for Standards in Haematology; British Society for Blood and Marrow Transplantation. Br J Haematol. 2012 Jul;158(1):30-45
- Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: the sixth special issue. Schwartz J, Winters JL, Padmanabhan A, Balogun RA, Delaney M, Linenberger ML, Szczepiorkowski ZM, Williams ME, Wu Y, Shaz BH. J Clin Apher. 2013 Jul;28(3):145-284

C9: CELLULAR THERAPY PRODUCT STORAGE

STANDARD:

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

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

Explanation:
The Collection Facility shall establish a process to be certain that cellular therapy products are stored in a manner that maintains their integrity and potency, and that products are not released before all release criteria have been met. Standard C9.1 requires that defined areas for storage be established and that these areas be controlled to prevent the possibility of mix-ups, contamination, or cross-contamination. This process is further defined as to require control of the storage duration and the appropriate storage temperature.

The Collection Facility should define what constitutes storage. Any duration of time between the end of the collection and distribution to a Processing Facility or to a recipient for administration constitutes storage. Particular attention shall be paid to the security of the facility and control of temperature and humidity when products are stored in the facility for extended periods, such as overnight to be transported with a second collection from the same donor. Storage temperature and duration shall be defined by the storing facility and shall include conditions for fresh, cryopreserved, and thawed cellular therapy products. Generally, only fresh products are stored in the facility. Products that are awaiting release testing results (i.e., CD34 cell assessment by flow cytometry or the completion of allogeneic donor eligibility determination) may be held in quarantine at one temperature (i.e., up to 4 hours at room temperature) but stored for longer periods at another temperature (i.e., 2-8°C). Temperature ranges and duration shall be determined for each type of product and should be based on the medical literature and/or on the facility's own data. For liquid products, including thawed products, temperature ranges, storage duration, and product expiration date and time shall be established to prevent inadequate viability and to decrease the risk of contamination. Likewise, transport and shipping temperature both from the facility to the Processing Facility and at distribution shall be defined.

Evidence:
The inspector should review the Collection Facility's established storage criteria for all relevant products, and inspect the storage conditions and space to confirm adequacy of separation to prevent contamination and mix-ups.

Example(s):
An end-of-collection label with all the information printed, including storage temperature and duration, should be kept on-site.

EU Directive 2006/86/EC requires that the expiry date shall be part of the product information for all tissues and cells.

C10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

STANDARD:

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

Explanation:
Cellular therapy products may be transported and/or shipped from the Collection Facility to a patient care unit or a Processing Facility within the same, adjacent, or remote buildings for administration, processing, or storage. There shall be a prospective agreement in place between the relevant Collection Facility, Processing Facility, and Clinical Program regarding transport and/or shipping conditions and the responsibilities of each facility.

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

Explanation:
The cellular therapy product shall be packaged to protect it from potential harm during transit and to prevent exposure of individuals involved in its transport or shipping from potentially infectious agents. When heat sealers are used on the tubing entering the primary container, a minimum of three (3) seals should be applied and the tubing disconnected by cutting through the middle seal to reduce the possibility of leakage. Primary collection bags shall be placed in a secondary securely sealed container such as a zip type bag. An apheresis progenitor cell product and concurrently collected plasma with the same identifier may be placed in a single secondary container. Multiple primary bags from the same donor may be placed into a single secondary sealed container of adequate size. Human tissue, regardless of infectious disease testing, shall be considered potentially infectious. Procedures will vary depending on the transport and/or shipping distance, whether or not the courier and product leave a building, and the nature of the outside container.

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

Explanation:
SOPs for transportation and shipping shall be included in an SOP and shall address issues of packaging, labeling, temperature, identification, safety, product integrity, and handling for any length of transit.

Example(s):
Distribution is any transportation or shipping and delivery of the cellular therapy product intended for human administration. The cellular therapy product has been determined to meet release criteria or urgent medical need requirements. Shipping is 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. For example, cryopreserved cord blood units are shipped in a vapor shipper from a cord blood bank to a tissue establishment (Processing Facility).

STANDARD:

C10.3.1 *Cellular therapy products that are transported and/or shipped from the collection site to the Processing Facility shall be transported and/or shipped in an outer container made of material adequate to withstand leakage of contents, impact shocks, pressure changes, temperature changes, puncture, and other conditions incident to ordinary handling.*

Explanation:

These SOPs shall secure maintenance of the cellular therapy product components within a specified range of temperature during transportation or shipping. The cellular therapy product temperature during transit is dependent upon a number of variables, including: the transport time, ambient temperature ranges, initial temperature, size of the product, and characteristics of the specific container system. The ideal transport temperature may range from 2-24˚C. There shall be a prospective agreement among the collecting, processing, and receiving facilities regarding transport and/or shipping conditions. Most products should not be transported at temperatures above 24˚C. Products not previously cryopreserved should never be allowed to cool to temperatures of or below freezing. Transport between facilities shall always consist of the use of an outer container that protects the product from adverse conditions encountered during transport (air pressure and temperature changes, rough handling), and has been validated to maintain the agreed upon transport temperature. For products transported between sites of a single cellular therapy program, the distance between the Collection Facility and the Processing Facility varies widely. For situations where transport from the Collection Facility to the Processing Facility requires only minutes, as long as the product is transported safely, a controlled temperature environment is optional. Transport over longer distances, for more extended periods of time, or transport outside of a building may require that a controlled temperature environment be maintained using an outer container and method validated for the temperature range specified.

For non-cryopreserved cellular therapy products requiring a controlled temperature, a validated thermally insulated outer container should be used with cold packs added as necessary to maintain the required temperature.

Containers for transport of cellular therapy products that are shipped from the Collection Facility or are transported on public roads shall be made of durable material and insulation that will withstand leakage of contents, shocks, pressure changes, and temperature extremes. The containers shall be validated prior to use to achieve proper performance for all expected extremes and maintenance of desired internal temperature. Subsequently, container performance should be verified at least twice yearly, during the warmest and coldest weather periods common for the area.

STANDARD:

C10.3.2 *If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.*

Explanation:
If a patient has undergone high-dose marrow ablative treatment in preparation for transplant, the cellular therapy product is essential for the patient's survival since it may not be possible to obtain additional marrow or blood from the original donor or a second donor in time to prevent complications from aplasia. For this reason, it is important that the product be entrusted to a knowledgeable individual who accompanies it from the distributing facility to the receiving facility.

STANDARD:

C10.4 *The cellular therapy product shall be transported and/or shipped with required accompanying records as defined in the transportation and shipping Standard Operating Procedures and in compliance with C7.4.4 and C7.4.5.*

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

Explanation:

Accompanying documentation shall include all documentation of allogeneic donor eligibility as defined in Appendix IV. It is not necessary that the records in their entirety accompany a cellular therapy product from the Collection Facility to the Processing Facility. Donor eligibility documents can be summarized. However the entire document must be readily and easily accessible when needed.

Labeling requirements are defined in Appendices II and III.

C11: RECORDS

STANDARD:

C11.1 *GENERAL REQUIREMENTS*

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

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

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

C11.1.2 *Records shall be maintained in such a way as to preserve their integrity, preservation, and retrieval.*

C11.1.3 Records shall be accurate, legible, and indelible.

C11.1.4 Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities, and their recipients and donors, shall be established and followed in compliance with applicable laws and regulations.

Explanation:
Each Collection Facility has the flexibility to develop individualized systems of maintaining and organizing records as long as certain objectives are achieved. The record-keeping system must be documented and should include, but need not be limited to:

- Location of new and completed forms.
- Method of error correction that prevents obscuring the original entry and indicates the date and identity of the individual modifying the record.
- Method to prevent destruction or loss of the record.
- Method of document modifications and distribution.
- Time of retention and proper storage location.
- System to maintain confidentiality of records.
- Methods for filing and transfer of records to archival storage.

Records may be maintained in more than one location, provided that the records management system is designed to confirm prompt identification, location, and retrieval of all records.

The Collection Facility must make provisions for all records to be maintained for the required period of time in the event that the facility ceases operation. Records that allow the tracking of a cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor must be maintained even when products are transferred to another facility.

Evidence:
The inspector should review the appropriateness of the storage of recent records, the adequacy of the system used for maintaining archived records, and the storage conditions for ensuring confidentiality and accessibility.

Example(s):
It is recommended that recent records be kept on-site and archived records are readily accessible within a reasonable time frame. Records may be maintained as original paper records, electronic files, photocopies, microfiche, or microfilm. Suitable equipment must be available for reading and/or photocopying records maintained on microfiche or microfilm. Electronic records must be backed up on a regular basis and stored to prevent their loss.

Secure storage may consist of maintaining the records in a locked room with access restricted to authorized personnel and/or the use of locked file cabinets. Examples of insecure storage include unsecured patient records; patient charts left unattended in areas where unauthorized personnel and/or visitors may have access, or unattended computer screens displaying patient information in such areas; indiscriminate discussion using patient-specific identifiers in the presence of unauthorized personnel or visitors; patient information posted on chalk or bulletin boards that is potentially visible to unauthorized personnel and/or visitors; and release of confidential information without appropriate consent and approval.

STANDARD:

C11.2 *Apheresis Collection Facility records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years by the Collection Facility, or longer in accordance with applicable laws and regulations, or a defined program or institution policy.*

Explanation:

Because QM documents provide evidence of compliance with the QM requirements, they should be maintained for as long as they are applicable to the processes, equipment, supplies, and reagents currently being used. Archived records do not need to be immediately available.

The validation study for a current collection procedure needs to be maintained regardless of how long ago the study was performed in order to demonstrate compliance with validation requirements.

Evidence:

Collection Facilities must identify applicable laws and regulations, and applicable regulatory authorities, in preinspection documentation for FACT or JACIE inspectors to reference when preparing for the inspection.

The inspector should review the Collection Facility's records related to QM including documentation of periodic personnel training and cellular therapy product characteristics, and inspect the QM documents to confirm compliance with the facility's requirements. Likewise, the inspector should examine paperwork to determine if adequate records are maintained that identify the processes, equipment, supplies, and reagents currently being used for all significant steps of collection.

STANDARD:

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

C11.2.2 *Cleaning and sanitation records shall be retained for at least three (3) years or longer in accordance with applicable laws or regulations, or by a defined program or institution policy. All other Apheresis Collection Facility records shall be retained as in C11.2.*

Explanation:

An exception to the 10-year requirement for retention of Apheresis Collection Facility records is for the documentation of cleaning and sanitation. These records only need to be retained for at least 3 years after creation but should include cleaning schedules, methods, and identification of personnel responsible for cleaning. There should also be documentation for the initial training and retraining of personnel as needed.

STANDARD:

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

Explanation:

Records related to cellular therapy products should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for collection is critical for tracing purposes in the event of a problem, recall, or adverse event.

Evidence:

The inspector should ask who is responsible for records and where these records are maintained, and determine if an organized system is in place that allows timely retrieval.

This can be accomplished by selecting products from the Processing Facility and utilizing the product unique identifier to trace the records to the Collection Facility. The person responsible for records can then demonstrate where the records are maintained and how they are organized. The records related to the collection procedure should be provided in a timely fashion. The records should then be reviewed and the manufacturers and lot numbers of all reagents and supplies used in the collection should be available in the records.

Example:

In the U.S., NMDP requires that records pertaining to the traceability and tracking of all aspects of the manufacture of the HPC product be retained indefinitely, as should records of adverse reactions and post-donation complications, treatment interventions, and recovery.

Per the EU-Tissue Directive, tissue establishments must keep the data necessary to ensure traceability at all stages. Data required for full traceability must be kept for a minimum of 30 years after clinical use.

STANDARD:

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 laws and regulations for a minimum of ten (10) years after the administration of the cellular therapy product, or, if not known, ten (10) years after the date of the distribution, disposition, or expiration of the product, whichever requires the longest maintenance period.*

Explanation:

Patient and donor files (either electronic or hard copy) must be maintained with a secure system that guarantees absolute confidentiality and is in compliance with applicable laws and regulations on confidentiality and data protection.

Evidence:
The inspector should be alert to breaches in policy that potentially compromise patient or donor confidentiality. The inspector should ask who is responsible for research records and where these records are maintained, and determine if an organized system is in place that maintains patient confidentiality.

Example(s):
In the U.S., NMDP requires that consent documents, screening and testing records, and records pertaining to allogeneic cell product collection, processing, labeling, packaging, storage, distribution and final disposition be maintained indefinitely.

In the U.S., HIPAA regulations on confidentiality and data protection apply. In the European Union, the comparable regulation is Directive 95/46/EC.

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

Explanation:
Records related to cellular therapy products collected under IRB-approved research protocols should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information. If research records are stored independently of patient records, the same considerations regarding confidentiality apply. The sponsor of the research, IRB, and/or governmental authorities may place specific requirements for long-term maintenance of research records.

Likewise, retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for collection is critical for tracing purposes in the event of a problem, recall, or adverse event.

Evidence:
The inspector should ask who is responsible for records and where these records are maintained, and determine if an organized system is in place that allows timely retrieval of research records.

STANDARD:
C11.6 *ELECTRONIC RECORDS*

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

Explanation:
The definition of an electronic record is, "A record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer."

This standard requires Collection Facilities to establish and maintain a current listing of all critical electronic record systems specific to cell collection. As facilities utilize more electronic systems, it is important that they maintain a list of which ones are critical.

Electronic records are considered critical when any one of the following points occurs:

- Used as a substitute for paper.
- Used to make decisions based upon the data stored and/or created by the electronic record system (including outcome analysis).
- Used to make calculations via automated functions,
- Used to create and/or store information that are inputs into critical processes (whether the electronic record system is used during critical processes or used as source data for critical procedures).

Critical procedures are listed in C4 and include collection procedures, labeling, storage conditions, and distribution.

It is not the intent of the Standards to include hospital-based systems and clinical medical records. These systems are typically inspected by hospital-based regulatory and accrediting organizations. Furthermore, Collection Facilities may not have the authority to direct validation studies on these systems. Any data system that does exist within the scope of control of the facility is required to meet these standards.

Each Collection Facility must determine in advance whether the staff will depend on an electronic record or a paper record to perform a regulated activity. This determination should be documented for all records created and maintained by the facility.

Evidence:
Inspectors should assess the Collection Facility's list of critical electronic record systems to confirm it includes all electronic record systems used by the facility that meet the criteria in this standard. Additionally, a list that matches critical record types to specific record systems should be provided preinspection (e.g., electronic laboratory record versus paper eligibility record).

The inspector should determine the scope of electronic records used by the Collection Facility and any circumstances where the electronic record is used as a substitute for a paper record.

If electronic records are used in addition to paper records, the inspector should evaluate the electronic records to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.
- The system has limited access by authorized individuals.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.
- Documentation that the individuals performing the development, maintenance, or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- The electronic system is not the sole method for storing or retrieving needed records.

Example(s):
Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

If an electronic record of the location of a cellular therapy product in storage is printed for the chart and the information is verified by a signature or initials, and this printed record is then used by personnel to retrieve the product at the time of distribution, the electronic record is not considered to have been used as a substitute for a paper record.

If a computerized system (word processor) is used to generate SOPs, validation is not required since the quality and safety of a cellular therapy product would not be directly affected. However, if a computerized system is used to make a critical calculation (i.e., T cell dose, DMSO concentration, CD34 cell recovery) and the electronic calculation is the only calculation performed, validation is required to assure that the calculation is always performed correctly under any circumstances. However, if the computerized calculation is used to confirm a manual calculation, and the manual calculation is used for manufacturing purposes, the extent of validation need not be as extensive as in the previous example.

In the U.S., for electronic records used as a substitute for paper, the inspector should refer to the FDA document Part 11, Electronic Records; Electronic Signatures - Scope and Application, for guidance to assess the validation procedures (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072322.pdf), as well as the applicable requirements of HIPAA. In the European Union, the inspector should refer to the Model Requirements for Electronic Records and Document Management (MoReq) (http://ec.europa.eu/).

STANDARD:

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 all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation in the event that critical electronic record systems are not available. The alternative system shall be validated and Apheresis Collection Facility staff shall be trained in its use.*

C11.6.7 *For all critical electronic record systems, there shall be written 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.

Explanation:
The final review and acceptance of entered data does not require a second individual to verify the data. Nor does the identification of individuals responsible for record entries need to be automated. The intent of the standard is to be certain all data is verified to be correct and to maintain documentation of who has entered pieces of information.

STANDARD:

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.

Example(s):
To identify individuals responsible for record entries, several options exist. Examples include using a sign-in sheet when using the system or using a worksheet to create an audit trail of each data element. More sophisticated systems usually have an automated system that tracks record entry based upon an individual's log-in credentials.

STANDARD:

C11.6.8 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:

Explanation:
Establishment of an electronic record keeping system requires validation. The extent of validation is somewhat dependent upon whether the computerized system was developed in-house, custom-built by an outside vendor/consultant, or developed from off-the-shelf software. More importantly, the extent of validation is dependent upon whether the electronic records are used as a substitute for paper records.
When computers are used to generate paper printouts of electronic records, and the printouts are the "official" records used for the performance of further activities, the electronic records are not considered to be used as a substitute for paper records. If hard copies are scanned, there shall be a program that creates searchable documents to facilitate inspection and review.

The decision to validate a computerized system, and the extent of validation, should be determined by a documented risk assessment regarding the potential of the system to affect the quality and safety of a cellular therapy product and/or the integrity of a record. Finally, if hard copies are scanned, there shall be a program that creates searchable documents to facilitate inspection and review.

When electronic records are used as a substitute for paper, validation procedures include such things as:

- Documentation of development requirements and function.
- Verification that calculations are performed correctly.
- Evidence that records reproducibly contain the desired information.
- Tests of system functions under "worst case" scenarios such as system overloads (e.g., too many simultaneous users, too many simultaneous processes being performed [such as too many programs open on Windows desktop]), power failures, etc.
- A method for data verification before final entry.
- Internal consistency checks to verify that values are within defined ranges.
- Restricted entry of data to match predefined value limits.
- Required entry of data with field information limited with choices for data consistency.
- Source data is derived from pre-defined sources such as fixed forms. "Monitoring for data integrity" means establishing assurances that data has not been changed either by accident or by intent, and requires access to original documents whenever possible, along with a plan for verification of the electronic system data by comparison to original data. Evidence of a schedule of regular back-ups that include storage of back-up data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the back-up copy.
- Documentation of the database system, including written methods for data entry and generation of printed reports that include all of the information entered into the database, acceptable sources of the entered data, and a description of system maintenance and development history.
- Formal and documented training in system use requirements for all personnel.
- Evidence of SOPs in place for computer record-keeping systems.
- Regular quality audit trails (especially when users are expected to create, modify, or delete regulated records during normal operation).
- A mechanism to report deviations to report and resolve problems.
- Evidence that changes to records do not obscure previous entries.
- Documentation that deleted electronic files have been converted to non-electronic media such as microfilm, microfiche, or paper in a manner that preserves the content and meaning of the record.

Any identifier generated by the system must be unique, and this process must be validated.

STANDARD:

C11.6.9.1 Training and continued competency of personnel in systems use.

Explanation:

Personnel must be trained to appropriately use all critical electronic record systems (including record entry, verification, and revision) and back-up processes when the critical systems are not available. This training must be continuous, including initial training and ongoing training as SOPs are revised and issues with the use of critical electronic record systems are identified.

STANDARD:

C11.6.9.2 Monitoring of data integrity.

C11.6.9.3 Back-up of the electronic records system on a regular schedule.

C11.6.9.4 System assignment of unique identifiers.

C11.7 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

C11.7.1 The Apheresis Collection Facility shall furnish to the facility of final disposition a copy of all records relating to the collection procedures performed in so far as they concern the safety, purity, or potency of the cellular therapy product involved.

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

Explanation:
In the event that two or more facilities participate in the collection, processing, or administration of a cellular therapy product, the records of each participating facility must clearly indicate the extent of each facility's responsibility. The Collection Facility's records should include relevant contracts and agreements. The entire record of the outside facility(ies) need not be duplicated for the facility record. However, the facility record should allow tracing and tracking of relevant information to the correct source.

The Collection Facility should verify that such relevant and appropriate records will be maintained by the facility that performs the work. Records of allogeneic donor eligibility screening and testing must be provided to the facility. Maintenance of records must be specified in the SOPs and it must be clear who is responsible for maintaining records. In general, records should be sufficiently detailed to enable tracking and tracing from a donor to a recipient or final disposition and vice versa.

Records of documents showing areas of responsibilities must be documented and should include, but need not be limited to:

- Contracts and agreements.
- Donor work-up.
- Allogeneic donor eligibility and screening.
- Equipment maintenance.
- Staff education on the specific population being cared for.
- Patient outcomes reporting.
- Distribution and storage of cells.

Donor and recipient confidentiality must be maintained through the use of identifiers whenever the identity of the donor and recipient must remain anonymous. The location of each facility must be known to the relevant personnel at each facility, but donor identity should not be known to the recipient, and recipient identity should not be known to the donor. Facilities that participate in programs such as the NMDP will have well-defined SOPs for divided responsibility. Applicable rules and regulations regarding the sharing of confidential information must be followed.

It is the responsibility of the Collection Facility to furnish to all other facilities involved in the processing and/or administration of the cellular therapy product any data so far as it concerns the safety, purity, and potency of the product involved.

Evidence:
The inspector should determine if divided responsibility occurs regarding any aspect of the transplant process, and ask to review a relevant recipient file to confirm that an appropriate mechanism is in place to track the process from beginning to end and trace the process from the end to the beginning.

The inspector should review the applicable SOPs regarding dissemination of collection data and verify that the process is in place.

Example(s):
For example, the Collection Facility may manufacture cellular therapy products for multiple clinical programs. A list of each facility showing its responsibility for collection, processing, or administration of the product should be provided for inspector review prior to the inspection. The facility record should indicate where the product was collected, stored, and/or administered but does not need to contain a record of the supply and reagent lot numbers used for steps performed at the Processing or Clinical Facilities.

C12: DIRECT DISTRIBUTION TO CLINICAL PROGRAM

STANDARD:

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

Explanation:
Cellular therapy product distribution may be collected for administration or further manufacturing. The intent of referencing D7, D10, D11, D13, and the Appendices may be relevant to one or both purposes. If the Collection Facility distributes cellular therapy products directly to a Clinical Program for administration or subsequent processing, the facility is responsible for the requirements defined in sections D7, D10, D11 and D13 (in these sections, wherever "processing" is referenced, "collection" shall be substituted).

A few exceptions exist to the Collection Facility assuming responsibility for sections D7, D10, and D11; the exceptions are as follows:

- Generally, Collection Facilities do not have the capability to re-inventory products and, thus, cannot accept products for return.
- Receipt of products does not apply Collection Facilities.

Collection Facilities must use processing facilities that meet the FACT-JACIE Standards for its significant activities, but may occasionally collect for research in which subsequent processing must be performed by a third-party manufacturer. In those rare cases, it is especially important to consider the referenced processing requirements.

Evidence:
The inspector should examine distribution records to determine purposes of collection (administration or further manufacturing). Compliance with Sections D7, D10, D11, D13, and the Appendices can then be evaluated.

An Collection Facility that distributes cellular therapy products to a Clinical Program for purposes of administration, and/or to a Processing Facility for further manufacturing will provide an SOP, or other paper or electronic documentation, demonstrating compliance with clinical or further manufacturing standards in D7, D10, D11, D13, and the Appendices.

See guidance in referenced sections for additional details.

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 Distribution and Receipt

D12 Disposal

D13 Records

PART D: PROCESSING FACILITY STANDARDS

D1: GENERAL

STANDARD:

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

Explanation:

Part D Standards apply to the processing of cellular therapy products, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source). The Standards cover all processing in the facility regardless of product destination.

Processing Facilities are not required to serve Clinical Programs or Collection Facilities that are FACT or JACIE accredited; however, the general philosophy of the Standards and accreditation programs are to encourage all organizations to become accredited in order to demonstrate that they meet minimum requirements for quality cellular therapy. Third parties who perform contracted services related to cell processing for the Processing Facility must be in compliance with the Standards as they relate to the third party's interactions with the facility.

It is not the intent of the Standards to address processing of tissues or cells that are obtained from cadaveric donors. Nor do the Standards apply to vascularized organs obtained from living donors. Although many of the existing FACT-JACIE Standards may be applicable to other types of cellular therapy products, deviations from the Standards can only be cited for products specifically covered by them.

Evidence:

Processing Facilities will provide information to FACT or JACIE, as appropriate, regarding the cell types and processing methods within their facilities. This confirms that an appropriate inspection team is selected and that the on-site inspection agenda adequately covers all processes.

Example(s):

In the U.S., processing of MNCs and some HPCs will often be under IND; however, unless otherwise stated, the Standards still apply to those cells and processing methods conducted within the Processing Facility. Inspection and accreditation will be limited to these facilities; separate facilities and laboratories in which cell processing takes place will not be inspected and will therefore not receive accreditation.

In the EU, cellular therapy products to be used in clinical trials (EU Directives 2001/20/EC and 2001/83/EC) and Advanced Therapy Medicinal Products (Regulation 1394/2007) must be manufactured in GMP-licensed facilities. The manufacturing of cellular therapy products in these facilities can be accredited by JACIE if pursued, but this GMP-facility can also supply the accredited facility with their products under a service level agreement.

STANDARD:

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

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

Explanation:
FACT and JACIE are voluntary inspection and accreditation programs sponsored by the American and European Societies for Blood and Marrow Transplantation and the International Society of Cellular Therapy. Professional standards are designed to provide minimum guidelines for quality medical care and laboratory practice. Compliance with the Standards does not guarantee compliance with all applicable laws and regulations. Governmental regulations must also be followed. It is the responsibility of the individual Processing Facility to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the facility may apply; for example, when a facility is sending or receiving cellular therapy products to or from outside of its immediate jurisdiction. Requirements also vary based upon the type of product, the stage of research, etc.

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

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

A copy of a validated FDA registration document(s) should have been sent to the FACT office with the accreditation application materials. If such a copy is not provided to the inspector prior to the inspection, in the U.S., he/she may ask to see it on site. The Processing Facility Director or Medical Director should know who in the institution is responsible for the registration, and where a copy may be obtained. It is not appropriate to request a faxed copy from the regulatory agency during the on-site inspection.

In the EU, the inspector would expect to see the tissue establishment license by the Competent Authority and, if applicable, a GMP-manufacturing license if ATMPs are being manufactured at the same site.

Example(s):
Products that are cultured prior to use, such as antigen-specific T cell lines or mesenchymal stromal cells, would be considered to be extensively or substantially manipulated. In such cases, the processing would be regulated through an IND or IDE (in the U.S.) or as an ATMP (in the EU). When those requirements are more stringent than the Standards, the regulatory requirements must be followed.

In the U.S., minimally manipulated cellular therapy products from related donors are largely regulated under the 21 CFR 1271 GTP regulations (covered under section 361 of the Public Health Service Act, and therefore are referred to as 361 products), with the exception of products collected from marow. However, if cellular therapy products are from an unrelated donor, or are extensively manipulated, combined with a device, or if their use is non-homologous (does not perform the same function in the recipient as in the donor), they fall under the 21 CFR 210, 211 GMP regulations. GMP products are regulated under the Public Health Service Act 351 and therefore are referred to as 351 products. Minimally manipulated HPC, Marrow is currently not regulated under either of these federal regulations.

In the Member States of the European Union (EU), both HPCs products and MNCs products fall under the European Directive 2004/23/EC on all tissues and cells, "Setting standards on quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells," and the implementing directives 2006/17/EC and 2006/86/EC. Under the directives a tissue establishment license from the Competent Authority (CA) is required and the tissue establishments need to notify the CA of serious adverse events and reactions of tissues and cells. Additionally, some member states require specific authorizations delivered by the CA for minimally manipulated cell products that are not classified as medicinal products.

Directive 2001/83/EC regulates products that are classified as medicinal products (MP). These include somatic cellular therapy MPs and gene therapy MPs. The regulatory framework on Advanced Therapy Medicinal Products (ATMP) (e.g. Regulation (EC) No. 1394/2007) includes tissue engineered products as well. Engineering is defined as having been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. Substantial manipulation is defined by manipulations that are not considered as substantial, like centrifugation, selection, cryopreservation, etc. Cells that are not substantially manipulated but are not intended to be used for the same essential function or functions in the recipient as in the donor also fall under this regulation. The consequence of classification as a MP is that a GMP license is required for the production of these cells. Furthermore, each Member State in the EU may add regulations to the directives, that also must be followed. Member State-specific regulations will not be detailed here.

STANDARD:

D1.3 *The Processing Facility shall have a Processing Facility Director, a Processing Facility Medical Director, a Quality Manager, and a minimum of one (1) additional designated staff member. This team shall have been in place and actively performing cellular therapy product processing for at least twelve (12) months preceding initial accreditation.*

Explanation:

Facilities are required to have been in place and operating with trained staff under the direction ofthe Processing Facility Director and Processing Facility Medical Director for minimally one year prior to initial accreditation. Given the variation in complexity of Processing Facility procedures, facility experience is best qualified as a minimum period of time in operation rather than as a minimal number of procedures performed. It is recognized that there may be minor staff changes over the one-year period, but the positions of major responsibility should have remained constant.

It is possible that a facility seeking renewal accreditation will have undergone leadership changes within a year of the renewal date. In that case, as long as a director (Processing Facility Director or Medical Director) has the required credentials specified in D3, the facility is eligible for renewal accreditation.

During this 12-month period, Processing Facilities need to process enough cellular therapy products to compile an adequate amount of data to validate processes and demonstrate compliance with the Standards. Facilities should have provided service for the minimal number of autologous and allogeneic transplants required for the associated Clinical Program to be eligible for FACT or JACIE accreditation.

Personnel competency must be maintained even if a Processing Facility's activities decline throughout an accreditation cycle. If no cellular therapy products are processed in an extended amount of time, competency must be maintained and assessed using mock products similar to a cellular therapy product.

Evidence:
The inspector should verify that both key staff and management have been in place and operating for one year or more at the time of the initial inspection and confirm that a sufficient amount of processing has been performed to demonstrate compliance with the Standards.

D2: PROCESSING FACILITY

STANDARD:

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

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

Explanation:
The layout and design of the Processing Facility must minimize the risk of error and permit effective cleaning and maintenance in order to avoid cross-contamination and mix-ups. The facility should be situated in an environment that presents minimal risk of causing contamination of materials and products and allows personnel to perform their duties safely.

The physical facility must include ample lighting, a temperature-controlled environment, and access to sinks for hand washing and disinfection.

Evidence:
Processing Facilities must submit a floor plan of the facility prior to the on-site inspection. Inspectors use these floor plans to gain a preliminary understanding of the designated areas and how processes and products flow throughout the facility. The inspector will tour the facility during the on-site inspection, including all locations where cellular therapy products are received, processed, stored, and distributed. The areas should be designed to facilitate proper workflow and cleanliness.

The inspector should observe the organization, design, location, lighting, ventilation, and amount of space to determine if the facility is adequate for the number and types of procedures it performs, and to minimize the risk of introduction, transmission, or spread of communicable disease. In addition to processing space, there should be adequate desk space for segregation of worksheets and documents essential for processing each product to avoid mix-ups of documents from products that are being processed simultaneously.

When an accredited Processing Facility is to be relocated, qualification and validation must be performed to confirm the new space meets the Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT accreditation policies (available on the FACT website). The Processing Facility is expected to submit a description and floor plans of the new facility, Quality Management (QM) documents, and expected relocation date. If a JACIE-accredited facility intends to relocate, the facility should submit plans and descriptions of the relocation to the JACIE office. Most relocations will be assessed during regularly scheduled inspections or interim audits; however, if there are any concerns with the information submitted by the facility, a relocation inspection may be necessary.

Example(s):
A cluttered Processing Facility without a defined workflow is evidence that the facility does not have adequate space or is poorly designed. The inspector should be able to identify where receiving, labeling, processing, storage, and record keeping is taking place.

STANDARD:

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

Explanation:
When liquid nitrogen is used in the Processing Facility, proper ventilation and the use of oxygen sensors are required. The risk of asphyxia should be assessed wherever liquid nitrogen is used or stored. A low oxygen sensor will alert staff when there is an oxygen-deficient atmosphere in the room.

Examples:
Risks to asphyxiation are real and dangerous low levels of oxygen do occur. As reported in the article, *Deputy dead, several taken to hospital in liquid nitrogen incident,* from WSPA 7 News in South Carolina, a liquid nitrogen incident claimed the life of a deputy and risked the lives of several others after responding to an activated freezer alarm. The article can be found at
http://wspa.com/2017/02/05/deputy-dead-several-taken-to-hospital-in-liquid-nitrogen-incident/.

STANDARD:

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

Explanation:
The Processing Facility must be secure and limited to authorized personnel, including when personnel are present. Authorized personnel may include non-technical staff, such as cleaning or maintenance staff who may require access to the facility. Training and orientation should be documented for each individual that is allowed access to the facility.

Evidence:
The system to prevent unauthorized persons from entering the Processing Facility at all times should be clearly apparent or, if not, then demonstrated to the inspector. The inspector should confirm that the facility is located in an area accessible only to authorized personnel. In addition, the inspector should verify the following: there are appropriate signs throughout the facility, the facility is locked when unattended, and personnel wear proper identification badges (where those are required).

Example(s):
Limited access can be maintained through prominent display of appropriate signs and by installation of locks that limit entry to only authorized individuals (electronic entry systems, keypad systems, or keyed locks) would all be acceptable.

STANDARD:

D2.1.4 *The Processing Facility shall be divided into defined areas of adequate size to prevent improper labeling, mix-ups, contamination, or cross-contamination of cellular therapy products.*

Explanation:
There must be clearly designated areas for product receipt and storage that are separate from the processing area. This standard may be interpreted differently for smaller facilities (e.g., processing less than 50 cellular therapy products per year) versus larger facilities. An SOP should be on-site to confirm segregation when multiple products are being processed simultaneously (e.g., three technicians working on a long bench, management of data entry into an electronic device at the point of processing).

If research activities are performed in the proximity of the Processing Facility, the facility must demonstrate adequate separation of processing and research activities. Human and non-human cells must not be in areas proximate to each other. Cellular therapy products, supplies, and reagents must be clearly segregated either by physical methods or by proper use of signs.

Evidence:
A demonstration by Processing Facility staff of where each activity is typically performed and how a cellular therapy product moves through the facility can demonstrate compliance or illustrate problems. The inspector should inquire as to how the facility segregates products and product paperwork if more than one product is undergoing processing on a given day. Inspectors should note what safeguards are in place to prevent mislabeling, inappropriate product release, or mix-ups that could result in cross-contamination of either products or product records.

If research activities are performed in the same area, the Processing Facility should maintain evidence of cleaning of shared equipment. The facility should demonstrate segregation of cellular therapy product records, the product itself, supplies, and reagents. For shared equipment, the facility must have documentation that maintenance schedules are followed.

STANDARD:

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

Explanation:
If the location of the liquid nitrogen freezers prohibits limited access (e.g., is a shared facility with other users), individual freezers containing cellular therapy products for recipients must be securely locked. Storage facilities must exist that clearly separate and distinguish tissues and cells prior to release and/or in quarantine from those that are released, and from those that are rejected, in order to prevent mix-up and cross-contamination between them. A process must be in place for secure quarantine of products with incomplete or unacceptable release testing results to prevent inadvertent release without proper authorization. Cryopreserved products stored in quarantine must be clearly labeled as such, although they do not have to be stored in freezers dedicated to that purpose.

The standard also applies to products stored overnight as fresh samples in refrigerators (quarantine or non-quarantine) before further processing or for distribution.

Evidence:
Processing Facility personnel can be asked to demonstrate the process for release of a cellular therapy product in quarantine to confirm that such products cannot be released without proper approvals.

STANDARD:

D2.2 Processing Facility parameters and environmental conditions shall be controlled to protect the safety and comfort of personnel.

D2.3 There shall be a written assessment of critical facility parameters that may affect processing, storage, or distribution.

D2.3.1 The written assessment shall include temperature, humidity, air quality, and surface contaminates.

D2.3.2 Critical facility parameters identified to be a risk to the cellular therapy product shall be controlled, monitored, and recorded.

Explanation:
The Processing Facility must identify the facility parameters that should be controlled and monitored based on their potential effect on cellular therapy product quality. The facility must perform an assessment of facility conditions to determine if any parameters need to be controlled, monitored, and recorded. This includes parameters that may directly affect the product, and also conditions that would diminish the integrity of supplies and equipment or the performance of personnel (such as temperature or extreme humidity). Some equipment have operating limits but others do not.

There must be ongoing monitoring of any parameters that have been determined to be critical. These parameters should be defined by an SOP and compliance documented through quality records. Risk should be reassessed with the occurrence of any significant change.

Evidence:
The Processing Facility should assess the risk of parameters, such as temperature and humidity, that could influence the quality of the cellular therapy product, spread contaminants in the environment, or interfere with equipment or personnel performance.

If no parameters are controlled, the Processing Facility must provide documentation of its reasoning prior to the inspection. It is the inspector's responsibility to determine while on site if the facility parameters affecting cellular therapy product viability, integrity, contamination, sterility, or cross-contamination identified by the facility are appropriate. If the inspector believes a parameter that is not identified should be controlled, this will be indicated in the inspector's report and included for discussion by the FACT or JACIE Accreditation Committee.

Example(s):
On-site inspections have revealed instances when humidity did impact the safety of the cellular therapy product. For example, in one particularly humid climate, liquid nitrogen freezer lids defrosted enough to prevent them from completely closing.

STANDARD:

D2.3.3 *The Processing Facility shall qualify environmental control systems and validate cleaning and sanitation procedures appropriate for the environmental classification and degree of manipulation performed.*

Explanation:
Methods to process cellular therapy products that expose them to greater risks of contamination or cross-contamination, such as open systems, warrant more stringent environmental controls. The requirement for surface microbial monitoring is intended to provide control where the cellular therapy product is handled and/or processed directly, rather than where product is contained and transiently stored. If a Processing Facility uses procedures that may result in contamination or cross-contamination, it must assess if air quality and surface contaminates must be controlled.

Environmental monitors for measures of air quality, such as particle counts and/or microbial colony counts are recommended, and should be based upon risk assessment for the identified measures.
The typical Processing Facility may not require a classified environment provided that processing steps requiring exposure to the environment are performed in a biosafety cabinet. However, a facility that extensively manipulates cellular therapy products and performs procedures with many "open" steps, such as transfer to another container without the use of a sterile connecting device, or entering a product by a spiking method outside of a biological safety cabinet, requires a greater level of environmental control. Environmental monitors for controlled space should include measures of air quality, such as particle counts and microbial colony counts, to minimize airborne contaminates.

Evidence:
The inspector should verify that the environment is suitable for the type of manipulations carried out in the Processing Facility, and that processing steps take place in an appropriately controlled environment. There must be ongoing monitoring of any parameters that have been determined to be critical, and these parameters should be defined by an SOP, and compliance documented through quality records.

Example(s):
If the Processing Facility performs more than minimally manipulated procedures or procedures with many open steps, the environmental conditions and monitoring of laminar flow cabinet and clean room shall be defined in accordance with EN/ISO 14644 methodology.

Contaminants in the Processing Facility can be minimized through air filtration, and by ensuring that the air pressure within the facility is positive to the surrounding areas (room pressure monitors should be used).

EU guidelines are more specific. Where products are exposed to the environment during processing, an air quality with particle counts and microbial colony counts equivalent to those of Grade A is required with a background environment appropriate for the processing of the cellular therapy product, but minimally equivalent to GMP Grade D in terms of particles and microbial counts. See the European Commission Directive 2006/86/EC and EU Guidelines to Good Manufacturing Practice (GMP), Annex 1 01 March 2009:
http://ec.europa.eu/health/files/eudralex/vol-4/2008_11_25_gmp-an1_en.pdf
and http://files.hpci.ch/hh/documents/guidelines/hh_gl_gmp.pdf.

Cleaning agents and disinfectants used in areas where the cellular therapy products are handled should be alternated though this is not specifically required.
More than one type of disinfectant is recommended according to section 61 of Annex 1, EU GMP guidelines.

STANDARD:
D2.4 *The Processing Facility shall document facility cleaning and sanitation and maintain order sufficient to achieve adequate conditions for operations.*

Explanation:
Processing Facility cleaning and sanitation must be performed on a regular basis in order to prevent contamination and cross-contamination of cellular therapy products. The methods used must be specified by an SOP (see D5.1). While the bench-top, biological safety cabinet, and equipment surfaces are most often cleaned and disinfected by facility personnel, other surfaces that may be cleaned by outside vendors, such as floors, walls and ceilings, also fall under this standard. The facility, together with the cleaning services vendor, must establish SOPs for this activity, and these SOPs should assign responsibility for who performs the sanitation procedures, the methods used, and the schedule. Facility cleaning must be documented and the records maintained for at least three (3) years.

Frequency of cleaning and sanitation should be based on environmental monitoring, the number and nature of cellular therapy products processed, and on incidence of microbial contamination in the Processing Facility. The facility should verify that disinfectants and detergents used are adequate to reduce the risk of contamination.

A system of rotating cleaning agents and disinfectants should be in place, and environmental monitoring with swabs or contact plates should be conducted in areas where processing occurs. A system of actions and alerts should be used when monitoring detects that contamination is present in the product or in the facility.

Evidence:
Records of cleaning and sanitation activities and concomitant microbial monitoring within the Processing Facility should be available for inspector review. SOPs that include agents to be used, frequency, responsibility, and, in the case of an outside vendor, its qualification, must be available for review.

Example(s):
Cleaning by a service vendor can be documented using a checklist completed by its staff, confirming that cleaning was performed according to the method and schedule defined by the appropriate SOP.

GMPs contain more detailed requirements, and the extent to which they must be followed depends on the type and stage of the cellular therapy product. GMPs for "351" products in the U.S. (i.e., products regulated solely under section 351 of the Public Health Service (PHS) Act), can be found in 21 CFR parts 210, 211, and 610. GTPs for "361" products can be found in 21 CFR 1271.

STANDARD:
D2.5 There shall be adequate equipment and materials for the procedures performed.

Explanation:
The amount of relevant equipment in the Processing Facility should be appropriate for the type of processing performed, proportionate to the volume of work done, and should be conveniently located. It is not acceptable to share equipment with other laboratories under conditions in which the sterility, integrity, and/or viability of the cellular therapy product may be compromised.

For critical pieces of equipment (e.g., biological safety cabinets or centrifuges), there should be back-up equipment immediately available, or a well described back-up plan should exist in the case of primary equipment failure (see D5.1). This plan should identify alternative equipment that can be used and should describe how that equipment is qualified for use to confirm it meets the requirements of the procedure.

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

The inspector should review documentation that adequate materials are present, and have been present, for the level of activity conducted by the Processing Facility. A well-stocked supply cabinet or supply area would indicate adequate materials are in inventory. Frequent "emergency" orders would suggest that an inadequate supply of material is being kept in inventory.

Example(s):
Examples of inadequate equipment include:

- Sharing a biological safety cabinet for the purpose of cell processing with any other laboratory whose activities might pose a risk of microbial contamination; for example, samples used by a microbiology department and research staff.
- Having limited and/or remote access to a cell counter, leading to processing delays.
- Using a refrigerator and/or freezer for products or reagents that is used for food or beverages.
- Performing different procedures on multiple products in the same biological safety cabinet simultaneously.

Documentation of "just-in-time" policies and SOPs for management of materials needed for cellular therapy product processing is acceptable so long as this practice can be confirmed by the inspector as having the desired result.

STANDARD:

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.*

Explanation:
The facility policies and SOPs, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to governmental regulations regarding safety. Processing Facilities should post warning signs wherever radioactive materials are in use. Safety, infection control, or biohazard waste disposal procedures that are unique to the facility must be covered in a Processing Facility SOP Manual. The use of electronic training programs that cover safety and infection control is acceptable, but there must be evidence that the staff has reviewed this information.

All persons who may come in contact with human blood or body fluids must wear appropriate personal protective equipment. This includes those exposed to cellular therapy products. The type of exposure that may be encountered will determine the appropriate suitable protection. If aerosol exposure is likely, a mask, goggles, and gowns or aprons should be worn. Gloves must be worn whenever potential infectious exposure exists and when aseptic procedures are required to protect the personnel and product. The use of personal protective clothing must be defined by an SOP (see D5.1).

Activities such as eating, drinking, and smoking must be prohibited in the Processing Facility.

Evidence:
If a processing procedure is underway during the day of inspection, the inspector should observe personnel for use of protective clothing and other biosafety precautions and verify if this is being done according to written instructions. The inspector should examine employee files for compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures. Compliance with national and international regulations should be addressed by the Processing Facility and verified by the inspector. The presence of unnecessary or non-functioning equipment, excessive traffic from unauthorized personnel, and inappropriate storage of reagents or supplies may also contribute to an unsafe environment and should be noted by the inspector.

Example(s):
Safety training, including universal precautions ("standard" precautions per the Center for Disease Control) for handling cellular therapy products, is a requirement of OSHA in the U.S. Equivalent regulations apply in other countries.

STANDARD:
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 hazards.*

Explanation:
Each Processing Facility shall have a written safety manual readily available in the facility. Policies and SOPs describing institutional policies are also acceptable, as long as facility-specific requirements are included, and there is evidence of document review by relevant personnel.

An adequate means of egress in areas where liquid nitrogen is stored, moved (e.g., elevators), or transported, is required for the safety of personnel, and, potentially, the public.

Evidence:
The inspector will review the written safety manual (including a description of the general liquid nitrogen safety plan) to verify how personnel are prepared to handle accidents and emergencies, and verify who is responsible for maintaining the emergency supplies. The inspector will also verify who is responsible for notifying and reporting events, when applicable.

Example(s):
The SOP manual may be an institution-wide document available by hard copy or electronically. Access to the institutional safety manual solely by computer is not acceptable without a written policy describing how to access the information in the event of a computer failure or down time.

STANDARD:
D2.8 *All waste generated by the Processing Facility activities shall be disposed of in a manner that minimizes any hazard to facility personnel and to the environment in accordance with applicable laws and regulations.*

Explanation:
Poor management of medical waste exposes personnel, waste holders, and the community to injuries, infections, and toxic effects. Hazardous waste generated by the Processing Facility's activities includes a broad range of materials, including used supplies, sharps, chemicals, radioactive material, viral vectors, genetically modified cells, and the cellular therapy products themselves. All medical waste shall be discarded in a safe manner according to written protocols for the disposal of biohazard waste (see D5.1) and in accordance with applicable governmental laws and regulations. Contaminated materials shall be placed in appropriate bags and containers marked with the international infectious substance symbol. Radioactive and chemical waste must be discarded using methods approved by appropriate governmental agencies. General waste that contains information that would constitute a breach of confidentiality if it became available to unauthorized persons, such as paper, CDs, disks etc., should be stored in a secured container before disposal and ultimately shredded or destroyed (see D5.1).

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

Example(s):
Contaminated materials may be typically discarded after autoclaving, decontamination with hypochlorite solution, ultra-high temperature incineration, and, in some locations, through the use of a sanitary landfill. Sharps like needles, blades, etc., whether or not they are infected, should be considered highly hazardous health care waste and placed for disposal in puncture proof containers. Chemicals such as cytostatic drugs, used in purging procedures, shall be discarded in accordance with applicable regulations.

STANDARD:
D2.9 *Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.*

Explanation:
When handling potentially hazardous substances, facility personnel must use appropriate protective attire. To prevent the spread of hazardous substances, protective attire must be removed before leaving the workspace.

D3: PERSONNEL

STANDARD:
D3.1 *PROCESSING FACILITY DIRECTOR*

D3.1.1 *There shall be a Processing Facility Director with a medical degree, doctoral degree, or equivalent degree in a relevant science, qualified by a minimum of two (2) years training and experience for the scope of activities carried out in the Processing Facility.*

Explanation:
The Processing Facility Director must be an individual with a medical degree, doctoral degree, or an equivalent degree in a relevant science. A non-physician director may hold a doctoral degree in any of the biological sciences and must have practical and relevant experience in cellular therapy product processing.

The Processing Facility Director must be qualified by training or experience (or combined training and experience) for the scope of activities carried out by the Processing Facility. The director must demonstrate competency according to the scope of his/her responsibilities.: The Director should understand the procedures, identify critical points and expected outcomes, be capable of making improvements and corrections in procedures and accompanying documents , and understand basic laboratory techniques used by the laboratory. In addition, he/she must have practical training, experience , and be knowledgeable for each new procedure that is introduced into the facility, even if he/she is not responsible for performing the procedure (e.g., DC vaccines, MSC culture, flow cytometry). Experience requirements may exceed those required by the Standards based on applicable laws and regulations.

Evidence:
The Processing Facility Director is required to submit a Curriculum Vitae (CV) that demonstrates two (2) years of combined training and/or experience. Alternatively, written confirmation can be a letter from each of the directors of the programs, departments, and/or institutions where this experience was obtained. The letter must include at least the types of cellular therapy products, processing methods, and job duties in the Processing Facility. If it is not possible to obtain letters from the directors where initial experience was gained, letters from directors at subsequent places of experience are acceptable.

Some regions of the world may have degrees that are equivalent to the doctoral degree. If a Processing Facility Director has such a degree, significant and compelling information regarding the degree requirements must be submitted to demonstrate equivalency.

Documentation of degrees and experiences should be submitted in advance, so the inspector can review the documentation prior to the on-site inspection.

Example(s):
Training consists of a total of two years of formal postdoctoral training in processing or clinical laboratory training following fellowship. The Processing Facility Director's experience and training may include formalized Fellowship in Transfusion Medicine or Post-Doctoral training in performing or supervising cell processing procedures relevant to cellular therapy.

An anatomic pathologist/dermatologist who is actually functioning day-to-day in a cell processing role for two years is an example of relevant experience.

EU regulations require the responsible person to have minimally two years practical experience in the relevant fields. The Processing Facility Director can be the responsible person (according to the European Directive 2004/23/EC).

STANDARD:

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

Explanation:
The Processing Facility Director is responsible for all SOPs and administrative operations of the Processing Facility, including compliance with the FACT-JACIE Standards and with all other applicable governmental laws and regulations. Specific duties of the director, or designee approved by the director, required by the Standards include:

- Development of and compliance with the Quality Management Program.
  - Approval of the Quality Manager.
  - Designation and review of proficiency tests.
  - Review of adverse events and deviations.
  - Report on quality program to Clinical Program Director.
- Definition of tests and procedures for cellular therapy product assays.
- Review of processing records prior to distribution.
- Review and approval of labels.
- Review results of microbial cultures.
- Authorization of release of products.
- Authorization of return of products not meeting return requirements.

The Processing Facility Director may have other responsibilities, but he/she or a designee should be available to Processing Facility personnel at all times. The Processing Facility Director's active involvement in the laboratory is strongly encouraged. Knowledge of day-to-day activities in addition to the specific duties listed above allows for the Processing Facility Director to be aware of overall operations in the facility. Programs that process a large number of products or perform complex processing should ideally employ a director with a minimum of 50 percent effort committed to the laboratory. The director's responsibilities should be outlined in a job description or in the SOP Manual for the facility. Although a designee may fulfill some of the responsibilities of the director, ultimate responsibility for the above duties will rest with the director.

Evidence:
The inspector should verify that the Processing Facility Director has a sufficient on-site physical presence to execute the above responsibilities. Evidence may be confirmed by examining documents, records, audits, and other records requiring director review in order to confirm that he/she is available to the Processing Facility personnel when needed. Evidence should also be present to confirm that the responsibilities of the director are actually performed by the designated individual, and in a timely fashion.

STANDARD:

D3.1.3 *The Processing Facility Director shall have performed or supervised a minimum of five (5) cellular therapy product processing procedures in the twelve (12) months preceding accreditation and a minimum average of five (5) cellular therapy product processing procedures per year within each accreditation cycle.*

Explanation:
Experience and training are expected only for the type of collection for which the Processing Facility Director is responsible. The director shall have performed or supervised a minimum of five (5) processing procedures in the year preceding accreditation and shall have performed or supervised a minimum average of five (5) processing procedures per year within each accreditation cycle.

STANDARD:

D3.1.4 The Processing Facility Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.

D3.1.4.1 Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.

Explanation:

The Processing Facility Director must participate regularly in educational activities related to the processing or use of cellular therapy products. The purpose of this requirement is for key personnel to keep up with current advancements in the field.

Evidence:

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

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

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Example(s):

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

Examples of appropriate continuing education activities include:

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

STANDARD:

D3.2 PROCESSING FACILITY MEDICAL DIRECTOR

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

Explanation:

The Processing Facility Medical Director must be a physician licensed to practice medicine in the area in which the Processing Facility is located and must have a minimum of two (2) years combined postdoctoral training or practical relevant experience in the preparation and clinical use of cellular therapy products.

The Processing Facility Medical Director must be qualified by training or experience for the scope of activities carried out by the Processing Facility. Experience requirements may exceed those required by the Standards based on applicable laws and regulations.

Practical relevant experience might mean day-to-day interaction in the preparation of and clinically-relevant attributes of cellular therapy products, attending scientific conferences with clinical and cell processing content, or clinical and cell processing regulatory activities.

Evidence:

To fulfill this standard, the Processing Facility Medical Director must provide a photocopy of his/her current national and/or local governmental license and a current CV. Since documentation of the medical degree is required to obtain a medical license, the license will be considered to be documentation that the director is a physician. The inspector can review these documents for evidence of experience prior to the on-site inspection.

Written confirmation can be a letter from each of the directors of the programs, departments, or institutions where practical relevant experience was obtained. The letter must include at least the following information: type of cellular therapy products, summary of role in release of products, and a description of job duties. If it is not possible to obtain letters from the directors where initial experience was gained, letters from directors at subsequent places of experience are acceptable.

The Processing Facility Medical Director is required to submit a CV that demonstrates training and/or experience prior to the on-site inspection. The inspector should review this information in advance, and request additional information if there are questions. Evidence of experience should be apparent. Documentation of the procedures performed or supervised should be available.

Example(s):

Experience can consist of time spent in training in another Processing Facility or on-the-job training. The Processing Facility Medical Director's experience or training may include Fellowship or Post-Doctoral training, but must include at least one year of experience in performing or supervising cell processing procedures relevant to cellular therapy.

EU regulations require the responsible person to have minimally two years of practical experience in the relevant fields (according to the European Directive 2004/23/EC).

ASBMT offers an Online Learning center that hosts recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning.

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at:
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

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

Explanation:
The Processing Facility Medical Director is directly responsible for the medical aspects of the processing procedures. Specific responsibilities requiring documentation of director review include:

- Review of adverse events associated with cellular therapy product administration.
- Authorization for the distribution of non-conforming cellular therapy products and products released due to urgent medical need.
- Review and approval of clinically-relevant SOPs.
- Approval of medically-relevant planned and unplanned deviations from SOPs.
- Notification when medically-relevant end-points are not achieved.
- Authorization for cellular therapy product discard.

The Processing Facility Medical Director may have other responsibilities, but he/she or a designee should be available to Processing Facility personnel at all times. The director's responsibilities should be outlined in a job description.

Evidence:
Evidence of availability may be confirmed by examining documents, processing records, audits, and other records requiring the director's review in order to confirm that the director is available to the facility personnel when needed.

Example(s):
ABO incompatibility in relation to volume is a specific topic that requires dedicated training and competency assessment, as cellular therapy product issues are different among apheresis, marrow collection, and cord blood collection.

Similarly, cord blood preparation for administration requires clinicians have dedicated training and competency in providing proper orders for washing, diluting, or reducing red cells from the cellular therapy product.

STANDARD:

D3.2.3 *The Processing Facility Medical Director shall have performed or supervised a minimum of five (5) cellular therapy product processing procedures in the twelve (12) months preceding accreditation and a minimum average of five (5) cellular therapy product processing procedures per year within each accreditation cycle.*

Explanation:
Experience and training are expected only for the type of collection for which the Processing Facility Medical Director is responsible. The director shall have performed or supervised a minimum of five (5) processing procedures in the year preceding accreditation and shall have performed or supervised a minimum average of five (5) processing procedures per year within each accreditation cycle.

STANDARD:

D3.2.4 *The Processing Facility Medical Director shall participate in ten (10) hours of educational activities related to cellular therapy annually at a minimum.*

D3.2.4.1 *Continuing education shall include, but is not limited to, activities related to the field of HPC transplantation.*

Explanation:
The Processing Facility Medical Director must participate regularly in educational activities related to the processing and use of cellular therapy products. The purpose of this requirement is for key personnel to keep up with current advancements in the field.

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

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

The requirements listed above may be provided in a variety of formats, including reports or listings submitted to professional organizations to obtain related credentials. Content must reflect regular education in cellular therapy and/or diseases in which cellular therapy is a therapeutic option.

Example(s):
Evidence of compliance may include either a formal or informal study. Educational activities do not necessarily require large financial resources. The Processing Facility may choose to establish its own guidelines for the number of hours from each type of activity that can be counted toward the minimum requirement in this standard.

Examples of appropriate continuing education activities include:

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

ASBMT offers an Online Learning center that hosts recordings from BMT Tandem Meetings, recordings from the Clinical Education Conference, and ASBMT Online Seminars.
These can be accessed at
http://asbmt.org/professional-development/online-learning.

Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at:
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

D3.3 QUALITY MANAGER

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

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

Explanation:

The Processing Facility must identify at least one person with responsibility for Quality Management. The title held by this individual may differ among facilities and is not relevant as long as the duties include those described in the Standards. The Processing Facility Quality Manager shall be an individual with an undergraduate degree in the field of health sciences or biological sciences and who has training in the field of cellular therapy product processing.

The Quality Manager has responsibility for preparing, reviewing, approving, and/or implementing QM policies and SOPs and must confirm that they are in compliance with the Standards and all applicable laws and regulations before implementation. A key role of the Quality Manager is to develop systems for auditing Processing Facility activities to confirm compliance with the written SOPs.

The Processing Facility Director or other knowledgeable personnel may play a role in conducting or reviewing audits, especially audits that may include work performed by the Quality Manager. The director as specified throughout the Standards may play an active role in reviewing the work of the technologists, including QM procedures. The director is ultimately responsible for the QM Plan and proper implementation of the plan for the Processing Facility. SOPs should clearly define the role(s) of the Processing Facility Director, Processing Facility Medical Director, the Quality Manager, and other QM personnel in the QM Program.

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

Example(s):
Formal training may include practical work experience in a Processing Facility, fellowship, or a certification program.

For Processing Facilities that perform minimal manipulation (e.g., 361-designated products) and have a low processing volume, the Standards do not prohibit the Quality Manager from participating in facility activities, as many facilities or institutions may not be large enough to support QM staff for the cell processing facility alone. However, the Quality Manager should not review or approve technical procedures for which he/she is solely responsible. In such cases, that review should be delegated. The Quality Manager may review SOPs where he/she has contributed to the activity following a reasonable time period to reduce the potential for bias. What constitutes a reasonable time lapse may vary based on the type of activity being reviewed. Calculations requiring a double check before proceeding to the next processing step may need to be reviewed within a few minutes or hours, whereas audits more often will be performed weeks or months after the activity that is being audited was performed. The reasonable time period for specific activities to be reviewed may be defined by the Processing Facility's policies and SOPs.

The Processing Facility Director or Medical Director can also assume the Quality Manager role as long as there is evidence of external review of his or her activities (e.g., by the institutional quality department or other supervisory individual) related to proper implementation of a QM Plan for the Processing Facility. Such a situation may occur more often in a small facility (two to three full time employees) where technical responsibilities do not allow time for the activities of QM supervision and the complexity is restricted to minimal manipulation of homologous products.

STANDARD:

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

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

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

There are many ways to meet this standard, and the standard is not meant to be prescriptive. A total of 10 hours in combination of these topics is required. Each topic does not need to be covered in 10 hours individually. The inspector should assess the documented number and content of continuing education activities and use his/her judgment to determine whether or not a QM Supervisor meets this standard.

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

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

Example(s):
Evidence of compliance may include either a formal or informal study. Educational activities do not necessarily require large financial resources. The Processing Facility may choose to establish its own guidelines for the number of hours from each type of activity that can be counted toward the minimum requirement in this standard.

Examples of appropriate continuing education activities include:

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

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Other organizations also offer conferences on specific cellular therapy topics, including the European School of Haematology (ESH) - European Society for Blood and Marrow Transplantation (EBMT) Training Course on Haematopoietic Stem Cell Transplantation. Other EBMT educational opportunities are available at:
http://www.ebmt.org/Contents/Education/Pages/Education.aspx.

STANDARD:

D3.4 STAFF

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

Explanation:

There must be sufficient technical and other support staff for the scope and number of services provided. The facility shall have an adequate number of trained processing personnel to perform all processing activities in compliance with the FACT-JACIE Standards and other applicable governmental laws and regulations. Trained and competent technical personnel sufficient for the type of processing performed and in proportion to the volume of work are required.
The Processing Facility Director should indicate personnel responsible for specific activities in the Processing Facility, and must confirm that they are approved for the execution of those activities. Their continued competence must be documented.

Some Processing Facilities have processing volumes low enough for one staff member to perform the processing; however, there must be a contingency plan in the event that staff member is unable to perform the necessary duties (e.g., illness, unexpected emergencies). Access to additional qualified individuals to process cellular therapy products and prepare them for administration when back-up is needed must be available, although these individuals do not have to be directly employed by the facility.

Evidence:

The adequacy of staffing may be ascertained by reviewing full-time and part-time staffing levels, staff turnover, and frequency and types of errors, accidents, and deviations from SOPs. The inspector must review the plan for staffing in the event of absences. It may also be useful to talk directly with the technical personnel regarding workload requirements and the adequacy of staffing. The inspector should confirm the documentation of continued competency assessment.

D4: QUALITY MANAGEMENT

STANDARD:

D4.1 There shall be a Quality Management Program that incorporates key processing 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.*

Explanation

The QM Program includes a description of the strategy (QM Plan) and the associated policies and SOPs that drive the operation of the QM Program. Development of a comprehensive QM Program is often the most challenging and time-consuming exercise that a Processing Facility encounters when preparing for FACT or JACIE accreditation.

Example(s):

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

STANDARD:

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

Explanation:

The QM Plan is the written document that outlines how the QM Program (quality assurance, control, assessment, and improvement activities) is implemented.

The Standards have a broad scope of requirements for the QM Plan to comply with cGMP, cGTP, and other applicable international regulatory requirements.

The QM Plan must detail all key elements that affect the quality of cellular therapy products. The specific SOPs to be followed for each of these elements does not have to be fully described in the QM Plan, but must be referenced within the plan and linked to the appropriate document where the details are described.

The thoroughness and attention to detail of the written QM Plan is an indication of how QM is perceived and executed within the Processing Facility.

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

Evidence:
The written QM Plan for the Processing Facility will be provided to the inspector prior to the on-site inspection. If policies and SOPs are referenced in the QM Plan, they may be requested in advance to enable the inspector to review the details of the QM program. The inspector is expected to evaluate implementation of the QM Plan at the facility and assess the understanding of QM by the staff. An incomplete, too broad (i.e., a shared plan covering an entire Transfusion Medicine department), or poorly written QM Plan may be an indication that QM is not deemed an integral and important component of the facility. Under these circumstances, the inspector should pay particular attention to evaluating the QM efforts of the facility during the on-site inspection process. The inspector should specifically look for documentation of compliance for QM activities not directly performed by facility staff and seek evidence that QM activities link to the Clinical Program, Collection Facility, and Processing Facility.

STANDARD:

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

Example(s):
There shall be an individual (i.e., the Processing Facility Director or designee) at the facility in charge of the elements of the QM Plan that are directly related to the facility. A designee must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. Delegation of a designee must be documented, either in the QM Plan or in SOPs related to it.

Evidence:
QM Plan review and approval should provide evidence of the Processing Facility Director's and designee's (if applicable) involvement.

Example(s):
A designee can be a member of another department, such as an institutional Quality Assessment and Improvement or Compliance Department, who devotes some time to the QM activities of the Processing Facility, or he/she could be a member of the facility's team. The same person may be responsible for QM of all components of the cellular therapy program or each individual area (clinical, collection, processing) may have a distinct individual responsibility for QM, as long as there is a mechanism for sharing of information to all participating entities.

STANDARD:

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

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

Explanation:
The organizational chart should include titles of key positions and the reporting structure for the Processing Facility and the QM Program.
The inspector will verify that the organization and daily function is as described. Organizational chart links must illustrate relationships to Clinical, Collection, and Processing Facilities that meet these standards.

The description of the operation of the QM Program should include the processes in place to accomplish its goals (e.g., meetings, participants, schedule, reporting, and documentation). Lines of responsibility and communications must be clearly defined in a way that is understood by all involved.

Evidence:
The organizational chart for the Processing Facility, will be provided to the inspector prior to the on-site inspection. The inspector will verify that the organization and daily function is as described. Organizational chart links must illustrate relationships to clinical, collection, and processing facilities that meet the Standards.

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

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

STANDARD:
D4.4 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures addressing personnel requirements for each key position in the Processing Facility. Personnel requirements shall include at a minimum:*

Explanation:
The QM Plan, as approved by the Processing Facility Director, identifies the key personnel for whom documentation of training, competency, and continuing education is expected. These must include all individuals responsible for critical elements of the Processing Facility. Documentation of training for each individual must include all procedural skills routinely practiced. These requirements are detailed in D3.These requirements apply to all personnel in these positions, including those not directly employed by the Processing Facility but who perform processing services.

Evidence:
The inspector should review training records to verify compliance with these regulations. Organization-specific issues and safety training are generally covered by orientation programs and continuing education programs, but inclusion of this content should be confirmed by the inspector. The inspector should review policies or SOPs describing the elements of staff training and continued competency as described in D4.4.

The inspector should review the records of one or more employees to confirm that all of the required elements are documented.

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

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

Legal and regulatory context can be demonstrated by including training related to GTP, GMP, and the Standards.

STANDARD:

D4.4.1 A current job description for all staff.

D4.4.2 A system to document the following for all staff:

D4.4.2.1 Initial qualifications.

Explanation:
Initial qualifications generally include minimal educational requirements, formal training that is either required or preferred, and licensing or certification.

STANDARD:

D4.4.2.2 New employee orientation.

Explanation:

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

Evidence:

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

STANDARD:

D4.4.2.3 Initial training and retraining when appropriate for all procedures performed.

Explanation:

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

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

Example(s):

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

STANDARD:

D4.4.2.4 Continued competency for each critical function performed annually at a minimum.

Explanation:
Competency is the ability to adequately perform a specific procedure or task according to direction. Processing Facilities must have a system for documenting competency for each critical function performed by a staff member (see Part A for the definition of "critical").

Example(s):
Competency and may be assessed by direct observation, the use of written tests, successful completion of proficiency surveys, review of processing procedure end-points, or other ways as determined by the Processing Facility. Procedures for personnel training and competency assessment must be documented and reviewed.

Evidence:
The inspector should review records of employees' initials and annual competency.

STANDARD:

D4.4.2.5 Continuing education.

Explanation:

Staff should adhere to local and governmental continuing education requirements. The inspector should find evidence of suitable educational opportunities for staff related to their duties, such as quality-related meetings, webinars, and/or FACT or JACIE training sessions, if applicable.

Evidence:
The inspector should review policies or SOPs describing the elements of staff training and continued competency as described in D4.4.
The inspector will review the records of one or more employees to determine whether all of the required elements are documented.

STANDARD:

D4.5 The Quality Management Plan shall include, or summarize and reference, a comprehensive system for document control.

D4.5.1 There shall be a current listing of types of documents that are considered critical and shall comply with the document control system.

Explanation:
The QM Program must maintain a list of all active critical documents. For example, all SOPs required by the Standards must be considered to be critical documents, and must be controlled. Processing Facilities may call documents different names, and may identify additional types of documents as critical within the scope of the document control system.

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

STANDARD:

D4.5.2 *There shall be policies and Standard Operating Procedures for the development, approval, implementation, distribution, review, revision, and archival of all critical documents.*

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

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

Evidence:
The inspector should review active controlled documents to ensure they have been written correctly, approved by the appropriate staff before being implemented, and comply with the document control system and the Standards. The inspector will observe how the Processing Facility controls modifications of documents and whether retrospective review is possible.

Example(s):
The process by which processing is performed may require multiple SOPs, forms, and worksheets to be in place. This process might include a description of product receipt, sampling, testing for CD34 cell content, labeling, and cryopreservation, among others

STANDARD:

D4.5.3 The document control system shall include:

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

Explanation:

The Processing Facility should be consistent in the format or design of controlled documents.

Documents authored by the Processing Facility should follow the document control system, however departmental and institutional documents may differ.

Evidence:

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

STANDARD:

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

Explanation:

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

Evidence:

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

STANDARD:

D4.5.3.3 A system for document approval, including the approval date, signature of approving individual(s), and the effective date.

Explanation:

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

Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate person entered the signature.

Evidence:
The inspector must verify that records indicate consistent approval of controlled documents.

STANDARD:

D4.5.3.4 A system to protect controlled documents from accidental or unauthorized modification.

Explanation:
The methods of document distribution and storage should control or prevent unwanted or unauthorized document modification or duplication. Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software (to lock specific areas or a specific document to prevent printing) or having copies clearly printed with an expiration date or watermarked as copies. The intention is to make sure that only the currently approved document is available for use.

Evidence:
The inspector should review the storage and access of currently approved documents and archived documents to verify strict access control.

STANDARD:

D4.5.3.5 Controlled documents shall be reviewed every two years at a minimum.

D4.5.3.6 A system for document change control that includes a description of the change the signature of approving individual(s), approval date(s), communication or training on the change as applicable, effective date, and archival date.

Explanation:
A change control system must include at least the following elements: change proposal; review of proposed change; analysis of change for compliance with standards and applicable law; risk and impact assessment on existing process and controlled documents; approval of change and revision of documents; communication and/or training on the change as applicable; and implementation of the change. Change in practice should not occur before change in the appropriate controlled document has been made and approved. If immediate implementation of a change is required prior to official document edits, then the department should issue a planned deviation documenting this deviation from routine practice. A copy of the new document reflecting the changes could suffice for a description of the change.

The effective date of a controlled document is an assigned date following approval when the controlled document, such as an SOP, worksheet, form, or other document must be followed by trained personnel. For instance, a staff member may not perform a new or modified SOP until he or she has reviewed the SOP and completed required training and competency assessment. The amount and format of training and competency assessment may differ based on complexity of the changes. Electronic signatures are acceptable but must be controlled in a manner that allows verification that the appropriate person entered the signature.

Evidence:
The change control process should be reviewed to assess if it is effective to prevent unintended changes to processes or controlled documents.

STANDARD:

D4.5.3.7 Archived controlled documents, the inclusive dates of use, and their historical sequence shall be maintained for a minimum of ten (10) years from archival or according to governmental or institutional policy, whichever is longer.

Explanation:
Documentation is especially important for the investigation of errors, accidents, suspected adverse events, biological product deviations, and complaints, since these investigations are frequently retrospective in nature. If outcomes change over time, one needs to be able to go back to previous versions of controlled documents to determine if an operational change is the cause.

Evidence:
The inspector will examine how the Processing Facility archives controlled documents, whether retrospective review is possible, and whether previous documents can be identified (e.g. unique identifier, version, and name).

Example(s):
The archival system may contain items such as date removed, version number, reason for removal, and identification of the person who performed removal.

STANDARD:

D4.5.3.8 A system for the retraction of obsolete documents to prevent unintended use.

Example(s):
Processing Facilities may have forms, worksheets, etc., that are printed and distributed. There should be a system in place to recover these obsolete documents to prevent unintended use.

STANDARD:

D4.6 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the establishment and maintenance of written agreements with external parties providing critical services that could affect the quality and safety of the cellular therapy product or welfare of the donor or recipient.

D4.6.1 Agreements shall be established with external parties providing critical services.

D4.6.2 Agreements shall include the responsibility of the external party performing any step in collection, processing, testing, storage, distribution, or administration to comply with applicable laws and regulations, these Standards, and the standards of other required accreditation agencies.

D4.6.3 Agreements shall be dated and reviewed on a regular basis.

Explanation:

The Processing Facility must have policies and SOPs describing the requirement, development and maintenance of written agreements or contracts with external organizations or individuals providing a critical service for the program (e.g., donor or recipient work up prior to transplant, collection, processing, testing, storage or administration of cellular therapy products, donor or recipient follow up post transplant). This standard does not apply to entities within the Processing Facility's institution.

The burden to determine compliance with the requirements of the accrediting organizations is on the Collection Facility, not on FACT or JACIE. Agreements must address other accreditations required by FACT.

Written agreements should clearly define the roles and responsibilities of each party for the performance of critical tasks. Written agreements should be dated, reviewed, revised and approved by both parties and legal if necessary, on a regular basis as defined by the program, and at least every two years. The policy or SOP for written agreements, or each individual agreement should describe the maintenance of records following termination of the agreement.

Programs should have an awareness of, and a review plan for, all agreements including those that the program does not control (i.e. does not develop or provide authorized signature), but which are relevant to the clinical care of the patient and/or donor or impact upon the cellular therapy product. A master list of written agreements and a checklist could assist with appropriate review and ensure that important elements are included, and a designee in the program is notified when changes are made.

Evidence:

Written agreements that match current practices must be available for the inspector to review on-site.

Example(s):
It is recommended that a Processing Facility have a contingency plan in the event that it is unable to provide services as intended (e.g., significant personnel change or natural disaster). The contingency plan may require a written agreement with an external facility.

Examples of written agreements with external parties include memorandums of understanding, purchasing arrangements, service level agreements, contracts and preventive maintenance arrangements. Specific examples include written agreements with external facilities used for the storage of cryopreserved cellular therapy products or for laboratories performing testing of cellular therapy products.

Such agreements may include, but are not limited to, donor qualification, determination of donor suitability and eligibility allogeneic donor only, collection of the cellular therapy product, donor or product testing, and long-term storage.

STANDARD:
D4.7 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for review of outcome analysis and cellular therapy product efficacy to verify that the procedures in use consistently provide a safe and effective product.*

Evidence:
The inspector should confirm documentation of all activities from definition of expected outcome to process improvement, when indicated. There must be evidence of ongoing analysis of data in addition to mere data collection. The inspector should ask to see the data and/or minutes of meetings, including the personnel in attendance and where data are presented.

STANDARD:
D4.7.1 *Criteria for cellular therapy product safety, product efficacy, or the clinical outcome shall be determined and shall be reviewed at regular time intervals.*

Explanation:
Outcome analysis involves the collection, evaluation, and distribution of patient outcome data. Processing Facilities must request day of engraftment data from the Clinical Program, and maintain and analyze critical outcome data to verify that the procedures in use consistently provide a safe and effective product.

The responsibility of facilities is to assess the impact of cellular therapy processing on outcomes to identify trends. When HPC products are being used for nonhomologous use (i.e., HPC, Marrow for the treatment of cardiac failure) other criteria need to be defined and monitored. Product efficacy based on outcome may be more difficult to document for other therapeutic cell products and that assessment will differ for each product type. If a Processing Facility is manufacturing by contract, the outcome criteria may be less rigorous and may include such items as administration safety. The QM Plan must also address the need for the development of a validated potency assay as regulated products enter the later stages of clinical trials. Generally, the Clinical Program is responsible for defining outcome criteria although the Processing Facility may contribute to the defined criteria through consultation and implementation of assays. Evaluation of patient outcome is required to confirm that the highest quality product has been manufactured and distributed. Any unexpected outcomes should be investigated and corrective action or process improvement implemented. Facility personnel should evaluate all aspects of the processing procedure related to any unexpected outcome, including delayed or failed engraftment. This evaluation should be documented, and, if indicated, the facility should initiate corrective action.

If a Processing Facility provides products to one or more Clinical Programs, it is the responsibility of the facility to solicit engraftment data from each program. There must be evidence of ongoing analysis of engraftment data in addition to mere collection. Outcome analysis should not only be performed on individual cellular therapy products, but on Processing Facility data as a whole to identify overall trends. The analysis should include observed ranges of engraftment for the various products and transplant procedures performed by the program. Product characteristics, especially cell dose, should also be considered in such analysis. The Clinical Program is most qualified to determine what constitutes an acceptable time to engraftment. These data can be used to identify changes that might require further investigation. The responsibility for the collection and analysis of outcome data is an example of a QM requirement that may or may not be performed entirely within the Processing Facility. However, it is the responsibility of the facility to have (or provide) access to this data to both the Clinical Program and the Collection Facility. Chimerism assays can be used as a tool for the assessment of the product quality of allogeneic HPC products administered after non-myeloablative treatment.

When the Processing Facility is only receiving products manufactured by an external facility and preparing them for administration, the facility must still perform some outcome analysis although the outcome criteria may be less rigorous (such as focusing only on safety of the administration rather than potency). In these cases, the facility must still be able to request or have access to other outcome data from the manufacturer when needed to perform investigations of adverse events, errors, or accidents.

It is expected that criteria for which reasonable data can be obtained (product safety, product efficacy, and the clinical outcome) be determined and reviewed.

Evidence:
The inspector should confirm documentation of all activities from definition of expected outcome to process improvement, when indicated. The inspector should ask to see the engraftment data and/or minutes of meetings(including the personnel in attendance) where engraftment data are presented.

Example(s);
Chimerism studies may be used to analyze the outcome of DLIs.

If a poor outcome occurs when the cellular therapy product is received from an external source, it is important for the Processing Facility to be able to share results and to trace back to the product source for information such as sterility testing, cell type, etc.

STANDARD:

D4.7.2 *Both individual cellular therapy product data and aggregate data for each type of cellular therapy product shall be evaluated.*

D4.7.3 *For HPC products intended for hematopoietic reconstitution, time to engraftment following cellular therapy product administration shall be analyzed.*

Explanation:
The responsibility for the processing and analysis of outcome data is an example of a QM requirement that may or may not be performed entirely within the Processing Facility. It is acceptable to share the same data between clinical, collection, and processing; however, the Processing Facility is responsible for ensuring it has access to clinical outcome data to enable it to adequately assess that its processes do not negatively impact outcome.

Outcome analysis should include each individual product or recipient to assess efficacy or safety as appropriate; however, that assessment alone is insufficient to meet this standard. The intent of the standard is that similar recipients of a similar product be assessed together for efficacy, safety, trends, and opportunities for improvement. Individual programs will choose how to aggregate data based upon the size and complexity of the Clinical Program.

Example(s):
As an example, timely engraftment of the HPC product in a recipient following a dose intensive regimen is directly related to the quality of the HPC product. Therefore, the Processing Facility personnel must be aware of the time to neutrophil and platelet engraftment for all recipients for whom they have supplied products. This information can be solicited directly by the facility or presented by another section of the cellular therapy program at a common QM meeting where facility personnel are in attendance.

STANDARD:

D4.8 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures, and a schedule for conducting, reviewing, and reporting audits of the Processing Facility's activities to verify compliance with elements of the Quality Management Program and operational policies and Standard Operating Procedures, applicable laws or regulations, and these Standards.*

Explanation:

Audits represent one of the principle activities of the QM Plan. An audit is a documented, independent inspection and retrospective review of an establishment's activities to determine if they are performed according to written SOPs Compliance is verified by examination of objective evidence. Audits are conducted to be sure that the QM Plan is operating effectively and to identify trends and recurring problems in all aspects of Processing Facility operation. Processes to be audited should include those where lack of compliance would potentially result in a nonconforming product or an adverse event. The QM Manager or designee should identify areas to be audited and audit frequency. –The audit process should occur throughout the year with reporting of audit results, corrective action, and follow-up on a regular schedule, at least once a year. A schedule of prospective audits is expected. There may be other audits required in response to specific events.

Evidence:

The Processing Facility should facilitate the on-site inspection with a concise presentation of recent audits, supported by policies and SOPs, and including documentation of corrective and preventive action and follow up. Examples of how results are trended and presented to relevant directors and staff are also helpful. The inspector should review audit results and schedule of planned audits, but it is not the intent to use a facility's audits to identify deficiencies during an inspection; the inspector shall maintain the confidentiality of the information.

Example(s):

Audit schedules can be flexible and can be created through use of an Excel spreadsheet or table. Other examples of audits within the Processing Facility include:

- Adherence to policies and SOPs (e.g., correct labeling SOPs).
- Presence in the facility of written medical orders prior to processing and administration of products.
- Equipment maintenance performed according to schedule.
- Sterility testing results present in the processing record.
- Documentation of processing facility cleaning before, after, and between products.

These audits may be on-site inspections by contracting personnel or self-assessments performed by the Processing Facility or other members of the program.

An audit process or report could include the following elements:

- Audit title.
- Audit type (e.g., Yearly Key Element, 2-Year Key Element, Focused, Follow-up).
- Clinical site or unit (e.g., pediatric, adult).
- Date audit is assigned, including name and title of staff who assigned the audit.
- Name and title of staff assigned to complete the audit.
- Audit period (date range).
- Audit parameter description.
- Date audit started and completed.
- Audit findings and recommendations.
- Timeline for follow up.
- Signatures and Comments.
    - Auditor signature and date.
    - Quality Manager signature, date, and comments.
    - Clinical Program Director signature, date, and comments.
    - BMT quality committee chair signature, date, and comments.
- Documented staff review and date of review.
- Quality meeting results presentation date, if required.

STANDARD:

D4.8.1 *Audits shall be conducted by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.*

Explanation:

The individual(s) performing an audit does not need to be external to the Clinical Program, but he/she should not have performed the actions being audited.

The auditor must be knowledgeable in auditing techniques.

STANDARD:

D4.8.2 *The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, implement corrective and preventive actions when necessary, and follow-up on the effectiveness of these actions in a timely manner.*

Explanation:
There must be regular auditing of critical activities; frequency will depend on the importance of these activities, and to some extent on the results. Where there are published studies, these should be used to help assess audit results. For example, product yields may be expected to fall within a certain range based on national or international data. Although the yields continue to fall within that range, a trend downward to the lower end of the expected range may indicate a need to investigate the cause (e.g., new staff, a new piece of equipment, a reagent unexpectedly received from a different supplier).

Evidence:
The audit process and example audits must demonstrate that this is an ongoing process and that the QM records demonstrate corrective actions or process improvement activities that are based on audit findings. Additionally, when audit results identify corrective action or process improvement, there should be a date designated as the expected date of completion of the corrective action, and a planned time to re-audit the process to verify that the corrective actions were effective.

STANDARD:

D4.8.3 *Audits of critical processes shall be performed including the following annually at a minimum:*

D4.8.3.1 Management of cellular therapy products with positive microbial culture results.

Explanation:
The intent of this Standard is to only audit what is applicable to the Processing Facility's defined responsibilities.

Standard;

D4.8.3.2 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

Explanation:
For Processing Facilities that have agreements or contracts with external facilities for any critical steps (collection, processing, cryopreservation, labeling, or distribution) in processing or product testing, it is essential that audits include a review of those facilities so as to confirm that the requirements of the agreements have been met. Such reviews should be performed on a regular basis and should also be performed after there has been a change in the agreement or in governmental regulations that are required to be followed by the agreement.

STANDARD:

D4.9 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for the management of cellular therapy products with positive microbial culture results that address at a minimum:*

D4.9.1 *Documentation and product labeling.*

D4.9.2 *Product quarantine.*

D4.9.3 *Criteria for product release.*

D4.9.4 *Identification of individuals authorized to approve release, including the Processing Facility Medical Director at a minimum.*

D4.9.5 *Notification of the recipient's physician, collection facility, and any other facility in receipt of the cellular therapy product.*

D4.9.6 *Investigation of cause.*

D4.9.7 *Reporting to regulatory agencies, if appropriate.*

Explanation:

The Processing Facility shall monitor all products, minimally after processing, for microbial contamination. For non-cryopreserved products, the results of such testing will not generally be known prior to administration. Preliminary or final results should be available for cryopreserved products prior to administration.

The cellular therapy program (i.e., Clinical Program and Collection and Processing Facilities) must develop an integrated approach to the management of cellular therapy products with positive microbial culture results that are identified before or after the products have been administered.
Policies and SOPs are required across areas of an integrated cellular therapy program to manage the aspects for which the particular area of the program is responsible. This requirement may be satisfied with a single policy or SOP or there may be separate documents. For each topic, SOPs should detail what action is to be taken, who is responsible to take the action, and the expected timeframe of the actions. Different approaches to management may be acceptable if these approaches are consistently followed and meet regulatory requirements.

The Processing Facility is usually the first facility to be notified of a positive culture result. There should be timely notification of the Collection Facility, which should in turn investigate all records related to that collection to determine if anything in the collection process could have contributed to the positive culture result. Notification of clinical staff of the positive culture result is critical so that appropriate patient care can be delivered to the donor, and, if the product has already been administered, to the recipient. If the product has been shipped or transported to another Processing Facility, that facility must also be notified.

Policies and SOPs should cover investigation of the cause of the positive culture result, including at least evaluation of the collection and processing events for evidence of breach of aseptic technique, determination if the donor had any evidence of sepsis at the time of collection, investigation of laboratory culture procedures to rule out a false positive result, contamination of the sample in the microbiology laboratory, or other causes that do not indicate compromise of the product that might explain the positive result. Since a positive microbial culture is a biological product deviation, all of those related requirements apply.

There should be a policy or SOP for the disposition of a cellular therapy product that is found to be positive for microbial contamination prior to administration that includes criteria for when such products may be used, how the recipient is to be notified and provide consent, release criteria, and labeling. The Clinical Program is typically responsible for recipient notification and consent, and must assist with urgent medical need documentation. Biohazard label and warning statements must be used as required by D7 and applicable laws and regulations.

Evidence:
The inspector may ask to see the processing record of a cellular therapy product that was found to have a positive microbial culture and review how the Processing Facility managed the process.

Example(s):
It is recommended that products with a known positive culture be labeled in a fashion similar to that used for products from donors with a positive infectious disease test result. These products should be kept in quarantine due to possible cross-contamination.

In the U.S., regulations for 351 and 361 products should be followed and the cellular therapy program should have policies that cover responsibility for reporting. In the EU, all adverse events shall be reported to the relevant competent authority.

Example of investigation and follow up of a positive culture result may include:

- Review of processing records for any indication of breech in sterile technique or other adverse event, particularly if extensive processing was required.
- Documentation of proper equipment cleaning, particularly for the biological safety cabinet.
- Review of environmental conditions for sources of possible contamination (BSC sterility testing, particle counts).

- Review of staff competency for possible trends.
- Follow up and review of findings from the collections area for possible breach in aseptic technique, donor sepsis or other issues.
- Follow up of the recipient for adverse reaction to administration, infection by the contaminating organism, or other adverse event.

Evidence of investigation of cause, outcome analysis and any preventive/corrective action taken as a result of the investigation should be communicated to all areas of the program (clinical, collection and processing) and be evident in minutes of QM meetings.

STANDARD:

D4.10 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for occurrences (errors accidents, biological product deviations, adverse events, adverse reactions, and complaints). The following activities shall be included at a minimum:*

Evidence:

The inspector should expect to find a documented process for occurrences that includes detection, investigation, documentation, corrective action, preventive action, and follow up. This should be reviewed by the Processing Facility Director and Quality Manager or designee, and reported , as appropriate, to the Collection Facility, the Clinical Program Director, and appropriate governmental agencies. These occurrences and trends should be reported, as appropriate, to the Clinical Program Director, and appropriate governmental agencies.

STANDARD:

D4.10.1 *Detection.*

Explanation:

A goal of a QM Program is to continuously improve processes. Monitoring events and trends facilitates recognition of improvement opportunities. There must be a process to detect, evaluate, document, and report occurrences in a timely fashion to key individuals, including the Processing Facility Director and appropriate governmental agencies, as appropriate. The Processing Facility should define errors, accidents, deviations, adverse events, adverse reactions and complaints in SOPs and describe when, how, by whom and to whom each is reported. Programs can use the definitions stated by applicable regulatory agencies. See the definitions of each of these types of events in the Standards, Part A (Definitions). Management of each of these types of occurrences is slightly different; however, the same steps (detection, evaluation/investigation, documentation, determination of corrective and preventive action, and reporting) apply to all .

It is recommended that Processing Facilities also define, document, investigate, implement corrective action, report, and track and trend less serious events relating to product processing, such as fever during administration, fluid overload, etc. This practice may lead to significant process improvements within the cellular therapy program.

Cellular therapy products affected by biological product deviation(s) are released by the Processing Facility for use by the Clinical Program only when the benefit outweighs the risk to the patient and no alternative is available, although in some cases, the information is not known until after the administration of the product has occurred. The most common biological product deviations encountered involve products with a positive microbial culture or products from ineligible donors.

STANDARD:

D4.10.2 Investigation.

D4.10.2.1 A thorough investigation shall be conducted by the Processing Facility in collaboration with the Collection Facility and Clinical Program, as appropriate.

STANDARD:

D4.10.3 Documentation.

D4.10.3.1 Documentation shall include a description of the occurrence, the involved individuals and cellular therapy product(s), when the occurrence occurred, when and to whom the occurrence was reported, and the immediate actions taken.

Explanation:

As in the investigation, documentation of the involved individuals in any occurrence should not be punitive. This information should be used for investigation and trending purposes to identify potential corrective and preventive actions, such as the need for additional training, staff resources, etc.

STANDARD:

D4.10.3.2 All investigation reports shall be reviewed in a timely manner by the Processing Facility Director, Medical Director or designee, and the Quality Manager.

D4.10.3.3 Cumulative files of occurrences shall be maintained.

D4.10.3.4 Cumulative files shall include written investigation reports containing conclusions, follow-up, corrective and preventive actions, and a link to the record(s) of the involved cellular therapy products, donor(s), and recipient(s), if applicable.

Explanation:
If there is a complaint of product performance, delivery of service, or transmission of disease, it must be investigated and resolved. In this context, a complaint should be considered as information that implies the product or service did not meet quality specifications, failed to function as expected, or resulted in an adverse event or reactions for the recipient.

The FDA definition of a complaint is more restrictive and deals primarily with the transmission of a communicable disease likely due to the cellular therapy product or to a failure to comply with practices that might increase the risk of transmission of a communicable disease. Corrective action or process improvement must be implemented to prevent re-occurrence as defined by an SOP.

The inspector should review the complaint file and determine if corrective, preventive, or process improvement actions have been identified, implemented, and are adequate to prevent future occurrences, and that regulatory agencies have been notified where that is required.

Evidence:
The Processing Facility should be prepared to show examples of the cumulative files of occurrences that have occurred and been managed according to this process. If any deviations have been reported to a governmental agency, the report(s) should be available for inspector review.

Example(s):
Communication of occurrences, investigations, and conclusions may occur in many formats, such as reporting during a regularly scheduled QM meeting with inclusion in the meeting minutes. Alternatively, a separate report may be generated, distributed, and signed by the appropriate individuals, including the Processing Facility Director, Processing Facility Medical Director, and potentially the Clinical Program Director. As appropriate, some documentation should be included in specific cellular therapy product records related to specific incidents or reactions.

STANDARD:

D4.10.4 Reporting.

D4.10.4.1 When it is determined that a cellular therapy product has resulted in an adverse reaction, the reaction report and results of the investigation shall be made available to the donor's and recipient's physician, as applicable, other facilities participating in the manufacturing of the cellular therapy product, registries, and governmental agencies as required by applicable laws and regulations.

D4.10.4.2 Occurrences shall be reported to other facilities performing cellular therapy product functions on the affected cellular therapy product and to the appropriate regulatory and accrediting agencies, registries, grant agencies, sponsors, IRBs, or Ethics Committees.

Explanation:
The FDA defines an adverse reaction as an adverse event involving the transmission of a communicable disease, cellular therapy product contamination, or failure of the product's function and integrity if the adverse reaction a) is fatal, b) is life-threatening, c) results in permanent impairment of a body function or permanent damage to body structure, or d) necessitates medical or surgical intervention. Adverse reactions may also include unexpected reactions to the graft that are designated as possibly, probably, or definitely related. For suspected adverse reactions to administration of products, the results of investigation and any follow-up activities must be documented. Adverse reactions meeting the FDA definition of products regulated under GTP (allogeneic HPC, Apheresis and HPC, Cord Blood, T Cells) or GMP (products produced under IND or IDE) must be reported to FDA within their specified guidelines. Reporting to other oversight organizations may also be necessary (e.g., accrediting agencies, registries, grant agencies, and IRBs or Ethics Committees).

The EU Directive 2004/23/EU distinguishes between serious adverse events, which are incidents, errors etc., which have potential consequences, and serious adverse reactions, which are actual reactions in donor or recipient. Both must be documented and reported. "Serious adverse event" is defined as any untoward occurrence associated with the procurement, testing, processing, storage, and distribution of tissues and cells that might lead to the transmission of a communicable disease; to death or life threatening, disabling, or incapacitating conditions for patients; or which might result in or prolong hospitalization or morbidity. "Serious adverse reaction" means an unintended response, including a communicable disease, in the donor or in the recipient, associated with the procurement or application of tissues and cells that is fatal, life threatening, disabling, incapacitating, or which results in or prolongs hospitalization or morbidity.

EU Commission Directives 2006/17/EC and 2006/86/EC include equivalent requirements for non-conforming products.

If an unexpected or serious adverse reaction occurs due to cellular therapy product collection or administration, for which there is a reasonable possibility that the response may have been caused by the product, the report of the adverse reaction and its outcome and investigation should be communicated to all facilities associated with collection, processing, and/or administration of the

product. This includes graft failure. Usually the Clinical Program is responsible for making the initial report; however, each involved facility must participate in the investigation and evaluation of the potential cause, particularly related to its own SOPs that were involved.

Examples:

The following are examples of adverse events that must may need to be reported :

- Adverse events involving the transmission of communicable disease.
- Product contamination.
- Adverse reactions that are fatal, life threatening, result in permanent impairment of a body function or permanent damage to body structure, or necessitate medical or surgical intervention.

STANDARD:

D4.10.5 Corrective and preventive action.

D4.10.5.1 Appropriate action shall be implemented if indicated, including both short-term action to address the immediate problem and long-term action to prevent the problem from recurring.

D4.10.5.2 Follow-up audits of the effectiveness of corrective actions shall be performed in a timeframe as indicated in the investigative report.

Explanation:

All events may not require corrective and preventive action (CAPA). Follow up after implementation of CAPA plans is critical to ensure effectiveness. Lack of effectiveness would indicate need to continue further investigation of cause or other contributing circumstances and additional actions. Programs should define in their policies when events warrant CAPA plans along with their plan to audit the effectiveness of the changes.

Investigations and corrective actions should, at a minimum, address:

- Identification of the involved individuals and/or cellular therapy product affected and a description of its disposition, where relevant,
- The date and time of the event,
- The nature of the problem requiring corrective action,
- To whom the event was reported,
- A description of the immediate corrective action taken,
- The date(s) of implementation of the corrective action, and
- Follow-up of the effectiveness of the corrective action, where relevant.

STANDARD:

D4.10.5.3 Investigations shall identify the root cause and a plan for short- and long-term corrective and preventive actions as warranted.

Explanation:

It is critical to investigate cause(s) of occurrences that pose significant risk or severity, and to establish and determine what corrective and preventive action will most likely be effective. The focus of the investigation should be to learn and improve, not to cast blame or be punitive. Often "systems" play a role in causation. Collection Facilities should be encouraged to stratify events according to risk or severity, and invest more time and energy into management of the more critical issues. Only an understanding of cause allows creation and implementation of new or revised systems, or controlled documents that will correct the issue and may prevent recurrence.

STANDARD:

D4.11 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for cellular therapy product tracking and tracing that allow tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

Explanation:

The Processing Facility must document a policy or SOP for tracking and traceability of each cellular therapy product through all steps from collection to administration or final disposition. Documentation in the medical record should include the proper product name, unique product identifier (ISBT 128 donation identification number or DIN, or Single European Code or SEC), content of the cellular therapy product, identification of the donor including medical record numbers, unrelated donor registry identifiers including Global Registry Identifier for Donors (GRID), allogeneic donor eligibility status, and the unique identity of the intended recipient including registry identifiers, where appropriate. There must be a process, including the use of the ISBT128 barcode or other barcode or unique numbering system, to track and trace specimens removed from a cellular therapy product for testing at an external facility such as an HLA testing facility, transfusion service, or microbiology laboratory. This process must ensure linkage between the results of testing and the original product. There should also be a means, direct or indirect, that will allow outcome information to be related back to any other facilities involved in collection, processing, and distribution of the product. The final disposition of the product must be documented, whether the product was administered, destroyed, released, or used for research, remains in storage, or other disposition. The tracking and tracing system must comply with all applicable laws and regulations and the Standards.

Evidence:
The inspector should review examples of processing records including worksheets and reports and final product labels to determine if tracing and tracking from donor selection through final product disposition and recipient identification is possible. All critical steps should identify who performed the procedure and when they were completed. The Processing Facility must have a system in place to request information, if not initially provided, to identify manufacturing procedures performed by external facilities (e.g., gene modified cellular therapy product).

Example(s):
A Processing Facility may assign an ISBT 128 DIN as a unique product identifier upon reception of a cellular therapy product from an unrelated donor collection facility that does not use ISBT 128 labeling, as long as tracking and tracing from the donor to the recipient is possible (i.e., the unique product number assigned at the collection facility is recorded in the processing record to maintain the linkage).

Full implementation of ISBT 128 labeling ensures tracking and traceability of the cellular therapy product and associated pilot vials and segments in a Processing Facility. However, if a Processing Facility removes specimens from a cellular therapy product and sends these to an external laboratory such as an HLA testing laboratory or a transfusion service for testing, the laboratory information system at the testing laboratory might not be compatible with ISBT 128 barcodes. If the testing laboratory assigns a new laboratory or barcode number to these specimens, there must be a system to link the reports generated following testing to the original cellular therapy product.

STANDARD:
D4.12 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for actions to take in the event the Processing Facility's operations are interrupted.*

Explanation:
Processing Facilities need to be prepared for situations that may interrupt typical operations so that such interruptions do not adversely affect recipients, donors, or cellular therapy products. While a policy or SOP is required for addressing emergencies and disasters (see B5), the Processing Facility must have a plan for how to handle interruptions that do not rise to the disaster level. It is difficult to anticipate every possible situation that may occur. Therefore, the Standards do not require the facility to outline actions for specific events; rather, the facility is required to describe actions to take when an interruption presents, including who needs to be contacted, how to prioritize cases, and key personnel to be involved in identifying alternative steps to continue functions, and notification of staff.

A contingency plan specific to the program would convey evidence that risk has been assessed for program-defined potential events of varying impact, such as a failure of the scheduling system, a water supply interruption, or shortage of a reagent. The plan should reflect differences between specific program needs and general hospital needs, and complement the hospital plan.

As more and more of the Processing Facility's documents exist on an electronic platform, there is increasing risk of temporary or permanent document loss. The institutional Information Technology Department generally confirms that software in use is validated for its function, and that there is a regular schedule of back up to allow for retrieval of information when necessary.

Freestanding facilities, as well as programs utilizing desktop storage, must have a plan to create a similar level of security. In either case, the program also needs a method to produce current versions of critical documents, such as preprinted orders, consent forms, SOPs, etc., when the electronic format is not available.

Policies, SOPs and associated worksheets and forms must be available to Processing Facility staff at all times. Arrangements must be made so that these documents are available in the event that the computer system goes down. Staff should have periodic training and review of alternate systems so they will be competent in the use of these systems should the need arise.

Evidence:
The inspector should review policies and forms to be used in case the electronic record keeping system is unavailable. The inspector should determine if cellular therapy products can be produced to the same standard of quality even if the electronic records are not available.

Example(s):
Examples include malfunctioning electronic records systems, drug shortages, power outages, equipment failures, supply shortages, etc. A contingency procedure would identify alternative sources of supplies, alternative supplies, and/or alternative preparative regimens.

In the example of failed electronic record systems, a Processing Facility may create hard copies of reports from the system that are periodically produced to be used as a manual record. There may also be forms to be completed that mimic entry screens. When calculations are utilized, there should be documentation of staff competency in performing these calculations manually in the event that the electronic system is unavailable.

STANDARD:

D4.13 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for qualification of critical manufacturers, vendors, supplies, reagents, equipment, facilities, and services.*

Explanation:
Quality can be maintained only if there is control over critical manufactures, vendors, equipment, supplies, reagents, services and the facility itself. Control of the manufacturing process can be attained by establishing minimal acceptance criteria for the reagents, materials, and supplies used in processing, and by maintenance and calibration schedules for equipment used to safeguard their proper performance as defined by an SOP (see D5.1).

The QM Plan must include a process to qualify reagents and supplies to safeguard their consistent function in validated procedures. This process must include the establishment of minimal standards for the acceptance of critical supplies and reagents and must document that those standards are met before they are made available for use. Even if supplies, reagents, and equipment are qualified, the manner in which they are used must also be qualified to prevent product mix-ups, contamination, or cross-contamination.

For further definitions and examples of qualification , see the JACIE *Quality Management Guide* (www.jacie.org/document-centre) or the FACT *Quality Handbook* (http://factwebsite.org/qm).

STANDARD:

D4.13.1 *Reagents that are not the appropriate grade shall undergo qualification for the intended use.*

D4.13.2 *Qualification plans shall include minimum acceptance criteria for performance.*

D4.13.3 *Qualification plans, results, and reports shall be reviewed and approved by the Quality Manager and Processing Facility Director or designee.*

Explanation:
A plan for qualification must be reviewed and approved prior to performing a qualification. Qualification of critical items should include:

- Design Qualification (DQ).
- Installation Qualification (IQ).
- Operation Qualification (OQ).
- Performance Qualification (PQ).

The qualification plan should be reviewed after the qualification to determine if all acceptance criteria were met. This process must include the establishment of minimal standards for the acceptance and must document that those criteria are met before use.

The Processing Facility must have a system in place that confirms that vendors provide materials in a timely and consistent manner that meets their acceptance criteria. Supplier qualification must also confirm that vendors are compliant with applicable governmental laws and regulations and that there is a system in place that is consistent with the Standards, such that they can demonstrate process control. Suppliers of laboratory services, such as the Flow Cytometry Laboratory or the Microbiology Laboratory that provides product testing, must also be qualified.

Evidence:
The inspector should find evidence of qualification of manufactures, vendors, supplies, equipment, facilities, services, and critical reagents . Qualification procedures should include instructions for requalification and under which circumstances qualification is required.

Example(s):
There are several ways to qualify a vendor of supplies, reagents, and services. The most effective is to perform an audit of the provider. Other, often more practical, methods may include one or more of the following:

- A review of third-party assessments by accrediting organizations such as FACT, JACIE, AABB, CAP or others.
- Remote audits by questionnaire.
- An ongoing dialog of resolution of service complaints or suggested process improvements.
- The sharing of internal audit findings and implemented corrective action plans from the provider back to the facility as evidence that deficiencies have been recognized and corrected.
- A documented review of the suppliers' past performance history.

Suppliers with pre-existing service agreements preceding the implementation of this standard can be qualified as meeting expectations by a retrospective review of the quality of service provided. Documentation, in the form of a brief written statement, that the service provider has met the Facility's requirements and worked with the facility to identify the cause of service failures and taken corrective actions in the past may serve as documentation of service provider qualification.
Critical reagents and supplies, that come into contact with donors, recipients, or cellular therapy products shall be sterile and approved for human use (appropriate grade for intended use).

Qualification of a readily used reagent in the field (e.g., ACD, NaCl, Plasmalyte) may consist of documented evidence of inspection of the reagent for discoloration and/or damage, use before the expiration date, and review of Certificates of Analysis prior to use.

Equipment qualification is performed to establish that equipment and ancillary systems are capable of consistently operating within established limits and tolerances. An example might be the qualification of a new controlled rate freezer.

Facility qualification is based on the level of manufacturing in the facility; and may range from a risk assessment to a full facility GMP qualification based on SOP and regulatory requirements.

STANDARD:

D4.14 The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for validation or verification of critical procedures.

D4.14.1 Critical procedures to be validated shall include at least the following: processing techniques, cryopreservation procedures, testing, labeling, storage, and distribution.

D4.14.2 Each validation shall include at a minimum:

D4.14.2.1 An approved validation plan, including conditions to be validated.

D4.14.2.2 Acceptance criteria.

D4.14.2.3 Data collection.

D4.14.2.4 Evaluation of data.

D4.14.2.5 Summary of results.

D4.14.2.6 References, if applicable.

D4.14.2.7 Review and approval of the validation plan, validation report, and conclusion by the Quality Manager and the Processing Facility Director or designee.

Explanation:

Validation is confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. A process (or SOP) is validated by establishing by objective evidence that the process consistently produces a cellular therapy product meeting predetermined acceptance criteria. Validations can be performed prospectively, concurrently or retrospectively.

Verification is the confirmation of the accuracy of something or that specified requirements have been fulfilled. Verification differs from validation in that validation determines that the process performs as expected whereas one verifies that the products of a process meet the required conditions.

Validation studies should be performed according to a validation SOP, utilizing a consistent format for approval of the validation plan, conduct of the studies, collection and documentation of results, data analysis, conclusions, and approval of the studies. A validation study performed because of a proposed change in a process or SOP shall include a documented assessment of the risk involved in the change to donor and recipient welfare and the quality and safety of cellular therapy products.

The design of the validation study should be adequate to determine if the process reproducibly achieves the purpose for which it is intended. The validation plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. Any change in the planned study that occurs during the study requires explanation. There should be an explanation, follow-up, and/or repeat of any test that fails to meet the expected outcome.

Validation should confirm acceptable endpoints can be achieved while maintaining purity, potency and safety of the cellular therapy product. Examples of acceptable endpoints may include nucleated cell recovery, viability, sterility, and red cell reduction.

In the Processing Facility, the following should be validated or verified:

- Processing procedures. All processing procedures must be validated. However, a published procedure adopted from another processing facility (e.g., hetastarch sedimentation for RBC depletion) may be verified so long as the conditions under which it is used are like those validated elsewhere.
- The intended use of equipment used for processing, release testing, or transport. The introduction of a piece of equipment such as a controlled rate freezer of the same model as already present in the facility would generally require a verification study, whereas the introduction of a different model or a model from a different manufacture would require a more extensive validation study.
- The intended use of reagents made on site and those not approved for clinical use. One would validate that a novel reagent used for RBC removal depletes RBCs to the required degree under all the conditions and for all the products that one would use the reagent for, but would then qualify each new lot of the reagent under more limited testing to safeguard its function.
- Labels. The validation of the label would demonstrate that the labels in use were checked against an approved template, were approved for use, maintain integrity during use, remain affixed or attached as required, are readable, do not contain any blank data points, and do include all of the required elements as listed on the label table (see Appendix II). Validation of the labeling process should demonstrate completeness and correctness of each data point, as well as the accuracy of data as shown by traceability and trackability of the product from donor to recipient or final disposition.
- Storage of the cellular therapy products prior to distribution
- Distribution of the product. This may include transported or shipped within or between facilities.
- Electronic records system, if applicable.

It is not the intent of the Standards to include hospital-based systems and clinical medical records. For further guidance see Standard D13.

When possible, reagents that have been approved for clinical use should be used for processing cellular therapy products. When this is not possible, a validation study must be performed using mock products with known values to document that the reagent or supply meets acceptable endpoints and does not cause harm to the product (purity, potency and safety) or the recipient of the product. Examples of acceptable endpoints may include but are not limited to nucleated cell recovery, viability, sterility, and red cell reduction.

Supplies or reagents not approved for human clinical use, or not for their intended use, may be used if:

- The supplies or reagents are specified in a SOP that has received Institutional Review Board (IRB) approval at the institution requesting FACT accreditation and/or Investigational New Drug or Device exemption from the FDA,
- The SOP that includes the specified supplies or reagents has been used in IRB-approved clinical trials and has been established in the medical literature to be acceptable for the purpose specified, or
- Appropriately qualified or validated.

Evidence:
The inspector should ask to see the SOPs for conducting validation studies and review a sample of validation studies. The inspector should note that studies are properly designed, objectively collect the required data, that outcome and intended actions are summarized, and that both the finalized plan and report are reviewed and approved by the Processing Facility Director and Quality Manager.

Example(s):
A change of reagents used for processing, such as cryopreservation, would need to be validated to verify cellular therapy product nucleated cell recovery, viability, sterility and potency are maintained at acceptable limits. The potential for adverse reactions and comparison of times to engraftment should also be examined.

Another example of a change that would need to be validated is a change to a different method of red cell reduction. Documentation of red cell content remaining in the products tested as well as confirmation of acceptable endpoints such as nucleated cell recovery and viability should also be included in evaluation of the new method.

For further definitions and examples of validation, see the JACIE Quality Management Guide (www.jacie.org/document-centre) or the FACT Quality Handbook (http://factwebsite.org/qm).

STANDARD:

D4.15 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for risk assessment in document control, change control, occurrence investigations, qualification, and validation.*

D4.15.1 *Changes to a process shall include evaluation of risk to confirm that the changes do not create an adverse impact or inherent risk elsewhere in the operation and shall be validated or verified as appropriate.*

Explanation:

Risk assessment is a process to assess and document the risks involved in a change in a practice, process, SOP, or environment that has the potential to affect a critical procedure; direct patient care; and/or the cellular therapy product integrity, sterility, viability, and/or recovery. Risk assessment shall be completed for changes in processes to critical procedures including collection, labeling, and storage.

Risk assessment is a process that may be documented in a validation plan or exist as a separate document and should include:

- Identification of a risk.
- Context.
- Evaluation.
- Risk assessment and impact.
- Management response.

Evidence:

The inspector should ask to see the SOP for risk assessment for changes to a practice, process, SOP, or environment and preferably an example of how it has been applied.

Example(s):

Identification of a risk can be made by providing a description of a potential or known risk. Establishing the context or scope means all the possible risks are identified and the possible ramifications or impact in all areas are analyzed thoroughly. Once the context or scope has been established successfully, the next step is identification and evaluation of potential risks either source or effect. During source analysis, the source of risks is analyzed and appropriate mitigation measures are put in place. This risk source could be either internal or external to the system. During problem analysis the effect rather than the cause of the risk is analyzed.

A general description of the issue and identity of the specific risk(s) should be included. After the risk(s) has been identified, it must be assessed on the potential of criticality or on their likelihood of occurrence and the potential impact including quantitative and qualitative evaluation. Risk prioritization is when the 'likelihood of occurrence × impact' is equal to risk.

There are many different approaches to calculating risk, and there are tools that can help assist in defining the probability of the effect occurring, the root cause, effects and magnitude of risk under different scenarios.

Once the risk assessment is established then a risk management plan can be developed and implemented. It comprises of the effective controls for mitigation of risk. Risk Management includes justification and rationale for accepting the risk and how to manage the impact if applicable. This can often be established in a simple one-page document for change with low impact and risk. An example might be a change in using another reagent or supply item of suitable grade.

Below is a risk assessment matrix that combines the concept of likelihood and severity. This may be useful for programs to utilize when assessing risk:

Risk Matrix		Probability (Likelihood of occurrence)		
		Occasional (Possible to occur in time, if not corrected)	**Likely** (Will probably occur in most circumstances)	**Frequent** (Expected to occur in most circumstances)
Severity of Incidence	**Minor** (low risk to the product or patient)	**Low (1)**	**Low (1)**	**Medium (2)**
	Moderate (Probable risk to product or patient)	**Medium (2)**	**Medium (2)**	**High (3)**
	Major (High risk to product or patient)	**High (3)**	**High (3)**	**High (3)**

STANDARDS

D4.16 *The Quality Management Plan shall include, or summarize and reference, policies and Standard Operating Procedures for obtaining feedback from associated Clinical and Collection Facilities.*

Explanation:

Feedback (including complaints) from donors, recipients, and legally authorized representatives may be obtained directly by the Processing Facility; however, it is also acceptable to use a hospital-wide system, such as patient satisfaction surveys, as long as the cellular therapy program is included and relevant issues can be readily identified.

STANDARD:

D4.17 *The Processing Facility Director or designee shall review the quality management activities with representatives in key positions in all elements of the cellular therapy program, at a minimum, quarterly.*

D4.17.1 Key performance data and review findings shall be reported to staff.

D4.17.2 The meetings should have defined attendees, documented minutes, and assigned actions.

Explanation:
QM activities shall be reported, at a minimum, quarterly to review the performance of the QM Program and its objectives. This is to determine whether the elements in the QM Plan are relevant and effective, and necessary actions are taken in a timely manner.

The frequency for data collection and analysis should be established in the QM Plan. Some indicators may be reported with each audit while others may be retrospectively analyzed and reported at defined intervals. The data should be analyzed, assessed, and trended over time to identify improvement opportunities on a regular basis, such as at each QM meeting. Strategies to effect improvement should be identified and implemented. The results of these implemented strategies should be measured and the improvement strategies either continued or new alternatives developed depending on the results.

Multidisciplinary meetings involve several academic disciplines or key personnel in an approach to make recommendations to a topic or problem.

The minutes and attendance list of regularly scheduled QM meetings are effective ways to document QM activities and communication of quality assessments to key individuals within participating facilities in the cellular therapy program.

Evidence:
The inspector should ask to see evidence that the outcome of quality assessments is communicated to key individuals within all participating entities in the cellular therapy program. The inspector should ask to see the minutes of the QM meetings, which should document who was in attendance and what topics were covered. At a renewal inspection, it is particularly important to ask for QM meeting minutes that represent the time since the previous accreditation in order to determine that the QM Program is and has been ongoing. Minutes should summarize activities such as training performed, documents reviewed, audits performed, and SOPs introduced or revised.

STANDARD:

D4.17.3 The Processing Facility Director or designee shall not have oversight of his/her own work if this person also performs other tasks in the Processing Facility.

Explanation:
Any person responsible for overseeing the QM activities should not be directly responsible for review of work solely performed by that person. It is important that the final review be non-biased, and that there has been sufficient time away from the work for the review to be objective. Alternatively, in small facilities where there may be only one person responsible for most of the processing activity, the Processing Facility Director, Processing Facility Medical Director, or a person from the Clinical Program or Collection Facility may be designated for review of these activities. It may be acceptable, however, for an individual to review his/her own work at a time and place removed from the actual performance of the work.

STANDARD:

D4.18 *The Processing Facility Director or designee shall annually review the effectiveness of the Quality Management Program.*

D4.18.1 *The annual report and documentation of the review findings shall be made available to staff, the Clinical Program Director, and Collection Facility Director.*

Explanation:
The overall effectiveness of the QM Program must be reviewed and reported to staff on an annual basis. The annual report will provide a year-long view of the overall function of the QM Plan, its effect on and interactions with the Clinical Program and Collection Facility, and provide clues on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated. If the Processing Facility is part of an integrated cellular therapy program, a single annual report is sufficient.

The annual report should also contain trending information related to key indicators that are monitored, patient outcomes, patient satisfaction, adverse events, and other important elements utilizing data from prior years.

Example(s):
Processing Facility Directors may wish to report on the performance of the QM Plan more frequently than once a year. If so, the report should utilize some data from the previous 12 months to provide a longitudinal perspective of how the QM Plan is functioning over time. In addition to relevant measures addressed in B4.1.2, the Processing Facility may consider including the following measures:

- Product outcomes (cell counts, viabilities, recovery data, sterilities),
- Facility and environmental monitoring data, and
- Other events such as complaints or deviations.

D5: POLICIES AND STANDARD OPERATING PROCEDURES

STANDARD:

D5.1 *The Processing Facility shall establish and maintain policies or Standard Operating Procedures addressing critical aspects of operations and management in addition to those required in D4. These documents shall include all elements required by these Standards and shall address at a minimum:*

Explanation:

Each Processing Facility must have written policies and/or SOPs that comprehensively address all aspects of the facility. An SOP gives specific step-by-step instructions on how to perform a particular task. A policy describes a course of action or mission statement in more general terms. The Standards allow the facility to create its document hierarchy how it sees fit. The facility is not required to have both a policy and SOP for each item, nor is a dedicated policy and/or SOP required for each item on the list as long as each item is addressed somewhere within the appropriate document. The items listed in D5.1 include the minimum requirements; a facility may exceed these requirements, but not omit any of these.

Policies and SOPs must comply with the document control requirements listed in D4. Review and approval of all policies and SOPs shall be performed at the time of document creation, at each revision, and every two years thereafter.

Evidence:

When multiple topics are covered by a single SOP, it will aid the inspection process if the Processing Facility prepares a crosswalk between the list of required SOPs in Standard D5.1 and the facility's SOP Manual.

The inspector will be provided a Table of Contents for the SOP manual with the pre-inspection material. This Table of Contents must include all policies and SOPs required by the Standards under which the Processing Facility operates. The Table of Contents should be examined by the inspector for evidence of SOPs addressing each item before arriving at the inspection site. Prior confirmation that a specific SOP has been generated will reserve limited on-site inspection time for evidence of implementation of written SOPs and other activities that can only be verified in person at the inspection site.

If a Processing Facility is operated out of a transfusion service and shares certain SOPs or policies with the transfusion service, then an index of the shared SOPs and policies should also be submitted.

Example(s):

Policies and SOPs can be generated within the Processing Facility or in collaboration with other institutional infrastructures. The facility may have a policy in place for patient confidentiality. The policy would provide a general overview of institutional SOPs and guidelines in place for the entire institution for patient confidentiality.

Both FACT and JACIE published Quality Handbooks to provide additional explanation of quality principles. These handbooks can be used as additional resources to develop policies and SOPs in compliance with the Standards. The handbooks can be found on the FACT and JACIE websites.

STANDARD:

D5.1.1 *Donor and recipient confidentiality.*

D5.1.2 *Cellular therapy product receipt.*

D5.1.3 *Processing and process control.*

D5.1.4 *Processing of ABO-incompatible cellular therapy products to include a description of the indication for and processing methods to be used for red cell and plasma depletion.*

Example(s):
ABO incompatibility in relation to volume is a specific topic that requires dedicated training and competency assessment, as cellular therapy product issues are different among apheresis, marrow collection, cord blood collection, and others.

Similarly, cord blood preparation for administration requires clinicians have dedicated training and competency in providing proper orders for washing, diluting, or reducing red cells from the cellular therapy product.

STANDARD:

D5.1.5 *Prevention of mix-ups and cross-contamination.*

D5.1.6 *Labeling (including associated forms and samples).*

D5.1.7 *Cryopreservation and thawing.*

D5.1.8 *Cellular therapy product expiration dates.*

D5.1.9 *Cellular therapy product storage to include alternative storage if the primary storage device fails.*

D5.1.10 *Release and exceptional release.*

D5.1.11 *Transportation and shipping, including methods and conditions within the Processing Facility and to and from external facilities.*

Explanation:
Processing facilities must have an SOP for both transportation and shipping, even if the Processing Facility does not currently perform one of those distribution methods. A need may arise for transportation and/or shipping on an ad hoc basis.

STANDARD:

D5.1.12 *Cellular therapy product recall, to include a description of responsibilities and actions to be taken, and notification of appropriate regulatory agencies.*

D5.1.13 *Cellular therapy product disposal.*

D5.1.14 *Critical reagent and supply management.*

D5.1.15 *Equipment operation, maintenance, and monitoring including corrective actions in the event of failure.*

D5.1.16 *Recalls of equipment, supplies, and reagents.*

D5.1.17 *Cleaning and sanitation procedures including identification of the individuals responsible for the activities.*

D5.1.18 *Environmental control to include a description of the environmental monitoring plan.*

D5.1.19 *Hygiene and use of personal protective equipment and attire.*

D5.1.20 *Disposal of medical and biohazard waste.*

D5.1.21 *Emergency and disaster plan, including the Processing Facility response.*

Explanation:
SOPs addressing safety, infection control, biohazard disposal, radiation safety, and planned emergency response to disasters may be standardized throughout the institution. However, in cases such as an institutional disaster plan, such plans usually outline general actions to be taken. In situations where institutional policies and SOPs are utilized, there must be a defined mechanism for review and approval. The Processing Facility's disaster plan must include actions to be taken in case of a disaster (such as how to locate and use emergency power) and include specifics such as how to proceed if a product is undergoing cryopreservation at the moment of the disaster or what to do if products need to be moved. Examples of disasters include fires, hurricanes, floods, earthquakes, nuclear accidents, etc. In cases where institutional policies and SOPs are inadequate to meet the Standards or where there are issues that are specific to the facility, the facility must develop its own policies and SOPs.

Example(s):
The article *Preparing for the Unthinkable: Emergency Preparedness for the Hematopoietic Cell Transplant Program* (Wingard et all, 2006) provides a framework for disaster plans that can be customized for individual programs: http://www.ncbi.nlm.nih.gov/pubmed/17085317.

The U.S. Food and Drug Administration offers information on its webpage titled, "The Impact of Severe Weather Conditions on Biological Products," at
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ProductSecurity/ucm147243.htm.

STANDARD:
D5.2 *The Processing Facility shall maintain a detailed list of all controlled documents, including title and identifier.*

Explanation:
Controlled documents must be maintained in an organized fashion so that all current documents can be found. Many Processing Facilities have adopted an electronic method of compiling its controlled documents.

Evidence:
The detailed list should be organized in such a manner that the inspector can ascertain that the controlled documents are comprehensive and define all aspects of the Processing Facility.

Example(s):
A Processing Facility may choose to have one detailed list of controlled documents, or divide controlled documents into several manuals by subject. A technical procedure manual in conjunction with a quality, a policy, and a database manual may serve to better organize information if the program chooses this format.

STANDARD:
D5.3 *Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified staff to follow and complete the procedures successfully. Each individual procedure shall include:*

Explanation:
The policies and SOPs must be detailed, unambiguous, and adequately define all operational aspects of the Processing Facility. Policies in general identify an intended goal and include the elements required to meet that goal. However, policies may need one or more associated SOPs to actually describe the actions that are taken. The minimal elements must be included on all SOPs; if one of the items is not applicable, this should be indicated with N/A.

Evidence:
The inspector should review the Processing Facility's SOPs to verify that each of the items required in this standard are present in the individual SOPs.

Example(s):
In some Processing Facilities, the actual "SOP" may be limited to minimal work instructions, and required elements such as a reference list may be found only in higher level documents. Such variability is acceptable if all elements are documented and readily available to staff.

It may be prudent to attach one or more completed forms to illustrate possible real life scenarios. Reference to additional SOPs and policies necessary to perform a procedure is required as is a listing of worksheets, forms and/or other necessary documentation. For electronic systems, use of links would be acceptable.

A review signature on the document itself or on a listing of the reviewed documents by name that includes the unique identifier and version is acceptable to document review. A validated electronic review system is also acceptable. A single page in the manual with a signature and a date is not sufficient since SOPs may be revised throughout the year.

Adherence to a uniform format is required to maintain documents. The following template example may be utilized, as applicable, to include the minimum information found in Standard D5.3.:

Title Bar:

1. Title:
2. Date:
3. Effective Date:
4. Date Created:
5. Retired or Archival Date:
6. Revision and Revision Date:
7. Review Date:
8. Version Number:

Example format:

Institution Name and Address (include Logo, if required)		
Document Title	Pages:	
	Reference Number:	e.g., FACTStd #
Prepared by:	Date Created:	
CLIA Approver: (if appropriate)	Effective Date:	
Approved by:		

Document Body
1. Objectives:
   1.1. Principle:
   1.2. Purpose:
   1.3. Scope:
   1.4. Responsibilities:
   1.5. Definitions:
2. Required Materials and Supplies:
3. Acceptable End Points and Range of Expected Results:
   3.1. Acceptable endpoints
   3.2. Range of expected values or results
   3.3. Course of action that need to be taken when expectations are not met
4. Procedure:
5. Reference to other SOPs or policies required to perform procedure
6. References:
7. Required Approval Signatures:
8. Approval of document revisions:
9. Associated Documents (Forms, worksheets, reports, labels, etc.):

STANDARD:

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.*

Example(s):
The Processing Facility should establish a range of acceptable results, when appropriate, for each procedure. Examples include nucleated cell recovery, absolute CD34 cell counts, viability, hematocrit, sterility, DMSO concentration, and plasma volume. The range for a given parameter can be determined within the facility by retrospective analysis of its own data. Determination of a mean ± 1 or 2 standard deviations from such an analysis may be used to define an acceptable range.

STANDARD:

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 *Reference to a current version of orders, worksheets, reports, labels, and forms.*

D5.3.8 *The Processing Facility Director or Medical Director shall approve, prior to implementation, new or revised controlled documents.*

Explanation:
FACT-JACIE Standards require documented review of each SOP by the Processing Facility Director or by the Processing Facility Medical Director every two years for procedures that affect the clinical use of the product. For example, SOPs or policies for reporting adverse reactions to product administration or SOPs for reporting the results of microbial testing should be approved and reviewed by the Processing Facility Medical Director. It is important that the documentation of review every two years clearly indicates the version of each SOP or policy that was reviewed.

Copies of current versions of worksheets, reports, labels, and forms, where applicable, must be present and may be identified in or be attached to each SOP. The purpose of this standard is to confirm that these documents are easily accessible to a reader of the SOP and that it is clear what documents may be required for the performance of that SOP. Review of SOPs should include review of the applicable worksheets, forms, and attachments.

STANDARD:

D5.4 *Controlled documents relevant to processes being performed shall be readily available to the facility staff.*

Explanation:
The written copy or electronic version (with provisions for hard copies as necessary) of the Processing Facility's policies and SOPs relevant to the work schedule and duties must be immediately available to all relevant employees in their working environment. Similar to the ability to divide related SOPs into different SOP Manuals, facilities may choose to only have necessary SOPs to perform specified processes at a workstation. However, all SOPs that an employee must comply with must be readily available to him/her for reference when needed.

If an electronic manual is used, there must be a mechanism to obtain access to the SOPs at all times, even if the network is not available. Policies, SOPs, and associated worksheets, reports, and forms must be available to each staff member at all times. The current version of electronic documents should be accessible with proper access codes.

Evidence:
The written copy or electronic version of the SOPs should be readily identifiable and available to the inspector. The inspector should expect to see the appropriate SOPs or electronic access to SOPs in all performance areas of the Processing Facility. The inspector should look for evidence that procedures are performed as written in the SOPs.

STANDARD:
D5.5 *Staff training and, if appropriate, competency shall be documented before performing a new or revised Standard Operating Procedure.*

Explanation:
Before a staff member is allowed to perform new and revised policies and SOPs, he/she must have reviewed and/or received training on the new document prior to performing the procedure. Processing Facilities are not required to train all staff members before implementing a new policy or SOP, but must document an individual's review and/or training before that person uses the revised policy or SOP.

Example(s):
Sometimes a revision to a policy or SOP is minor, such as an update to a referenced regulation or grammatical corrections. In these cases, full training may not be necessary. Review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

It is recommended that there be a specific signoff sheet for every policy and SOP and associated revisions to document that each staff member required to review a policy or procedural revision has done so prior to performing the tasks described. This could be done via an electronic system that identifies users and records their activity on the system. Training guides specific to each SOP and to any major revision also facilitate documentation of appropriate training of staff.

STANDARD:
D5.6 *All personnel shall follow the Standard Operating Procedures related to their positions.*

D5.7 *Planned deviations shall be pre-approved by the Processing Facility Director and/or Medical Director, and reviewed by the Quality Manager.*

Explanation:
Planned deviations should be approved within a peer-review process (i.e., more than one individual), but approval from the Processing Facility Director is required at a minimum. Processes set up for review of variances are not appropriate for emergency situations. Emergencies are not planned and should be addressed immediately. Retrospective review must be performed in compliance with processes designed for deviations.

D6: EQUIPMENT, SUPPLIES, AND REAGENTS

STANDARD:

D6.1 *Equipment, supplies, and reagents used to process cellular therapy products shall be qualified and used in a manner that maintains product function and integrity and minimizes risks of product mix-ups, contamination, and cross-contamination.*

D6.2 *Supplies and reagents used in processing, testing, cryopreservation, and storage shall be controlled by a materials management system that includes requirements for the following at a minimum:*

D6.2.1 *Visual examination of each supply and reagent used to manufacture cellular therapy products for damage or evidence of contamination upon receipt and acceptance into inventory.*

D6.2.2 *Records of receipt that shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and expiration date.*

D6.2.3 *Storage of materials under the appropriate environmental conditions in a secure, sanitary, and orderly manner to prevent mix up or unintended use.*

Explanation:
Once received, supplies and reagents used for processing must be stored in a manner that preserves their function and sterility. Evaluation of the storage during transport should also be included. For items requiring storage at defined specifications such as temperature and humidity, the conditions of the storage area must be monitored and documented.

Evidence:
The inspector should observe storage areas and confirm that supplies and reagents are stored under the conditions specified by the manufacturer. The inspector should confirm that the storage area is clean and sanitary and that suitability for use of supplies and reagents is not compromised during storage.

When refrigerators and freezers are used to store cellular therapy products, supplies, and/or reagents, the inspector should look for evidence that each is appropriately labeled and adequately separated so as not to cause confusion or compromise the integrity or sterility of the contents.

Example(s):
This can be accomplished by storing cellular therapy products on a designated shelf that is appropriately labeled for that purpose, utilizing designated labeled compartments, or by other procedures. It is recommended that outdated supplies and reagents and those not intended for clinical use be stored in a separate unit from those designated for patient care if possible. When this is not possible, outdated and/or research material must be clearly distinguished from clinical material and appropriately labeled.

STANDARD:

D6.2.4 Use of supplies and reagents coming into contact with cellular therapy products during processing, storage, and/or administration that are sterile and of the appropriate grade for the intended use.

Explanation:
Supplies and reagents that come into contact with cellular therapy products must be clinical or pharmaceutical grade, as appropriate, and free of microbial contamination. It is recognized that reagents not approved for human use were commonly used in the past, for example, the use of various tissue culture media. However, Processing Facilities are expected to keep up to date on current manufacturing techniques. For simple, routine processing and cryopreservation of HPC, several alternative reagents that are of clinical or pharmaceutical grade have been identified, and results of the studies utilizing these reagents have been published in the peer-reviewed medical literature for over 20 years.

A Processing Facility can become compliant with this standard by reviewing literature for alternatives or asking other Processing Facilities about their techniques. If no suitable, equivalent substitute can be identified for the specified purpose, the reagent must be qualified (see D4.13 and its guidance).

Evidence:
The inspector should request certificates of analysis (COA) or manufacturer documentation that the supply or reagent meets pre-determined specifications.

Example(s):
Examples include a COA for dimethyl sulfoxide or the manufacturer's certification of sterility.

STANDARD:

D6.2.4.1 Reagents shall undergo initial qualification, validation for the intended use, and additional qualification and validation upon significant changes.

D6.2.4.2 Where there are no suitable clinical or pharmaceutical grade reagents available, reagents shall undergo lot-to-lot functional verification.

D6.2.4.3 Lot-to-lot functional verification shall include acceptance criteria to confirm that new lots perform as expected compared to the previous lots.

Explanation:
There is no specific definition of what makes a reagent clinical or pharmaceutical grade. Therefore, the Processing Facility must review package inserts, labeling, and Certificates of Analysis (COA) in the context of cellular therapy to determine if the reagents will maintain the integrity of the cellular therapy product and the safety of the recipient.

Typically, reagents of clinical or pharmaceutical grade comply with the United States Pharmocopeia (USP) or EU-Pharmocopeia (Ph.Eur.) requirements and are manufactured in compliance with GMPs. For these reagents, initial qualification and validation for the intended use is required. As with all significant changes to materials or procedures, any significant change to a reagent (different reagent, different manufacturer, etc.) requires additional qualification and validation to demonstrate there are no adverse effects to processes.

Where there are no suitable clinical or pharmaceutical grade reagents available for the processing that is being conducted, or when reagents are being used under approved research purposes, Processing Facilities must perform more extensive qualification that demonstrates that the reagent is the only option available, safe for the intended use, and approved by the applicable regulatory authority. This may include:

- Use under IND, IDE, or other exceptions approved by the appropriate regulatory agency.
- Evidence of extensive experience with the reagent and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.
- Extensive literature supporting use of the reagent for the specified purpose and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.

If a reagent is not clinical or pharmaceutical grade, it must be of the highest grade (or purity) available and the Processing Facility must validate that the reagent is safe and effective for the specified purpose.

Reagents, including DMSO, that are not clinical or pharmaceutical grade or do not have regulatory approval (such as a license), must undergo lot-to-lot functional qualification. DMSO is specifically mentioned because it is a critical reagent that actually performs a function (i.e., it protects the cells themselves). Should a lot of DMSO not function as it is supposed to, there would be dire consequences to the cellular therapy product and its intended recipient.

Evidence:
To determine the grade of a reagent, the inspector can look at the label (including package inserts) and COAs. Labels may use different verbiage depending on the scope of the regulatory approval, but typically will provide enough information to determine whether the reagent requires additional or lot-to-lot qualification.

Example(s):
Qualification of a reagent used in processing (washing, freezing, or other product manipulation) can often be achieved by review of the COA. This document should list contents and concentration of the reagent and state if the reagent is sterile and safe for human use. Examples of statements that are used on COAs of reagents considered to be of the appropriate grade include:

- "A Sterile and Endotoxin Free (According to Ph.Eur./USP) Non pyrogenic cryopreservative solution."
- "Complies with USP" or "Complies with Ph.Eur."

- "This batch complies with the specifications of the USP and Eur.Ph."
- "Grade: USP" or "Grade: Ph.Eur."
- "Cryoprotectant for the cryopreservation of human cells and tissues for transplantation."

When DMSO lot-to-lot qualification is required as described above, the study could be accomplished by reserving two extra, small samples from each of several cellular therapy products for comparison. This method requires a very small percentage of cells collected. One sample can be cryopreserved and the other would not. A comparison of the two can then be performed to determine the effects of the DMSO. Advantages of this method are that no normal donors are required, no patient is at risk, and qualification data can be obtained. Generally, IRBs or ethics committees do not consider reagent qualification to be research, so special donor or recipient consent is not normally required. This would need to be confirmed with local requirements.

STANDARD:

D6.2.5 Cleaning and sterilizing of non-disposable supplies or instruments using a procedure verified to remove infectious agents and other contaminants.

Explanation:
For some specialized processing procedures, equipment or instruments that come into contact with the cellular therapy product may require cleaning and sterilization between uses. When this is the case, the Processing Facility must verify that the cleaning and sterilization methods used remove infectious agents.

Evidence:
The inspector should review the records of this verification process.

Example(s):
Surgical equipment for tissue manipulation such as scissors, forceps, scalpel handles, etc., are examples of non-disposable supplies or instruments that may be included in processing procedures.

STANDARD:

D6.2.6 Use of supplies and reagents in a manner consistent with manufacturer instructions.

Explanation:
It is recognized that reagents typically utilized in processing may be used for indications that are not specifically indicated on the manufacturer's instructions. In these cases, "consistent with manufacturer's instructions" would include considerations such as sterility and final mode of administration, and could be compliant with this requirement.

Evidence:
The inspector should request and review product package inserts and supply and reagent information that describes the supply or reagent and its intended use.

Example(s):
Package inserts from supplies and reagents such as antibodies, serum components, or packaging supplies would meet this requirement.

STANDARD:

D6.2.7 Process to prevent the use of expired reagents and supplies.

Explanation:
There should be a mechanism to monitor the flow of supplies and reagents within the Processing Facility to prevent the use of outdated supplies and reagents. This system should also be able to identify the location of a given lot of a supply or reagent in the event that there is a manufacturing recall.

Evidence:
The inspector should evaluate the inventory control system to determine if it is adequate to prevent the use of outdated or damaged supplies and reagents.

Example(s):
A first expired, first out system is one that is most commonly encountered. This mechanism can be tracked on paper or via a computer program.

STANDARD:

D6.3 There shall be a system to uniquely identify and track all critical equipment used in the processing of cellular therapy products. The system shall identify each cellular therapy product for which the equipment was used.

Explanation:
Cellular therapy product quality, as measured by adequate viability, integrity, lack of microbial contamination, or lack of cross-contamination may be affected by the equipment used for processing. Therefore, equipment used in processing must be identified and tracked. For this purpose, there must be a system by which the critical equipment can be uniquely identified.

It is also important that the system in use allows for the identification of all cellular therapy products processed using a given piece of critical equipment. An identifier must be assigned to critical equipment even if there is only one in the Processing Facility.

Evidence:
The inspector should request documentation that demonstrates that critical equipment is numbered in a consistent fashion, that the use of the equipment is tracked by some mechanism (usually date and time of use) as appropriate, and that the equipment can be traced back to each cellular therapy product that was processed using the equipment.

Example(s):
This can be achieved by using a pre-existing serial number, but may be better achieved by assigning a unique identifier that is visible on the piece of equipment. A more casual designation, such as "Brand X centrifuge," may be less desirable since over the course of time more than one centrifuge might fit that description. A reagent/consumables log in the processing record could be used.

STANDARD:

D6.4 *Equipment used in cellular therapy product processing, testing, cryopreservation, storage, and distribution shall be maintained in a clean and orderly manner and located to facilitate cleaning, sanitation, calibration, and maintenance according to established schedules.*

D6.5 *The equipment shall be inspected for cleanliness and verified to be in compliance with the maintenance schedule prior to use.*

Explanation:
Equipment used for processing or cellular therapy product testing must be located so as to allow access for maintenance and calibration at Processing Facility-described intervals. It is also important to maintain a schedule of equipment cleaning, sanitation, and disinfection that is described by an SOP (see D5.1).

The Processing Facility must perform a risk assessment (at a minimum to include the manufacturer's recommendations) of its equipment to determine how often the maintenance schedule must be reviewed and how compliance will be documented. Risk assessment is a process to assess and document the risks involved in a change in a practice, process, SOP, or environment that has the potential to affect a critical procedure; direct patient care; and/or cellular therapy product integrity, sterility, viability, and/or recovery.

Evidence:
The inspector should verify that equipment is evaluated for cleanliness and that maintenance records have been reviewed for compliance prior to use. The inspector should confirm by visual inspection that equipment can be easily accessed for cleaning, disinfection, and maintenance.

Example(s):
The Processing Facility should define in their policies and SOPs, the maintenance schedule for each piece of equipment used. A risk-based approached can be used when determining which items need to be inspected prior to each use, or after a defined number of consecutive uses (e.g., after every 10 uses). Manufacturers recommendations should always be followed, at a minimum.

STANDARD:

D6.6 *The equipment shall be standardized and calibrated on a regularly scheduled basis and after a critical repair or move as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.*

Explanation:
Equipment SOPs must also describe how the equipment is operated or refer to relevant operations manuals that are available within the Processing Facility. Maintenance and calibration are required to detect malfunctions and defects and to safeguard that the critical parameters are maintained within acceptable limits at all times. There must be a schedule for equipment maintenance and quality control.

Logs should be available near the equipment, or tags or stickers should be visible on the equipment, indicating that calibration parameters have been met, the date preventive maintenance and calibration were performed, and when such testing is next due. Where applicable, calibration procedures should include limits for accuracy and precision.

Evidence:
On site, the inspector should see a sampling of calibration records and confirm that traceable standards have been used. The inspector should look for SOP(s) describing the corrective action to be taken when precision and accuracy limits are not met, and written instructions to be followed if the equipment fails (see D5.1). Records to document these activities, including investigation of potential adverse events caused by cellular therapy products, should be available to the inspector.

Example(s):
Schedules may vary among Processing Facilities, based on frequency of use, performance stability, or recommendations from the manufacturer. It is recommended that recent records of regularly scheduled maintenance and QC be readily available for each piece of equipment.

STANDARD:

D6.6.1 *All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.*

Explanation:
Equipment identified by the Processing Facility to have a critical measuring function, such as thermometers, timers, and scales, must be calibrated against a traceable standard. A traceable standard is one that can be directly linked to a provider that has documented the accuracy of the measuring device.

Example(s):
Examples of traceable standards include National Institute of Standards and Technology (NIST) reference thermometers, stop watches, and tachometers. Other vendors may provide similar products but they must have a direct link to records indicating accuracy to a known standard. An alternative to using the actual traceable standard is to calibrate a similar device against the traceable standard and use the newly qualified device for routine measurements. If a traceable standard cannot be obtained, then the Processing Facility must document how they determined the measurement reading to be accurate.

STANDARD:

D6.6.2 *When equipment is found to be out of calibration or specification, there shall be a defined process for action required for cellular therapy products manufactured since the last calibration.*

Explanation:

When equipment is found to be out of calibration or specification, the validity of previous measurements and decisions based on those measurements should be reviewed. There should be documentation that the cellular therapy products manufactured during this period of uncertainty have been evaluated and determined to be conforming to specification or corrective action has been documented. This should include an investigation of potential adverse events to manufactured products using the equipment tracking system. Note that if critical equipment used in processing is located outside of the Processing Facility, such as sterilization equipment, it is the facility's responsibility to confirm that equipment is properly maintained and calibrated.

STANDARD:

D6.7 *There shall be a Standard Operating Procedure that addresses the actions to take in the event of equipment malfunction or failure.*

D6.8 *Equipment shall conform to applicable laws and regulations.*

Evidence:

Where applicable, the inspector should review documentation of relevant regulation for CE/UL marking.

Example(s):

An example of appropriate equipment marking is UL testing certification for a water bath/circulator.

European Directive 2006/17/EC Annex IV 1.3.10 specifies that where possible, equipment that is compliant with the CE Marking Directive must be used for cellular therapy product processing. CE marking is a declaration by the manufacturer that the product meets all the appropriate provisions of the relevant legislation implementing certain directives. Staff using such equipment must have appropriate training. For additional guidelines regarding this requirement, visit http://ec.europa.eu/.

In the U.S., Nationally Recognized Testing Laboratories (NRTL) are testing facilities recognized by OSHA and are primarily private-sector organizations that provide product safety testing and certification services to manufacturers. Underwriters Laboratories Inc. (UL), a recognized NRTL, is one such independent, not-for-profit product safety testing and certification organization that issues UL marks and certifications.

NRTLs cooperate with code authorities (e.g., building, electrical, fire, plumbing) to safeguard that the equipment installations they authorize will be safe for community use. For example, the UL Mark indicates compliance with the applicable safety requirements in effect in North America and is evidence of UL certification, which is accepted by model North American installation codes such as the National Electrical Code (NEC) and the Canadian Electrical Code.

In contrast, the CE Marking is not a safety certification mark, is generally based on self-declaration rather than third-party certification (e.g., NRTLs), and does not demonstrate compliance to North American safety standards or installation codes. A product that bears a CE Marking may also bear a certification mark such as a UL Listing Mark. However, the CE Marking and the UL Mark are not associated. For more information, visit:
http://www.osha.gov/dts/otpca/nrtl/index.html.

STANDARD:

D6.9 Lot numbers, expiration dates, and manufacturers of critical reagents and supplies and identification of key equipment used in each procedure shall be documented.

Explanation:

There must also be a complete record of lot numbers and expiration dates for reagents and disposables used for the procedure. Likewise, the identity of the key equipment used during processing must also be documented. It is critical to be able to link reagents, supplies, and equipment to the processing of each cellular therapy product in the case of an adverse event or recall of reagents, supplies, and/or equipment. Implementation of a carefully planned inventory control system helps to facilitate documentation of lot numbers; prevention of the use of outdated or quarantined supplies; and linkage of products processed to reagents, supplies, and equipment in a timely manner.

Evidence:

Processing chart records are required to contain a listing of the required reagent and supply lots and the equipment used. Those records should be available for inspector review.

STANDARD:

D6.10 The Processing Facility shall use an inventory control system to document the availability and identity of critical reagents and supplies. This shall include at a minimum:

D6.10.1 A system to uniquely identify and track all critical reagents and supplies used to manufacture cellular therapy products.

D6.10.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.

D6.10.3 A system to maintain adequate stocks of reagents and supplies for the procedures to be performed.

Explanation:

Critical materials must be defined by the Processing Facility and tracked under its materials management system. Processing records for each cellular therapy product must include the identity of all critical supplies and reagents used in the procedure. This is generally tracked by including a listing of the name of the item, manufacturer, lot number, and expiration date (where available) of the material in the processing record. The materials management system must also allow tracing of all products manufactured using a given lot of reagent or supply. There are a variety of ways this can be accomplished, so long as the information can be easily obtained.

Evidence:
The inspector should verify through review of records that supplies and reagents used in manufacturing can be traced to cellular therapy products manufactured using a specified reagent or supply.

A method to do this might include selecting a lot number of a reagent from the critical supplies and inventory list and asking for manufacturing records from products that are in inventory or have been released.

Example:
For situations in which there is a product recall of a lot of human serum albumin (HSA) found to be contaminated with a virus, it is important to be able to easily identify all products processed using that lot of HSA to be able to determine if they are suitable for use.

The inventory control system may be manual or electronic. Ordering and stocking procedures to limit the number of different lots of reagents and supplies in the Processing Facility at a given time may be part of an inventory control program.

D7: CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

STANDARD:
D7.1 ISBT 128 CODING AND LABELING

D7.1.1 Cellular therapy products shall be identified according to ISBT 128 Standard Terminology or Eurocode.

Explanation:
ISBT 128 is the international information standard for transfusion and transplantation. This standard terminology has been used in the Circular of Information (COI), as well. Initially, ISBT 128 was developed for blood and blood component transfusion to increase the capacity for electronic data, to increase security and accuracy, and to permit unique unit identification globally. ISBT 128 has now been extended to include cellular therapy products and tissues. ICCBBA is the not-for-profit organization (www.iccbba.org) that is responsible for the development and maintenance of the ISBT 128 standard. ICCBBA maintains the databases for facility identification and product coding, assigns new product codes, and provides technical support. Several volunteer technical advisory groups support and inform ICCBBA. The Cellular Therapy Coding and Labeling Advisory Group (CTCLAG) includes international representation from FACT, JACIE, ISCT, ASBMT, EBMT, NMDP, WMDA, ISBT, APBMT, and AABB. CTCLAG was formed to recommend standard definitions for cellular therapy products and rules for future assignment of cellular therapy product codes, to draft labels and a labeling strategy for cellular therapy products, and to draft an implementation plan.

The two main pieces of the standard terminology to unambiguously describe a product are class and attributes. Classes are broad descriptions of products (such as HPC, Apheresis), and attributes are additional characteristics that uniquely define the product. A group of attributes, called Core Conditions, are required; these conditions include anticoagulant and/or additive, nominal collection volume, and storage temperature.

There are also other characteristics called groups and variables that can be used to provide more information about the product. The intent is to capture relevant characteristics about the product from donor and collection through the final processing. In some settings, such as where multiple additives are used, the additional information is part of the accompanying documentation, especially where label space is limited. It is not intended that products would be relabeled at the bedside, so attributes such as "thawed" would only be applied if that process occurred in the laboratory.

Cellular therapy products characterized in this standardized way can be labeled using common, well defined terms that are printed in eye-readable format. The eye-readable terminology may be in the native language of the country in which the product is collected. The language also adapts to machine readable technologies such as bar codes. In this way, the products will be universally understood and international transport and exchange will be facilitated.

The standard terminology is structured in a manner that allows revisions, additions, and deletions as necessary on a continuous basis. In this edition of Standards, the common major classes of products are defined as was current at the time of publication. No attributes were included because of their sheer number and complexity and also, because this is a period of rapid growth in the use of ISBT 128 for cellular therapy. Modifications in definitions and additions will occur. As the responsible body for the database development and maintenance, ICCBBA is the appropriate authority for maintaining publications on current terminology. Facilities must use the terminology as defined in the ICCBBA document *Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions,* which is available at www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology. Facilities should refer to Chapter Three, Cellular Therapy, for current terms and definitions related to cellular therapy. Inspectors will inspect the facilities according to the current ISBT 128 terminology and definitions. Inspectors should review Chapter Three, Cellular Therapy, in this document before conducting an inspection. It would be helpful to have the document available for reference during the inspection as well.

If Processing Facilities have questions regarding ISBT 128 terminology, they can reference the Standard Terminology document, view the ICCBBA website at www.iccbba.org, or contact ICCBBA directly for additional information and assistance. The website also includes resources and tools for identifying and assigning standardized codes for cellular therapy products or requesting a code for a new unique product.

To utilize ISBT 128 to its full advantage by using its technical database in the unique identification of products worldwide and in the use of common language, facilities must register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each product's unique alphanumeric identifier. Facilities in or affiliated with hospitals may find that their Blood Bank has already registered and a unique facility code already exists. Stand-alone facilities can individually register and pay a nominal annual membership fee.

Eurocode International Blood Labeling Systems (IBLS) provides an international non-profit standard for labeling blood products and tissue to enhance security in blood transfusion and tissue transplantation.

The main benefits of Eurocode-IBLS are

- one bag - one number (unique product bag number worldwide)
- unique coding of product properties
- country codes following ISO 3166
- center codes according to national agreements
- matching enhanced space saving barcode systems
- charge-free access to all information via Internet

Eurocode IBLS assigns, publishes and maintains the databases for Eurocode facility identification (Center Codes) and product coding. Eurocode product codes also serve as part of the EU Single European Code for tissue (SEC).

Centers using Eurocode require a Eurocode membership. All resources such as Eurocode's technical specification, guidelines and the databases including all product and center codes can accessed freely on www.eurocode.org.

Eurocode product codes characterize each product by the product group it belongs to, supplemented by a set of properties laid out in up to 18 predefined categories such as anticoagulant used, storage temperature, donor/recipient relationship, intended use etc. These property categories are called "qualifiers".

Evidence:
Inspectors should examine the labels on site and the labeling process and SOPs to verify the appropriate use of ISBT 128 terminology is in use with regard to class and attributes or in case of Eurocode with regard to the qualifier properties of product codes in use.

Example(s):
The acronym HPC, A, would be an abbreviation acceptable in documents, and possibly on partial labels. However, the U.S. FDA does not allow abbreviations even on partial labels for licensed products.

Cellular therapy products with a biological license in the U.S. are subject to the bar code label requirements (21 CFR 201.25). The bar code, at a minimum, must contain the appropriate National Drug Code (NDC).

STANDARD:

D7.1.2 Coding and labeling technologies shall be implemented using ISBT 128 or Eurocode.

Explanation:
The use of ISBT 128 or Eurocode for all cellular therapy products provides a uniform coding and labeling system worldwide. Such standardization is even beneficial to, and thus required for, autologous cellular therapy products.

In the sixth edition, active implementation for ISBT 128 coding and labeling within the Marrow Collection Facility was required. In the seventh edition, implementation of ISBT 128 or Eurocode is required. The implementation of coding and labeling are supported by FACT and JACIE and numerous other organizations in the field for cellular therapy. On the ICCBBA website (http://www.iccbba.org), the most recent versions of the terminology are published, as well as resources to help centers implement ISBT 128.The Eurocode website (http://www.eurocode.org/index.html) includes guidelines, product codes, and other resources.

STANDARD:

D7.2 LABELING OPERATIONS

D7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products, product samples, and associated records.

Explanation:

The printing of labels can either be done by pre-printing sets of labels to be used during processing or by printing them "on demand". The use of any type of labels and the method of labeling must be part of a processing SOP or described in a separate labeling SOP. The SOP(s) describing the process for pre-ordering labels should include each of the following:

- Ordering: initial orders and reorders.
- Receipt and quarantine.
- Verification of accuracy.
- Proper storage.
- Version control.
- Inventory control.
- Destruction of obsolete or unusable labels.

Evidence:

Example labels will be available prior to the inspection visit, and label content (discussed below) will have been pre-reviewed by the FACT office or by JACIE inspectors. On-site, the inspector should verify that the labels submitted are in fact the labels in use at the Processing Facility. The inspector should focus more time on other aspects of the labeling process, specifically assessment of its adequacy to confirm proper identification of products and product samples.

STANDARD:

D7.2.1.1 Stocks of unused labels representing different cellular therapy products shall be stored in a controlled manner to prevent errors.

Explanation:
Labels must be stored in a designated area where access is limited to authorized personnel. Stocks of unused labels for different products must be stored separately to prevent errors. Labels should be organized physically or electronically so staff can readily identify the labels and be able to distinguish labels of different products from one another (e.g., by color-coding, size, or location). It is not acceptable to have different labels stored together with no separation. The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors.

Evidence:
The inspector should observe an organized storage area for the labels. There should be no obsolete version of labels available to staff, and labels in use must be the same as the approved labels.

Example(s):
Printed labels can be in containers to provide separation of each label type. Electronic labels can be in separate file folders for each label type.

STANDARD:

D7.2.1.2 Obsolete labels shall be restricted from use.

Evidence:
The inspector should verify that the destruction process is documented and that there are no obsolete labels in the collection labeling/storage area.

STANDARD:

D7.2.2 Pre-printed labels shall be held upon receipt from the manufacturer pending review and proofing against a copy or template approved by the Processing Facility Director or designee to confirm accuracy regarding identity, content, and conformity.

Explanation:
New labels must be placed in a quarantine area upon receipt. The new labels must be inspected for:

- Manufacturing or printing defects.
- Form or version number, if applicable.
- Legible and correct eye-readable information.
- Correct bar-code scanning.
- Identity to source (original) label that has been approved for use by the Processing Facility Director or designee.

Inspection must include comparison with a label approved by the Processing Facility Director or designee. The process and outcome must be documented prior to release of the labels from the quarantine area. It is recommended that the inspection of labels at receipt or after printing be performed by one person and independently verified by a second person. If bar code scanning technology is used, verification of appropriate scanning of the label should be included in this comparison before release.

Evidence:
The process should be reviewed by the inspector to confirm that the intended labels are being generated.

Example(s):
A log(s) or form(s) is often used to document receipt, quarantine, inspection against a master label book of pre-printed labels or label templates and evidence of accurate bar code scanning, as well as release for use or rejection pending disposal. Documentation should identify staff and dates when activities are performed.

STANDARD:

D7.2.3 *Print-on-demand label systems shall be validated to confirm accuracy regarding identity, content, and conformity of labels to templates approved by the Processing Facility Director or designee.*

Explanation:
"On demand" means that the labels are printed just prior to the labeling process. The system used to generate such labels must be validated to confirm that each label type is in compliance with the template approved by the Processing Facility Director or designee.

The plan will be dependent on the complexity of the labeling system but generally includes details about:

- Installation qualification (IQ), which tests and verifies that the hardware, software, and interfaces are installed properly and that the computer systems are maintained and backed up appropriately, including the user access and security requirements.
- Operational qualification (OQ), which tests operating parameters of the system at the limits , including process variables and repeated test cases to show system reliability under different conditions of use (typically the worst case scenarios).
- Performance qualification (PQ), includes test cases to demonstrate the system works as intended for use.

In case of "on-demand" printing of labels, the SOP should include each of the following:

- Lay-out of the labels.
- Transfer of information to the label.
- Verification of accuracy.
- Proper storage.
- Version control.
- Destruction of obsolete or unusable labels.

Evidence:
The validation of labels on demand and the complete process should be reviewed by the inspector to confirm that the intended labels are generated. The validation of automatic label generation, including test cases and associated documentation and software-defined tables, should be reviewed by the inspector and provides evidence of the mechanisms used by the software to control and verify label content, including the use of bar-coded information. Validation of software-controlled labeling systems used to create or modify labels should be documented in a validation plan at the site. Testing by the supplier or vendor is not adequate.

STANDARD:

D7.2.4 A system for label version control shall be employed.

Explanation:
The document control system used for these various elements and what constitutes a label version must be defined by the Processing Facility. Any change in the label or label element that would change the interpretation of the label would constitute a version change. The version number may or may not appear on the label, as defined by labeling process at each facility. Only the current version of each label should be available for use in the processing area. A process for controlled rotation of labels should be evident for inventoried labels.

Evidence:
The label version control should be reviewed by the inspector to confirm that the intended labels are generated. Older versions and the way old labels are being stored needs to be inspected. For label changes, there should be a process for controlled versioning and implementation of changes in manual or automated systems, including archived label examples or templates and reconciliation of available and inventoried labels, as applicable to the labeling systems in use. SOPs should address the timeframe for retention consistent with applicable laws and regulations.

Example(s):
Changes in the requirement for a uniform product proper name or changes in the wording of required statements or warning statements would require a version change to that label or label element. Log(s), form(s) and/or software validation documentation specific to a particular archived label should show label versions linked to specific dates of use.

STANDARD:

D7.2.4.1 Representative obsolete labels shall be archived minimally for ten (10) years after the last cellular therapy product was distributed with inclusive dates of use or as defined by applicable laws and regulations, whichever is longer.

Explanation:
Obsolete or unusable label stock should be defaced immediately to prevent their accidental use and then destroyed. However, as a controlled document, representative obsolete labels (or label templates) and their inclusive dates of service, must be archived minimally for 10 years.

STANDARD:

D7.2.5 *A system of checks in labeling procedures shall be used to prevent errors in transferring information to labels.*

D7.2.5.1 *Cellular therapy products that are subsequently re-packaged into new containers shall be labeled with new labels before they are detached from the original container.*

D7.2.5.2 *A controlled labeling procedure consistent with applicable law shall be defined and followed if container label information is transmitted electronically during a labeling process. This procedure shall include a verification step.*

Explanation:
This standard requires facilities to have a careful process for electronically transmitting information (such as with a bar code) and to double check the information rather than becoming solely dependent on the technology to work correctly.

STANDARD:

D7.2.6 *When the label has been affixed to the container, a sufficient area of the container shall remain uncovered to permit inspection of the contents.*

Explanation:
The inspector should examine labeled products on-site to verify that labels are firmly attached or affixed and that sufficient area of the product remains uncovered to allow examination of contents.

STANDARD:

D7.2.7 *The information entered on a container label shall be verified by one (1) qualified staff member using a validated process or two (2) qualified staff members prior to distribution of the cellular therapy product.*

Explanation:
When Processing Facilities print labels on demand, the manner in which the database is being generated needs to be validated. For automatic labeling systems using computer-assisted label verification of parts of the label, electronic verification must be part of the label system validation.

No fewer than two people must confirm that manually entered information on the label is accurate. One person may verify information if a validated process, such as computer checks or barcoding, is used. New labels are usually being generated only when the product is being processed. However, if relabeling needs to be conducted, for example, when confidentiality needs to be preserved in the case of a matched unrelated donor transplant, the SOP must include details on how to prevent errors. When transferring a cellular therapy product, labeling of new containers or samples shall meet the labeling requirements of the Standards, including documentation of verification of correct labeling information, whether by manual or automated methods.

Whether the Processing Facility verifies information by one qualified staff member using a computer-based system or by two qualified staff members, there must be documentation that the verification has been completed,

Evidence:
The inspector should confirm the Processing Facility has documentation that the process was complete, and verify that records of manual additions to product labels include the identity of the staff making the label modification and the staff verifying the information, and date. For systems using computer-assisted label verification (such as bar-code scanning), SOPs and records should show how the automatic verification works. If relabeling is performed, the relabeling SOP must be adequately described.

STANDARD:

D7.2.8 Labeling elements required by applicable laws and regulations shall be present.

Explanation:
Label elements that are required by governmental regulation must be clearly visible. The Collection Facility should review FDA, EU, and/or other applicable governmental requirements for labeling and format labels accordingly.

STANDARD:

D7.2.9 All data fields on labels shall be completed.

Explanation:
All data fields on labels must be complete. If information is not required, the data field should be marked "not applicable" or shall not appear.

STANDARD:

D7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

Explanation:
Indelible ink must be used to record any information entered manually on the label. To support label integrity, computer-assisted labeling should include a check to confirm label stock is appropriately aligned in the printer and ink is smear-proof. Labels must have been validated to assure they remain legible under the conditions in which they are used. This is of particular importance for labels used on cryopreserved products and after thawing of the product in a water bath.

STANDARD:

D7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

Explanation:
Adhesives that are applied directly to the cellular therapy product bag have the potential to leach through the plastic into the product itself. Processing Facilities must use materials that meet criteria, if any, established by applicable regulatory authorities.

Example(s):
Processing Facilities in the U.S. should contact the FDA regarding any labels affixed directly to the cellular therapy product bag to determine what data is needed to demonstrate that the labels meet FDA requirements. For further information, see the FDA document, "Guideline for the Uniform Labeling of Blood and Blood Components," (August 1985). This document is available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM080974.pdf.

STANDARD:

D7.2.12 The label shall be validated as reliable for storage under the conditions in use.

D7.3 PRODUCT IDENTIFICATION

D7.3.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any cellular therapy product to its donor, its recipient or final disposition, and all records.

D7.3.1.1 The cellular therapy product, product samples, concurrent plasma, and concurrently collected samples shall be labeled with the same identifier.

D7.3.1.2 If a single cellular therapy product is stored in more than one container, there shall be a system to identify each container.

D7.3.1.3 If cellular therapy products from the same donor are pooled, the pool identifier shall allow tracing to the original products.

Explanation:
The product identifier must be unique for each donation event so that all parts of the donation and samples collected are labeled with the same product identifier. Unique is defined as not being used for any other purpose. Thus it is not acceptable to use only patient information (such as medical record number or social security number) or only the donor information (name, medical record number, or registry identifier) to identify the product. Generally, a unique identifier also implies that there is reasonable confidence that it will not be used for another purpose. Products collected from a single donor at different times must be distinguished from each other by different unique product identifiers.

The essential point is that each product can be unambiguously traced from donor to recipient, and through all transport steps, processing and labeling steps, and storage locations. The label must clearly indicate the identity of the facility that assigned the product identifier, with the exception of cellular therapy products shipped by registries, where the source facility must remain confidential. In such cases the records that accompany the product must allow tracing to the Collection Facility.

Each Processing Facility must have a SOP indicating how a unique identifier is assigned and tracked to all parts of the donation and samples obtained at the time of donation and include acceptable modifications that can be made to the product label or identifier. When a product from a single donor is divided into multiple containers, each container must be uniquely labeled; however, that identifier must trace back to the original donation. In some cases, products collected on different days may be pooled for further processing. Note that only products from a single donor may be pooled unless specifically allowed for a given protocol by the appropriate regulatory authority. The pooled product must also be uniquely identified, and that identifier must trace back to include all l donations involved.

Product and donor samples collected at the time of cellular therapy product collection should be labeled so as to prevent misidentification. At a minimum, this must include the donor's name (except for the case of unrelated donors), product unique identifier, and date of sample collection.

One of the major purposes of ISBT 128 is to serve as an internationally harmonized product identification system. Implementation of ISBT 128 cellular therapy product labeling will eliminate the need for creation of a subsequent unique identifier when the product is distributed. The ISBT 128 identifier should be the main identifier for required tracking and tracing and Processing Facilities are encouraged to retain the original identifier upon receipt of the product rather than assigning a new unique identifier.

Example(s):
The donor or recipient registry number can be used by the local site as the sole or additional identifier if it is combined with other information that makes it unique, such as the collection date, so long as each product can be uniquely identified.

Identification of products with multiple containers may occur by modifying the unique identifier on each container with a suffix (either letter or number) or by modifying the cellular therapy product label on each bag (such as Bag 1 of 2, division codes added to the product code, etc.). If products are being pooled, the pool identifier must allow tracing to the original products. A pool identifier could be new (the pooled CPL11001 and CPL11002 could be CPL11003 so long as the new identifier is traceable to the original identifiers through the laboratory record), or could be a combination of the original identifiers (i.e., CPL11001+CPL11002).

EU Directive 2006/86/EC requires that the expiry date shall be part of the product information for all tissues and cells and there shall be an indication of the status of the product (in quarantine or ready for use). The unique identifier must be retained for 30 years per EU requirements.

Exceptions for assigning a new ISBT 128 identifier to cellular therapy products already given a unique identifier may include older cellular therapy products (products labeled prior to ISBT 128 implementation) and, potentially, products received from non-FACT or JACIE accredited sources.

STANDARD:

D7.3.1.4 Supplementary identifiers shall not obscure the original identifier.

Explanation:
The Processing Facility may assign additional identifier(s) to a product; however, it is recommended that no more than two sets of identifiers from separate facilities should be affixed to a product container and the original identifier may not be obscured. If a unique identifier is replaced with a new one, records must link the current unique identifier to the original.

STANDARD:

D7.3.1.5 *The facility associated with each identifier shall accompany the cellular therapy product.*

D7.3.1.6 *If the original identifier is replaced, documentation shall link the new identifier to the original.*

Evidence:
If supplementary identifiers are used, the inspector should check that the identifier is affixed to the cellular therapy products, verify the original identifier is not obscured, and the facility responsible for each identifier is part of the label or extended label. The Processing Facility must be able to provide evidence that if original identifiers are removed from the product, or if the product is repackaged, that the supplemental identifier is traceable to the original identifier. Typically this process is described in a policy or SOP.

Example(s):
Labeling records (forms and logs or computerized records) can be used to demonstrate that the original unique identity can be linked to the new identifier so that the Processing Facility and staff responsible for assigning new identity is documented and the records support traceability. Tracing a unit through the labeling process is an effective method to verify these standards are met.

A cellular therapy product initially labeled in compliance with ISBT 128 should not be relabeled. An exception to this would be a product that bears the identifier assigned by the distributing facility (e.g., cord blood collected by a hospital and distributed to the Processing Facility).

STANDARD:
D7.4 *LABEL CONTENT*

D7.4.1 *At the completion of processing and at distribution for administration, the cellular therapy product label on the primary product container and concurrent plasma container shall bear the information in the Cellular Therapy Product Labeling table in Appendix II.*

Explanation:
The required label content as specified in Appendix II represents minimum requirements, and must be present as indicated at the various stages of product collection, processing, and distribution.

Labeling must be consistent with national and local laws and regulations. Local interpretations may differ. The identity and address of the collection facility or registry as well as identity and address of the processing facility, as applicable, must be part of labeling at issue. The identity of an unrelated donor is not included in labeling due to confidentiality. This may be extended to the collection site per some interpretations of local laws and regulations.

Evidence:
Examples of all labels in use by the applicant organization will be provided to the inspector prior to the on-site inspection. For organizations performing both allogeneic and autologous transplants, examples of labels will include collection, processing, transport, and distribution labels for both types of transplant. In addition, labels illustrating each cellular therapy product source handled by the organization should be included. Partial labels, if used, should be included. Cryopreservation labels, tie tags, instructions to the infusionist, biohazard, and warning labels should also be included. If any expected label is not provided to the inspector prior to the inspection, the inspector should request it from the applicant through the FACT or JACIE office, as applicable.

Inspector should examine labels to confirm that confidential donor information is not included in the label per national and local laws and regulations and that appropriate identities and addresses of the collection site or registry and processing lab are part of the extended label, as applicable to the setting and that the information provided allows for adequate traceability to the donor of the product.

Example(s):
Labels (manual or computer generated) should be reviewed for autologous, related and allogeneic products, as applicable to the site, to verify the requirements of these standards are met.

Per EU Commission Directive, 2006/86/EC, the identity of the tissue establishment is part of the label at issue. In the U.S., the identity of the establishment responsible for determining the product meets release criteria and is available for distribution must be part of the label. This information may appear as part of the affixed, attached or extended labeling as part of the accompanying documentation per national and local laws and regulations.

STANDARD:

D7.4.2 *Each label shall bear the appropriate biohazard and warning labels as found in the Circular of Information for the Use of Cellular Therapy Products, "Table 2. Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."*

Explanation:
Table 2 of the inter-organizational Circular of Information for Cellular Therapy Products outlines when biohazard labels must be used. Biohazard labels can only be applied to products not required to be labeled biohazard when specific circumstances for their use are defined by Processing Facility or Clinical Program policy. Biohazard labels must not be applied indiscriminately.

Evidence:
The inspector should ask to see the SOP that defines the conditions for using a Biohazard Label and determine if the Processing Facility's SOPs are adequate and appropriately safe to prevent transmission of infectious disease.

The inspector should confirm that biohazard labels and warning statements are utilized as described in the COI Biohazard and Warning Labeling Table available at http://www.factwebsite.org/WorkArea/DownloadAsset.aspx?id=1335 Autologous product labels should be examined to confirm that "Not Evaluated for Infectious Substances" is present when the donor screening does not contain all of the elements listed.

STANDARD:

D7.4.3 *Any container bearing a partial label shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix II. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.*

Explanation:

If the Processing Facility utilizes a partial label, the inspector must confirm that the SOP describes the use of the partial label, provides an example of the partial label, and includes the mechanism for providing the additional information that is not included on the partial label.

Accompanying paperwork should be packaged in a secondary bag with non-frozen products for shipment or transport to the external facility or infusion site. The paperwork may be placed in the canister of a frozen product. When shipping or transporting multiple product bags from different donors using partial labels, it is not acceptable to include all the additional information on a single inventory sheet, but rather each product and paperwork from each donor should be segregated in a way to prevent mix-up.

Partial labels may be applied during processing (in process labels). This is the only case where partial labels are acceptable without additional information in an enclosed secondary container. Appropriate attributes should be applied to the label while it is undergoing different stages of processing to assure that other qualified processing personnel can identify which steps in the process have been completed.

Evidence:

Inspectors should verify partial labels meet requirements as defined in these standards and the Processing Facility SOPs. An inspector can ask to follow a cellular therapy product through the processing steps.

STANDARD:

D7.4.4 *The name and address of the facility that determines that the cellular therapy product meets release criteria and the name and address of the facility that makes the product available for distribution shall either appear on the product label or accompany the product at distribution.*

Explanation:

It is important for the staff of the Processing Facility to verify the accuracy of the donor and patient information and to confirm that the labels are verified for completeness and legibility before removing them from the processing area.

The label verification should include:

- Label is correctly affixed to the component (and/or tie tag).
- The correct label is positioned appropriately.
- The label is identical to the one specified in the SOP.
- Hand written information is written with blue or black indelible ink.
- All information is legible and accurate.
- The unique identifier is firmly affixed to the product bag and identical on associated forms and accompanying records and documents.
- The label is not damaged or defaced.

In addition, there should be a documented verification of patient and donor identity prior to issue.

Evidence:
The inspector should verify that labeling during processing, at the completion of processing, and at distribution contains all the information listed in Appendix II and contains appropriate biohazard and warning statements as specified in the COI Biohazard and Warning Label Table available at: http://www.factwebsite.org/uploadedFiles/COI-CT-2009.pdf.

Example(s):
Although it is not specified by the Standards, it may be useful to include information on the cell types present in the product. For MNC products in particular, the cell content may be critical to the efficacy or safety of the product and should be confirmed with the physician order prior to administration. Alternatively, this information may be in the accompanying records and should be verified by the processing and administration staff at the time the product is distributed for administration.

Cellular therapy products from unrelated donors shall contain the donor identification number supplied by the registry with or without the identification of the collection center, according to local laws or regulations.

STANDARD:

D7.4.5 *Cellular therapy products collected in or designated for use in the U.S. shall have the elements in the Accompanying Documents at Distribution table in Appendix IV accompany the cellular therapy product when it leaves the Processing Facility.*

Explanation:
See Appendix IV for explanations, evidence, and examples for products collected in or designated to the U.S.

STANDARD:

D7.4.6 *For cellular therapy products distributed before completion of donor eligibility determination, there shall be documentation that donor eligibility determination was completed during or after distribution of the cellular therapy product and that the physician using the product was informed of the results of that determination.*

Explanation:
The Processing Facility must inform the physician of the results of any testing or screening that was completed after the product was distributed. The provision of this information must be documented in the processing records. If any result is positive, it is the responsibility of the physician to notify the recipient and to document the patient notification in the clinical record.

Evidence:
SOPs and processes should define release criteria for incompletely tested products, including staff involved, notification of the recipient's physician, labeling, and donor eligibility completion. Inspectors should review the forms, logs or other documentation to confirm the eligibility was completed and the appropriate physician was notified. The inspector should be able to determine what was complete and incomplete at the time of release of the product and when and how the physician was notified of the pending results and information, as well as documentation that the physician acknowledged receipt of the information. Forms, logs or other documented records should clearly identify the staff involved in the notification process and timeframes involved.

STANDARD:

D7.4.7 *Cellular therapy products distributed for nonclinical purposes shall be labeled with the statement, "Not For Admin"*

D8: PROCESS CONTROLS

STANDARD:

D8.1 *There shall be a process for controlling and monitoring the manufacturing of cellular therapy products so that products meet predetermined release specifications.*

Explanation:
The establishment of process control is a primary objective of the Processing Facility QM Program. Since cellular therapy products are biological, there is inherent variation among products that cannot easily be controlled. The consistent use of validated processing procedures and the use of testing to monitor processing can greatly reduce variability and result in high quality products. SOPs are required that describe each processing procedure and its associated process control (see D5.1).

Example(s):
Processing records, batch records, and lot preparation sheets are all examples of documentation that, when used effectively, can assist with the controlling, monitoring, and documentation of cellular processing.

STANDARD:

D8.1.1 *The Processing Facility Director shall define tests and procedures for measuring and assaying cellular therapy products to assure their safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such tests and procedures shall become part of the permanent record of the product processed.*

Explanation:

The Processing Facility Director or designee is responsible for defining release criteria for cellular therapy products distributed by the facility and for identifying the tests to be performed and the testing intervals during processing. This information must be clearly outlined in an SOP (see D5.1). All test results that are available at release must be present in the processing record. Certain tests on the product or the donor are required to be performed by the Standards, including:

- ABO group and Rh typing on samples obtained on two occasions from an allogeneic donor.
- Microbial testing after processing.
- Post-processing TNC and viability for processing procedures that affect TNC or viability.
- Post processing CD34 cell assay on HPC products for processing procedures that affect CD34 cell content.
- Assay of target cell population for products that have been enriched or depleted.

Only the results of those tests defined by the Processing Facility Director need to be maintained in the facility records. HLA typing results should be part of the Clinical Program patient records. The results of this testing or other testing designated by the director may not always be required for release from the facility, although samples should have been obtained prior to release unless otherwise specified in SOPs.

Evidence:

The inspector should review processing records to determine if all required testing was performed within the required timeframe and if the results are recorded. Documentation that the cellular therapy product met release criteria prior to distribution must be present. For products that did not meet release criteria, the required documentation for exceptional release should be present.

Example(s):

For cellular therapy products that are CD34-enriched for the purpose of removing mature T cells, testing of the final product should include TNC (required for all processing that affects TNC), sterility testing (required for all products at administration), viability, CD34 cell content, and CD3 cell content. Other testing may be performed at the discretion of the Processing Facility Director.

For HPC, Apheresis products undergoing processing for plasma removal, so long as the Processing Facility can document that the plasma removal step does not significantly affect TNC, CD34 cell content, or viability, those tests would not need to be repeated after the plasma removal. However, those tests should have been performed prior to the plasma removal step.

STANDARD:

D8.1.2 *There shall be a documented system for the identification and handling of test samples so that they are accurately related to the corresponding cellular therapy product, donor, or recipient.*

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.*

Explanation:
This standard describes the processes required for obtaining and testing samples from cellular therapy products. It is critical that the sample obtained for testing represents the product to be tested. Most often this requires that a product be well-mixed prior to sampling and the sample to be taken at the appropriate step in processing.

Evidence:
To determine that test samples can be appropriately linked to the donor and/or recipient, the inspector should observe how sample tubes are labeled and distributed for testing and how results are posted.

Example(s):
Test sample labels should include the cellular therapy product unique identifier and the sample source (and if appropriate, the stage of processing), and there should be a mechanism that identifies the individual procuring the sample and the date and time it was obtained.

The supernatant may be considered representative of the cellular therapy product depending on when it is used and for what tests. For example, the supernatant of a cord blood unit at the time of the last wash for administration could be used for sterility testing. Supernatant from processing steps further upstream before cryopreservation would not be considered representative of the product because contamination could occur during or after storage. Supernatant would not be considered representative of the product for purposes of TNC or CD34 analysis; samples for these tests must come from the product itself.

EU regulations also require that there be a record of the location at which a specimen was taken.

STANDARD:

D8.1.3 *There shall be the establishment of appropriate and validated assays and test procedures for the evaluation of cellular therapy products.*

Explanation:
Test methods that are used for these assays are not specified by the Standards. Rather, it is up to the Processing Facility to determine what assays are appropriate and to confirm that they have been validated for the cellular therapy products that are being tested. Testing must be performed using appropriate equipment, reagents, and controls. Validation procedures should be determined by the program, and described in the program's standard operating procedures. Equipment control requirements may differ based on government regulations (e.g., U.S. regulations require daily controls, and European requirements specify "regular" controls). In the event an assay is unavailable (e.g., natural killer cells), defined release criteria such as those specified in an IND or ATMP must be utilized.

Evidence:
The inspector must utilize his or her judgment and knowledge of the field to assess if the appropriate assays are in use. For all procedures and assays utilized by the Processing Facility, including those considered uncommon for the facility, the inspector should verify that SOPs are in place, that there is a record of method validation, that reagent and instrumentation controls are used, and that there is evidence that the technologists performing the procedure have been trained, participate in proficiency surveys, and are evaluated for ongoing competency for these procedures. The inspector should pay particular attention to procedures and assays that may be newly implemented including flow cytometry, endotoxin and mycoplasma testing, cell selection, cell purging, etc. Methods for microbial testing, in particular, should have been validated for the range of cellular therapy products being tested.

The inspector may recommend periodic documentation of continued reproducibility. However, if a procedure requires more than minimal manipulation and additional cell counts are not performed, the inspector should ask to see evidence of reproducible recovery of cells in the form of a validation study. If such a study has not been performed, the inspector may determine that additional cell counting and viability assessment must be performed during and/or post-processing.

The inspector should ask to see evidence of reproducible recovery of CD34 cells as part of any validation study of processing procedures involving HPC products.

STANDARD:

D8.1.3.1 *For all cellular therapy products, a total nucleated cell count and viability measurement shall be performed.*

D8.1.3.2 *For HPC products intended for restoration of hematopoiesis, an assay measuring viable CD34 shall be performed.*

Explanation:
A number of published studies have shown a correlation between CD34 cell content and the kinetics of platelet and granulocyte engraftment below a threshold number of CD34 cells. Review of the CD34 cell content at the end of processing shown to affect CD34 cell content in conjunction with outcome analysis of time to engraftment should be used, especially for recipients whose engraftment appears to be delayed.

Post-thaw assessment of cellular therapy products that are directly thawed and administered is not typically performed, and cannot be easily done, especially if products are thawed outside of the Processing Facility. For products that are manipulated in the laboratory, such as those undergoing a

Dextran/Albumin wash, a TNC and viability assessment should be done. Repeat CD34 cell assessment of thawed cells is technically more difficult but should be performed in the context of procedure validation. Based on those results, the facility may not need to do this assay for every thawed product. In the case of cord blood units where CD34 test results may not be available, CD34 testing should be performed.

STANDARD:

D8.1.3.3 For cellular therapy products undergoing manipulation that alters the final cell population, a relevant and validated assay, where available, shall be employed for evaluation of the viable target cell population before and after the processing procedures.

Explanation:
Target relevant cells include those that affect the effectiveness and safety of cellular therapy products. This includes cells that perform the actual function intended by the product and cells that may cause side effects.

Example(s):
When processing procedure validation demonstrates a loss of CD34 cells and/or a loss in total nucleated cells (e.g., after density gradient separation for mononuclear cell preparation), testing for the affected cell type(s) must be performed at the end of processing and prior to administration or cryopreservation.

STANDARD:

D8.1.4 For tests required by these Standards performed within the Processing Facility:

Explanation:
Requirements of the Processing Facility providing these testing services must be in accord with the requirements for the same testing performed by a certified or accredited clinical laboratory. That is, while the facility does not have to be formally certified or accredited, there must be a process in place to safeguard that the results are accurate. Minimally the reagents used for testing should be confirmed to give the expected results using previously assayed control materials where those are available or compared to the previously used reagent lots. Instruments and test methods should include day of use positive controls, and appropriate controls for instrumentation function must be performed. Suitable control materials may not be available for manual procedures commonly performed in Processing Facilities, such as manual cell counts of Trypan Blue viability assessments. In such cases, processing personnel are required to participate in proficiency testing programs (when available) for the procedures and/or tests that they perform. While separate accreditation for the tests performed by the facility may be available, it is not required by the Standards. However, performance of such testing should be consistent with the standards of other such accrediting bodies.

STANDARD:

D8.1.4.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

D8.1.4.2 New reagent lots shall be verified to provide comparable results to current lots or to give results in agreement with suitable reference material before or concurrently with being placed into service.

Example(s):
Reference material for reagent and/or day of testing controls can be purchased as fixed cells for flow cytometry controls for lymphocyte subsets and detection of CD34 cells and for hematology analyzers. Processing Facilities should confirm that the control cells purchased are appropriate for the instrument in use. Fixed cells used as flow cytometry controls may also be used to confirm the activity of the 7-AAD viability assay since the majority of fixed cells will stain positive. The expected range of positive cells can be established for the control cell type used.

For CE-marked reagents, it is acceptable to use the Certificate of Analysis, datasheets, and visual inspection of the reagent as verification. The inspector should review the policy and SOP for evidence of good stock control.

STANDARD:

D8.1.4.3 Where available, controls shall be used each day of testing and shown to give results within the defined range established for that material.

D8.1.4.4 Function checks shall be performed for testing instruments prior to testing donor, recipient, or cellular therapy product samples.

D8.1.4.5 For tests performed within the Processing Facility, there shall be documentation of ongoing proficiency testing as designated by the Processing Facility Director. The results shall be reviewed by the Processing Facility Director or designee and outcomes reviewed with the staff.

Example(s):
Examples of testing with available proficiency testing programs include automated cell counting, colony assays, and flow cytometry. Several organizations (e.g., College of American Pathologists [CAP], Stem Cell Technologies, Communicable Disease Center, National Institute for Allergies and Infectious Disease, and United Kingdom National External Quality Assessment Schemes) provide a variety of proficiency tests applicable to the activities of a Processing Facility. Alternatively, the facility may establish its own proficiency testing program, particularly for site-specific activities not routinely performed by other laboratories and for which no external proficiency test is available. For tests such as manual cell counts the manual method can be compared with results obtained from a validated hematology analyzer. Likewise, Trypan Blue viability may be compared to flow based assays such as 7-AAD using the same samples. Total nucleated cell count for products whose function is dependent on cell dose is sometimes an appropriate surrogate for viability measurement.

STANDARD:

D8.1.5 Tests required by these Standards, not performed by the Processing Facility, shall be performed by a laboratory that is certified, licensed, or accredited by the appropriate laboratory regulatory agency.

Explanation:
Some of the specified testing may be performed by an external laboratory. Testing not performed by the Processing Facility must be performed by an appropriately certified laboratory. Such laboratories must have valid and current licenses and accreditation and are expected to meet minimally the same requirements specified for testing performed within the facility.

Evidence:
Documentation that external laboratories performing required testing are appropriately certified or accredited must be reviewed by the inspector. Although the actual certification certificates are not required to be on-site at the Processing Facility, they should be readily available for review.

STANDARD:

D8.1.6 *Infectious disease testing required by these Standards shall be performed using screening tests approved or cleared by the governmental authority for cellular therapy product donors.*

Explanation:
Communicable disease testing is specifically required by cGTP regulations to be performed using testing kits approved and authorized for donor screening in a laboratory that is accredited or licensed according to applicable laws and regulations. Since communicable disease testing is usually facilitated by the Clinical Program or by the Collection Facility and is performed prior to collection, the Processing Facility must have a system in place whereby a summary of these results are available to the facility. Standard B6.4.2 applies.

Evidence:
The inspector should be able to verify compliance with this requirement by reviewing a copy of communicable disease testing results with explanation of results and acceptable values. The tests used should be on the list of approved tests by the regulatory authority. The Processing Facility should also provide documentation that the laboratory providing those results is accredited or licensed as required.

Example(s):
An example of evidence that can be provided to the inspector may be communicable disease test reports from a licensed blood center testing facility.

In the U.S., testing is specifically required to be performed using test kits approved by the FDA for donor screening in a CLIA-accredited or FDA-registered laboratory.

STANDARD:

D8.1.7 *Cellular therapy products that do not meet allogeneic donor eligibility requirements, or for which allogeneic donor eligibility determination is not yet complete, shall be distributed only if there is documented urgent medical need for the product. Documentation shall include, at a minimum, the approval of the recipient's physician and the Processing Facility Medical Director 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 *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.*

Explanation:
Before processing begins, a physician's order must be received by the Processing Facility and must specify how and when the cellular therapy product should be processed as well as the identifiers of the donor and recipient. For example, if a product is to be split in order to infuse an initial cell dose and reserve the remaining cells for a subsequent administration (DLI or tandem transplant), this must be clearly indicated on the medical order. For standard processing procedures, precise parameters do not have to be indicated on the medical order as long as the SOP is sufficiently specific to indicate the appropriate end-points and expected ranges.

Stored cellular therapy products from more than one donor collected for a given recipient may be present in the Processing Facility. In such cases it is important that the physician order clearly specify the identifier of the donor to be used.

Evidence:
The inspector should review the physician order form in use and verify that it contains the required elements.

Example(s):
Examples of processing to be performed may include the extent of plasma and/or red blood cell depletion, purity of selected or purged cell products, cryopreservation volume and number of bags frozen, etc.

STANDARD:
D8.3 *For allogeneic cellular therapy products, information required by the Processing Facility prior to distribution of the product shall include:*

D8.3.1 *A statement of donor eligibility.*

D8.3.2 *For ineligible donors, the reason for their ineligibility.*

D8.3.3 *For ineligible donors or donors for whom eligibility determination is incomplete, documentation of urgent medical need and physician approval for use.*

Explanation:
Before the Processing Facility can distribute allogeneic cellular therapy products for administration, regulations require that donor suitability and allogeneic donor eligibility be confirmed. This determination is performed by the Clinical Program or Collection Facility, and not the Processing Facility.

In order to distribute the product after processing, donor eligibility and suitability information must be obtained from the facility making that determination. For allogeneic donors not meeting eligibility requirements, the reason must be provided and, for such donors, release cannot proceed without documentation that the criteria for urgent medical need have been met and the physician overseeing the recipient has approved use.

In some cases, a cellular therapy product may be needed before donor eligibility determination is completed. In those situations, the transplant physician must be notified that testing and screening has not been completed. See Appendix IV for the detailed requirements.

Evidence:
The inspector should request and review donor eligibility paperwork and urgent medical need documentation when required.

Example(s):
For example, allogeneic donor eligibility documentation with approval signatures can be used as documentation of compliance with this requirement.

STANDARD:

D8.4 Processing procedures shall be validated in the Processing Facility and documented to result in acceptable target cell viability and recovery.

D8.4.1 Published validated processes shall be verified within the Processing Facility prior to implementation.

Explanation:
The Processing Facility Director should determine what and how processing methods will be validated. Validation may be retrospective, concurrent, or prospective. Validation should include retrospective and/or ongoing evaluation of processing results, data analysis, establishment of expected ranges and means and/or medians, and periodic documentation that the procedure is yielding results within the expected range.

Any new procedures introduced into the Processing Facility should undergo prospective validation when possible. Prospective validation of a processing procedure may be accomplished by performing a mock procedure using a surrogate cellular therapy product. Surrogate products may include those collected for research with IRB approval, those previously collected and stored for a recipient who has no further need for that product, or blood products collected from donors for therapeutic purposes that are otherwise discarded. When no surrogate products are available for a full-scale procedure, validation using a small portion of a product and a scaled-down procedure may be adequate. Ultimately, validation of the quality of the product is determined by timely engraftment of the transplanted cells and the clinical outcome of the recipient. However, there should be *in vitro* studies demonstrating that the desired end-point of the processing procedure was achieved.

In some cases the Processing Facility may implement a processing procedure or process that has been validated by an external facility and/or has been published. In such cases it may not be necessary to undergo a full validation study; rather the facility may need only to verify that the procedure or process results in comparable cellular therapy products when performed locally. It remains important that a formal process be followed and that acceptance criteria that can be shown to be objectively met are established.

Evidence:
The inspector must review one or more validation or verification studies to confirm they are being performed as required by the Standards. It is not the position of the inspector to request validation for procedures that have not yet been unequivocally validated by the scientific community. The inspector should specifically review that all testing procedures are defined by SOPs.

Example(s):
For standard procedures that were adopted and implemented prior to establishment of the Standards and have remained unchanged, retrospective or concurrent validation is acceptable. Examples may include controlled rate freezing, cryopreservation using DMSO, automated cell washing, and buffy coat preparation and red blood cell depletion protocols.

STANDARD:

D8.4.2 *The Processing Facility shall use validated methods for preparation of cellular therapy products for administration.*

D8.4.3 *Cord blood units that have not been red cell reduced prior to cryopreservation shall be washed prior to administration.*

D8.4.4 *Cord blood units that have been red cell reduced prior to cryopreservation should be diluted or washed prior to administration.*

Explanation:
Processing of cord blood units (i.e., when to dilute and/or wash) may be dependent on many variables (e.g., ABO mismatches, RBC contamination content, pediatric risk factors).

The main goal of diluting and washing cord blood (CB) units is to remove red cell stroma which could result in toxicity at the time of administration. Diluting and washing a thawed CB unit also limits exposure of thawed cells and recipients to high concentrations of DMSO. The choice between dilution and washing takes into account the volume of the cryopreserved CB units, the number of CB units to be readministered, and the maximum tolerable volume of fluid to be readministered to the recipient. See Akel, S., Regan, D., Wall, D., Petz, L., & McCullough, J. (2014). Current thawing and administration practice of cryopreserved cord blood: The impact on graft quality, recipient safety, and transplantation outcomes. *Transfusion*. Advance online publication. doi: 10.1111/trf.12719.

STANDARD:

D8.4.5 *If the Processing Facility lacks experience with the type of cellular therapy product requested for a recipient, personnel shall obtain the manufacturer's instructions and follow these instructions to the extent possible.*

D8.4.5.1 The Processing Facility should verify the processing procedures utilizing practice units similar to the cellular therapy product intended for administration when feasible.

Explanation:
It is understood that there may be situations in which a Clinical Program requests the Processing Facility to store, thaw, and/or wash cellular therapy products with which the facility has little or no experience. In these cases, the facility's ability to perform validation studies is limited. The facility must communicate with the registry and/or third-party manufacturer regarding the manufacturer's instructions for preparation for administration to determine if the facility has the appropriate personnel competencies, equipment, storage space, supplies, and reagents.

Even if inexperienced with a certain type of cellular therapy product, it is still the responsibility of both the Clinical Program and the Processing Facility to verify that the facility's staff, supplies, reagents, and processes will protect cell viability and product safety. In these cases, Clinical Programs are required to request practice units for the facility to verify the processing procedure prior to performing the procedure on products intended for administration to a recipient.

Since different facilities may have different processing procedures for their cellular therapy products, it is important to document when the use of products manufactured using different procedures are administered and to document the processes that were used to prepare and administer such products.

Evidence:
Inspectors may verify compliance with this standard by reviewing the process for handling deviations, documentation of practice runs, concurrent verification studies, etc.

Example:
The Processing Facility may also wish to discuss with the registry and/or third-party manufacturer the red cell content of the product, the size of the unit, and potential alternative reagents if the facility does not have the manufacturer-recommended reagents on hand. Facilities may also consult with their peers regarding these issues.

FDA regulations require that manufacturers of cellular therapy products validate the thaw procedure and provide instructions to the clinical program administering the product. Transplant programs that receive cryopreserved CB units for transplantation are not manufacturers. Their processing laboratories' processes (thaw, dilute, wash, etc.) are considered "preparation for administration" of the product. Therefore, Processing Facilities can use their own validated procedures when preparing the cord blood for administration. It is recommended that the CBB's instructions be followed. Facilities wishing to perform their own validated method should have experienced staff.

STANDARD:
D8.5 Critical control points and associated assays shall be identified and performed on each cellular therapy product as defined in Standard Operating Procedures.

Explanation:
The Processing Facility Director is responsible for defining tests and procedures for measuring and assaying cellular therapy products to verify product quality and that they meet release criteria. It is further specified that tests should be identified that are critical to this objective and that those tests are defined by SOPs.

Evidence:
The inspector should request and review SOP(s) for cellular therapy products that clearly define the expected endpoints of processing. Critical control points for the assays or tests performed should be indicated in the SOP.

Example(s):
For example, if endotoxin is used as a release criterion, the processing SOP should indicate what the expected results are. In addition, if there are critical steps (control points) such as sample preparation that would affect the final result, these control points should be clearly indicated.

STANDARD:

D8.6 *Methods for processing shall employ aseptic technique and cellular therapy products shall be processed in a manner that minimizes the risk of cross-contamination.*

D8.6.1 *Where processing of tissues and cells involves exposure to the environment, processing shall take place in an environment with specified air quality and cleanliness.*

D8.6.2 *The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.*

Explanation:
The simultaneous presence of cellular therapy products from more than one donor in a Processing Facility is a frequent occurrence. SOPs must be in place to prevent the possibility of mix-ups or cross-contamination of products in such circumstances. SOPs should define safeguards to be employed, such as forbidding products from more than one donor to be in the Biological Safety Cabinet at any one time and should describe the cleaning and disinfection practices to be used for sequential processing using the same equipment.

Whenever possible, closed systems should be used for all processing steps. This is important not only to reduce the likelihood of microbial contamination during processing, but of cross-contamination with other infectious agents or even with cells from other cellular therapy products. GTP regulations specifically forbid the pooling of products from more than one donor during processing so as to reduce the risk of communicable disease transmission. Recently the use of cord blood from two or more donors for a single transplant procedure has been used. In such cases it is acceptable to sequentially thaw and infuse products from different donors, but it is not acceptable to pool the products into a single container for administration. For some cellular therapy products processed under approval by regulatory agencies as specified in INDs, IDEs, or equivalent approval pathway, pooled cells may be part of the manufacturing process. However, this step would have been reviewed by the competent authority and would thus be allowed under the FACT-JACIE Standards.

Evidence:
The inspector should observe the Processing Facility in operation and should ask personnel what processes are in place when multiple cellular therapy products are received into the facility on the same day. The inspector should determine (from direct observation and/or by reviewing SOPs) that aseptic technique is utilized during processing.

Example(s):
Other methods to prevent mix-ups may include identification of reagents as dedicated to a single processing procedure and a separation of records and labels to confirm that there is no mix-up of information.

STANDARD:

D8.7 *The Processing Facility shall monitor and document microbial contamination of cellular therapy products after processing as specified in Standard Operating Procedures.*

D8.7.1 *The results of microbial cultures shall be reviewed by the Processing Facility Director or designee in a timely manner.*

D8.7.2 *The recipient's physician shall be notified in a timely manner of any positive microbial cultures.*

Explanation:
Any portion of a processing protocol performed outside of a closed system should be closely monitored for microbial contamination. Use of a Biologic Safety Cabinet may be indicated. Biological Safety Cabinets should be routinely monitored for airflow and regularly maintained to safeguard the proper functioning of filters.

It is a requirement that microbial testing be performed post-processing at a minimum. Additional training in aseptic techniques and/or modification of cleaning protocols may be appropriate. Gram stains of cellular therapy products may be performed as a rapid release test but are not sensitive indicators of contamination and should not be the only form of contamination testing performed. Depending upon the culture methods used, it may be one to two weeks before final culture reports are available for Processing Facility Director (or designee) review. Once a microbial culture shows growth, the product is to be considered to have positive microbial cultures even if subsequent tests show no growth. Labeling, reporting, and other SOPs should not change. It is also inappropriate to wait for a second culture before notifying the physician.

It is the responsibility of the Processing Facility to confirm that the recipient's physician is notified of positive culture results in a timely manner. The timeframe for notification of positive microbial cultures should be defined in an SOP. There should be documentation that the most recent microbial reports available have been reviewed by the Processing Facility Director or designee prior to the release of cellular therapy products that have been cryopreserved. Cryopreserved products may be administered at the physician's discretion prior to the final culture reports or even in the presence of microbial contamination provided there is documented approval for release as part of the product record.

This documented approval includes approval by the Processing Facility Medical Director and the transplant physician. Policies and SOPs for the management of products with positive microbial culture results are required in D4. Contaminants should be identified to the level required to allow for antibiotic coverage appropriate to the organism(s) at the time of or following administration of a known contaminated product.

It is recommended that microbial testing also be performed after collection(prior to processing) in order to determine the likely source of contamination should the post-processing sample test positive.

When there is a positive result, the Processing Facility Director must review the report, and the Clinical Program must be notified as quickly as possible if the cellular therapy product has already been administered to a recipient. The Processing Facility must participate in the investigation with the clinical and collection representatives to determine if contamination occurred during collection or processing, or if the donor was septic at the time of collection.

Evidence:
The inspector should ask if any processing procedures are performed outside of a closed system, and review the records for those procedures. The inspector should review the microbiology report results to assess for microbial growth and determine the frequency of positive results.

In the event of frequent contamination, the inspector may recommend that microbial testing be performed at the initiation of processing and at intervals during processing to determine the point at which contamination occurs (e.g., when the facility received the product, while the product was in the microbiology lab, or during processing).

STANDARD:

D8.8 *Records shall be made concurrently with each step of the processing, testing, cryopreservation, storage, and administration or disposal/disposition/distribution of each cellular therapy product in such a way that all steps may be accurately traced.*

D8.8.1 *Records shall identify the person immediately responsible for each significant step, including dates and times, where appropriate.*

D8.8.2 *Records shall show the test results and the interpretation of each result, where appropriate.*

Explanation:
Records such as worksheets and batch records must be used during cellular therapy product processing and must be completed in real time as the procedure is performed. In the event that an error or adverse event results during or as a consequence of processing, it is important to perform an investigation in a timely manner. From the appropriate worksheet it must be possible to investigate each critical step, including identification of the individual responsible, and the reagents and equipment utilized.

The worksheet design must be such that the identity of the individual performing each significant step, or the same step over time can be easily determined. The worksheets also must serve as documentation that each step was performed as specified in the SOP and contain the results of in-process testing and calculations required for the next step to be performed. All personnel must be well informed of the procedures to follow when end-points are not met.

Since potency and efficacy may be affected by the competency of the individual(s) performing the processing, testing, cryopreservation, storage, administration, or disposal of a cellular therapy product, it is critical that the responsible individual(s) be identified for each significant step.

Evidence:
The inspector should examine paperwork to determine if adequate records are maintained that identify the responsible individual(s) for all significant steps of processing.

Example(s):
For example, cryopreservation of a bone marrow harvest may include: 1) receipt of the cellular therapy product into the Processing Facility with label and integrity checks, initial sampling, and cell counts, 2) a red cell depletion step (buffy coat preparation, density gradient separation, or other step), 3) washing or suspension of the cells in cryopreservation medium, and 4) the actual controlled rate freezing. Each of these is a discrete step that may be performed by different individuals. It is recommended that these critical calculations be performed at least twice and then re-checked by a second individual not involved in that processing step before proceeding to the next step.

Identifying the responsible individual(s) for each significant step is most easily accomplished by including a place for initials or other identification on relevant worksheets and forms.

STANDARD:

D8.9 *The Processing Facility Director or designee shall review the processing record for each cellular therapy product prior to release or distribution.*

Explanation:
The processing records must be reviewed in a timely fashion to detect errors that may affect patient outcome. The intent of timely review of processing records is to assure that isolated and/or systematic errors are detected as rapidly as possible. Certain records should be reviewed immediately in cases where an error would potentially cause a serious adverse event. Examples include: a) calculation of cell doses, b) labeling procedures, c) planned deviations from Standard Operating Procedures, and d) determination of reagent concentrations. Review of processing records may occur on several levels. Critical calculations should be checked by a second person whenever possible.

Other records may be reviewed within a reasonable time after processing. Examples include: a) sterility testing results, b) flow cytometry results, c) chart review, d) analysis of freeze curves, and e) reagent and supply lot number recording. All reviews and any follow-up actions must be documented. The entire processing record and recipient file should be reviewed as soon as possible after all results have been obtained.

The Processing Facility Director is responsible for determining when processing records and recipient files should be reviewed and by whom. Individuals assigned the responsibility for processing record review should not review their own work. There must be documentation that the patient's physician is notified when clinically relevant end-points are not met. Such deviations must include remedial actions when these are appropriate, which also must be documented in the processing record.

Resolution of processing errors or situations when cellular therapy products failed to meet specifications should include, at minimum, a summary of the investigation that was conducted (may be in the form of an adverse event report), corrective action, examination of relevant outcome data (i.e., engraftment, GVHD, or infection) and notification of appropriate individuals.

STANDARD:

D8.10 *There shall be documented notification to the recipient's physician and the Processing Facility Medical Director of clinically relevant processing end-points not met and remedial actions taken.*

Evidence:

The inspector should ask to see written procedures that describe the review process and indicate by whom and when the review takes place. Recipient files should be examined to verify that these procedures are in effect as described in the SOP. The Processing Facility should be prepared to provide examples of processing errors or cellular therapy products that failed to meet specifications so the inspector can determine how the situation was resolved.

Example(s):

The inspector should ask to see an event information report (or equivalent document) that describes the problem, indicates who was involved, when and how the event occurred, an investigation of the event, and any corrective and preventive actions taken to prevent a future occurrence (including follow-up activities).

STANDARD:

D8.11 *Processing using more-than-minimal manipulation shall only be performed with Institutional Review Board or Ethics Committee approval, with the written informed consent of the donor, if applicable, and the recipient of the cellular therapy product, and in compliance with applicable laws and regulations.*

D8.11.1 *The Processing Facility shall adhere to good manufacturing practices (GMP) appropriate for the degree of cellular therapy product manipulation.*

Explanation:

Due to the investigational nature of more-than-minimal manipulation, recipients and donors must sign consent forms for any graft manipulation beyond minimal as defined by the Standards and applicable laws and regulations. Assurance of recipient safety and the ability to conduct responsible research are equally important goals central to the missions of FACT and JACIE.

Evidence:
If procedures are performed in the Processing Facility other than minimal manipulation, the inspector should inquire if IRB and the appropriate IND or IDE approval has been obtained.

Example(s):
Many centers require that all processing procedures be performed with informed consent, while in others certain processing procedures have become standard of care. In these cases, the protocol per se is not IRB reviewed, but the recipient should still consent to the procedure. In most institutions, consent forms are not part of the processing record; instead, consent forms are part of the recipient or donor chart records. In such cases, the Processing Facility Director must know that consents have been signed and this should be verified by the inspector.

Minimal manipulation is defined by the FDA as "processing that does not alter the relevant biological characteristics of cells or tissues." If a Processing Facility does not perform more than minimal manipulation, then GMP does not apply.

STANDARD:

D8.12 For allogeneic cellular therapy products containing red blood cells at the time of administration:

D8.12.1 Results for ABO group and Rh type testing shall be available from two (2) independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

D8.12.2 Results for a red cell antibody screen on the recipient shall be available.

Explanation:
ABO group and Rh typing is performed on blood and/or cellular therapy products from allogeneic donors and recipients to avoid the unintentional use of ABO incompatible products containing RBCs or anti-RBC antibodies that might result in an adverse reaction during or after product administration. This testing is required to provide an easily and inexpensively obtained measure of patient safety from gross hemolytic reactions and/or late hemolytic reactions that might result from engraftment of B-lymphocytes producing anti-AB or anti-Rh antibodies, and is not intended in any way to be a poor secondary patient or donor identifier. While the Processing Facility will generally not be responsible for collecting these samples or conducting the testing on them, there should be documentation present to demonstrate that the facility has confirmed these results prior to product release.

The Standards require testing on two independently collected samples. The timing of the collection of these samples is not specified; however, the entire process of collecting the two samples must be distinct from one another (i.e., different needle sticks and different phlebotomists if staff allows). It is not acceptable to collect the two samples at the same time. The results of both tests should be available to clinical, collection, and processing. The cellular therapy program determines who collects the samples and who performs the testing. Note that these are minimum requirements, and the cellular therapy program may elect to perform more testing, more frequent testing, or testing on the first day of collection as it determines to be appropriate.

The Standards do not dictate how ABO and Rh incompatible cellular therapy products should be processed. However, the Processing Facility must have a policy regarding management of products that are ABO and/or Rh incompatible between donor and recipient (see D5.1). The policy should indicate when and if compatibility testing is to be performed, how many incompatible red blood cells (or volume of red blood cells) are acceptable for administration, and what, if anything, should be done in the case of ABO-incompatible plasma. The policy should also include instructions for recipients and/or donors with positive antibody screens (other than ABO antibodies). Processing protocols must clearly state how to achieve the stated guidelines for ABO and Rh incompatible products. There must be protocols indicating what the facility's responsibilities are and what should be done with the product in the case of an administration reaction that is suspected to be the result of red blood cell antibodies.

In the event that the Processing Facility routinely performs compatibility testing on all donors and recipients, regardless of the ABO type, consideration should be given to the consequences of labeling a product for administration as ABO incompatible. Under these circumstances there should be an SOP in the Clinical Program that explains and justifies the use of ABO-incompatible cellular therapy products and distinguishes these products from standard blood products. Likewise, if RBC compatibility testing is performed on some but not all donors and recipients, there must be an SOP available to the clinical staff that explains the circumstances under which RBC compatibility testing is and is not performed. If RBC compatibility testing is not performed and the label includes a place for these results, the label should be marked with "N/A" or other appropriate response.

Evidence:
The inspector will look for records of ABO and Rh typing results and antibody screening in the processing chart records.

Example:
Allogeneic donors may be tested at the time they are initially evaluated for donor suitability and eligibility and a second test may be performed at the time of cellular therapy product collection. Alternatively, both tests may be performed prior to collection.

STANDARD:
D8.13 *There shall be a Standard Operating Procedure to confirm the identity of cord blood units if verification typing cannot be performed on attached segments.*

Explanation:
The WMDA has reported an incident in which the incorrect cord blood unit was distributed and administered to a recipient, thus illustrating the importance of verifying the receipt of the correct unit. HPC, Cord Blood products are manufactured with a limited number of attached segments (one to three) when cryopreserved. Verification HLA typing is typically performed when a cord blood unit is under consideration for a recipient. Most Clinical Programs obtain verification typing on several units before they select the optimal unit for their patient. Thus, a given unit may be typed but not selected for administration by the initial Clinical Program requesting the first verification typing. Due to the limited number of segments attached to a given unit, verification HLA typing may not be repeatable by subsequent Clinical Programs. A unit that has been previously typed for verification may be selected by a subsequent Clinical Program without repeating this test, as long as the verification typing results match the original typing on the unit and are provided to the subsequent Clinical Program.

Example(s):
If no integrally attached segments or samples are available for verification typing, Clinical Programs may wish to verify typing by a more limited panel of HLA tests or with the use of other genetic markers, such as short tandem repeats (STRs).

STANDARD:
D8.14 One or more samples representing the cryopreserved cellular therapy product shall be stored.

D8.14.1 Sample(s) from cryopreserved cellular therapy products shall be stored under conditions that achieve a valid representation of the clinical product.

D8.14.2 Cryopreserved samples shall be retained according to institutional Standard Operating Procedures.

Explanation:
This standard requires that one or more samples of individual cryopreserved cellular therapy products be available in case further testing of the product is required. Samples from products that have been cryopreserved must be stored under conditions that allow the sample to represent the product. Such samples should be stored at the same temperature range of the product.

The method by which cellular therapy product samples are cryopreserved is determined by the Processing Facility Director. It should be acknowledged that methods for cryopreservation of a small aliquot versus the product may not be considered to produce identical results, regardless of whether they are frozen at the same time in the same controlled-rate freezer or separately using different procedures. However, the availability of a sample of the product to be administered has potential value for quality control and/or investigative purposes. Privacy regulations may prohibit the use of stored aliquots for research unless IRB approval is obtained.
The director should verify that appropriate consent and/or IRB approval is in place before stored aliquots are used for research projects. Routine tests performed on aliquots for quality control purposes should be determined by the director. For HPC products, this testing often includes the assessment of viability and cell recovery, CFU content, and CD34 content. Whatever testing is performed must be specified in the processing SOP and those tests must be validated and controlled.

For some cryopreserved cellular therapy products, storage of additional samples is not possible due to low volume and/or low cellular content of the final product. In such situations, a cell-free sample that represents final steps of the processing shall be stored so repeat evaluation of microbial contamination, if needed, can be performed. For example, the negative fraction from cell-enrichment processing may substitute for the supernatant from the final product wash in preparation for freezing. The most appropriate step during the processing to collect such a sample shall be determined by the Processing Facility Director.

The cellular therapy product sample(s) that are not used for testing must be stored according to institutional SOPs.

Evidence:
The inspector should request an inventory log for samples of cryopreserved cellular therapy products that are, or have been, stored.

Example(s):
It is preferred but not required that samples from cryopreserved cellular therapy products be stored in the same freezer as the product so as to represent not only the product freezing conditions but also the storage conditions.

It is also recommended, but not required, to store the samples(s) minimally 10 years after the final disposition (administration, transfer, or discard) of the cellular therapy product or until the patient expires. While there may be scientific value in maintaining product samples longer, it is appreciated that cryopreservation storage space may be at a premium. The inspector should review the Processing Facility's policies and SOPs for storage of archive samples.

D9: CELLULAR THERAPY PRODUCT STORAGE

STANDARD:

D9.1 *Processing Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper distribution of cellular therapy products.*

D9.2 *STORAGE DURATION*

D9.2.1 *Processing Facilities processing, storing, and/or releasing cellular therapy products for administration shall assign an expiration date and time for non-cryopreserved products and for products thawed after cryopreservation.*

D9.2.2 *There shall be a written stability program that evaluates the viability and potency of cryopreserved cellular therapy products, minimally annually.*

Explanation:
Product stability and establishment of product expiration depend on processing and storage methods. The validation of new cellular therapy products, or the validation of changes in processing or cryopreservation, require stability testing program be established and maintained.

There must be a stability program in place that evaluates cellular therapy products each year with predefined criteria, but is not prescriptive in terms of the number of products, which products are tested in a given year, or other details. Retrospective studies are acceptable. For cellular therapy products, potency is generally measured by CD34 recovery, in addition to total viability. For cellular therapy products in early phase trials, the stability program should be in place but may not have mature data available. The stability program for all cellular therapy products should assess characteristics that affect the safety and efficacy of the product including sterility, container and label integrity, and as other characteristics as defined by the program.

Example(s):
Stability testing can be performed using cellular therapy products stored for more than a year that are scheduled to be discarded and/or could be performed with samples from products that were frozen and stored under the same conditions as the actual product. Testing of products intended to restore hematopoiesis can include TNC viable cell recovery post thaw as a useful alert that there might be problems with the freeze run. An assessment of the recovery of viable CD34 cells or recovery of other cell populations where applicable, such as viable T lymphocytes recovery for cells to be used for donor lymphocyte administration, should be included. Processing Facilities are encouraged to discontinue any use of research-grade reagents and adopt single platform technology and diagnostic kits that include a viability marker.

STANDARD:
D9.3 TEMPERATURE

D9.3.1 Storage temperatures shall be defined in Standard Operating Procedures.

D9.3.2 Noncryopreserved cellular therapy products shall be maintained within a specific temperature range to maintain viability and function, to inhibit infectious agents, and for a period of time not to exceed that specified in Standard Operating Procedures.

D9.3.3 Cryopreserved cellular therapy products shall be stored within a temperature range, as defined in Standard Operating Procedures, that is appropriate for the product and cryoprotectant solution used.

Explanation:
The Processing Facility must establish a process to assure that cellular therapy products are stored in a manner that maintains their integrity and potency and that assures that products are not released prematurely before all release criteria have been met. Standard D2 requires that defined areas for storage be established and that these areas be controlled to prevent the possibility of mix-ups, contamination, or cross-contamination. This process is further defined as to require control of the storage duration and the appropriate storage temperature.

The Processing Facility should define what constitutes storage. Storage often occurs prior to processing, either within the Processing Facility or at the Collection Facility as well as after processing is complete. Storage temperature and duration shall be defined by the storing facility and shall include conditions for non-cryopreserved, cryopreserved, and thawed cellular therapy products. Products that have been processed and are awaiting the results of release testing (i.e., CD34 cell assessment by flow cytometry or the completion of allogeneic donor eligibility determination) may be held in quarantine at one temperature (i.e., up to 4 hours at room temperature) but stored for longer periods at another temperature (i.e., 1-8°C). Temperature ranges and duration must be determined for each type of product and should be based on the medical literature and/or on the facility's own experimental data. For liquid products, including thawed products, temperature ranges, storage duration, and product expiration date and time must be established to safeguard adequate viability and to decrease the risk of contamination. Processing procedures should specify the temperatures at which products are handled and processed prior to storage. Likewise, transport and shipping temperature both from the Collection Facility to the Processing Facility, and at distribution from the Processing Facility, must be defined.

The medical literature reports a variety of cryoprotectant agents used to store HPC products, as well as temperatures ranging from -80°C to liquid phase nitrogen (-196°C). The chosen storage temperature must be adequate for the preservation of the desired cell type, as documented either in the medical literature or the Processing Facility's own experience. When possible, storage of cryopreserved cellular therapy products at temperatures ≤ - 150°C is advisable. Methods to reduce the risk of contamination or cross-contamination must be included. No upper limit of storage time for products stored at temperatures equivalent to the vapor (-120°C to -155°C) or liquid phase (-196°C) of liquid nitrogen has been reported, provided the product has been maintained at that temperature throughout the storage period. The effects on storage time of temperature fluctuations above -120°C are largely unknown; however, failure to maintain the product in a frozen state can result in a loss of viability within minutes to hours. The viability of products in any low-temperature storage device that has not maintained the proper temperature is potentially compromised. The validation of cryopreservation procedures must include evidence that the prescribed storage temperature range adequately preserves the products being stored. Expiration date and time does not have to be assigned to cryopreserved products if storage conditions are shown to be adequate based on the medical literature and/or are justified by validation studies, where applicable.

In the case of autologous and/or related donations, donors, recipients, and associated clinical programs should be informed of the conditions of storage and storage duration, preferably before product collection.

Evidence:
Storage criteria must be defined by Processing Facility SOPs or policies. The inspector should review the facility's established storage criteria for all relevant cellular therapy products and any related contracts or consents. A written plan for determining the stability of cryopreserved products and the acceptable end point parameters must be present.

Example(s):
Informing donors, recipients, and associated clinical programs may be accomplished by informed consent, contractual agreement, or other legal means.

In the EU, the expiration date must be part of the cellular therapy product information for all tissues and cells. For licensed products, such as cord blood in the U.S., the Processing Facility should maintain the products at the temperature recommended by the organization that provided it. Applicable law may specify what testing and frequency of testing to establish cryopreserved product stability is required.

STANDARD:

D9.3.4 *Prior to receipt of a cellular therapy product from an external facility, there shall be confirmation that the product can be appropriately stored.*

Explanation:
The Processing Facility (or Clinical Program on its behalf) must communicate with the distributing external facility regarding the details of the cellular therapy product being sent, such as the size and type of the container, how many containers, appropriate storage conditions, etc.

Example(s):
Cord blood units are one example of a cellular therapy product for which special arrangements may need to be made at the Processing Facility. These products are often in canisters that may be too small for the racks typically used for other types of products and special arrangements should be made in advance.

STANDARD:
D9.4 PRODUCT SAFETY

D9.4.1 Materials that may adversely affect cellular therapy products shall not be stored in the same refrigerators or freezers as the cellular therapy products.

D9.4.2 For cellular therapy products immersed in liquid nitrogen, procedures to minimize the risk of cross-contamination of products shall be employed.

D9.4.3 Processes for storing cellular therapy products in quarantine shall be defined in Standard Operating Procedures.

D9.4.3.1 Quarantined cellular therapy products shall be easily distinguishable and stored in a manner that minimizes the risks of cross-contamination and inappropriate distribution.

D9.4.3.2 All cellular therapy products with positive infectious disease test results for relevant communicable disease agents and/or positive microbial cultures shall be quarantined.

D9.4.3.3 Processing Facilities storing cellular therapy products shall quarantine each product until completion of the donor eligibility determination as required by applicable laws and regulations.

Explanation:
Evidence has been published demonstrating the possibility of cross-contamination of cellular therapy products stored in the liquid phase of liquid nitrogen with infectious virus (Tedder RS, Zuckerman MA, Goldstone AH, Hawkins AE, Fielding A, Briggs EM, Irwin D, Blair S, Gorman AM, Patterson KG, Linch DC, Heptonstall J, Brink NS: Hepatitis B transmission from contaminated cryopreservation tank. Lancet 346:137-140, 1995).

Infections occurring in recipients following the administration of cryopreserved cellular therapy products shall be reported to the Processing Facility so that the facility can undertake an investigation of possible cross-contamination when unusual patterns are seen and report to the proper authority as required by law.

Quarantine is defined in A4 as the identification of storage of a cellular therapy product in a physically separate area clearly identified for such use, or through use of other procedures such as automated designation to prevent improper release of that product. It also refers to segregated storage of products known to contain infectious disease agents to reduce the likelihood of cross-contamination.

Quarantine of cellular therapy products that have not undergone complete allogeneic donor eligibility determination, are from known ineligible donors, or have not yet completed other required release testing (i.e., sterility cultures) is required. Quarantine does not require physical segregation of such products, but does require a mechanism to minimize the potential for cross-contamination of communicable disease agents and to prevent product distribution when release is not approved.

Appropriate labeling should be used to distinguish cellular therapy products that are in quarantine, such as the use of quarantine tie tags that clearly state that the product may not be released without physician notification and approval.

Evidence:
The inspector should review the Processing Facility's program to reduce the likelihood of cross-contamination of containers in liquid phase storage. The inspector should review the systems that are in place to distinguish quarantined cellular therapy products and to prevent their inappropriate release.

Example(s):
A quarantine program may include but may not be limited to the following practices:

- Protective outer coverings over the primary freezing bag.
- Use of vapor-phase storage.
- Use of mechanical freezer storage.
- Use of a validated electronic release system that prevents inappropriate release of cellular therapy products.

These procedures are recommended at this time, but until scientific studies validating the effectiveness of one or more of these approaches are available, no standard method can be specified.

Quarantine may be accomplished physically by storing quarantined cellular therapy products on a separate shelf or in a separate rack or compartment of the storage unit. The methods suggested above are effective in minimizing the potential of cross-contamination of products that are stored frozen. Non-cryopreserved products may more appropriately be stored in a separate area in the Processing Facility while release testing is being performed. If an electronic system is used for product release, an audit trail that indicates who was responsible for the release must exist.

STANDARD:
D9.5 STORAGE MONITORING

D9.5.1 Refrigerators and freezers used for storage where cellular therapy products are not fully immersed in liquid nitrogen shall have a system to monitor the temperature continuously and to record the temperature at least every four (4) hours.

Explanation:
It is required that the storage temperature be monitored on a continuous basis and that temperatures be recorded at not less than a four-hour interval for vapor phase storage. Temperature records of stored cellular therapy products, including alarm conditions, must be reviewed prior to product distribution. Failure of the device to maintain the target temperature represents a deviation that must be documented and that includes the appropriate investigation and follow-up actions required to

determine the integrity and potency of the product. The Processing Facility should establish critical values that, if exceeded, require documentation in the processing and storage records for those products in the storage freezer that did not maintain target temperature. In the case of suspected thawing of cryopreserved products, the recipient's primary transplant physician must be notified. The primary transplant physician, in collaboration with the Processing Facility Director or designee, makes a decision regarding continued storage of the product. As specified elsewhere in the Standards, the facility must have written SOPs specifying actions to be taken in the case of cryopreservation failure.

STANDARD:

D9.5.2 *There shall be a mechanism to confirm that levels of liquid nitrogen in liquid nitrogen freezers are consistently maintained to assure that cellular therapy products remain within the specified temperature range.*

Explanation:
For cellular therapy products stored in liquid nitrogen, temperature monitoring does not have to be continuous or even every four hours, but at intervals determined by the Processing Facility Director to be sufficient to safeguard levels of liquid do not fall below set limits between measurements. The objective is to confirm that products are continuously maintained at the target storage temperature. Validation studies may be especially important to assure that the level limits that trigger alarms are suitable to allow sufficient time to rescue products before they reach temperatures that might compromise their viability and functionality.

STANDARD:

D9.6 *ALARM SYSTEMS*

D9.6.1 *Storage devices for cellular therapy products or reagents for cellular therapy product processing shall have alarm systems that are continuously active.*

Explanation:
The failure of mechanical or liquid nitrogen freezers can result in the loss of potentially irreplaceable cellular therapy products stored for future use. It is essential that precautions be taken to prevent loss of any stored products. Alarm systems and mechanical freezers must be supplied with back-up power systems (battery- or generator-based) to confirm they are continuously active.

Evidence:
The inspector should review records of storage device alarm checks of function and triggering at the appropriate limits (temperature, liquid level, etc.).

STANDARD:

D9.6.2 *Alarm systems shall have audible and visible signals or other effective notification methods.*

D9.6.3 *Alarm systems shall be checked periodically for function.*

D9.6.4 *If trained personnel are not always present in the immediate area of the storage device, a system shall be in place that alerts responsible personnel of alarm conditions on a 24-hour basis.*

D9.6.5 *Alarms shall be set to activate at a temperature or level of liquid nitrogen that will allow time to salvage products.*

D9.6.6 *Written instructions to be followed if the storage device fails shall be displayed in the immediate area of the storage device and at each remote alarm location.*

Evidence:
The inspector should review the action plan in case of failure, including the mechanism for notifying responsible Processing Facility personnel. The inspector should also verify that instructions to be followed in the event of a storage device failure are posted in the immediate area of the storage device. The inspector should review these instructions.

Example(s):
Instructions may include information on "who to contact," and is particularly applicable in Processing Facilities that do not provide 24-hour service, but have arranged with their institutions' facilities and engineering departments, security, or other service departments to be the on-site responder to a freezer alarm. Instructions may also include "what to do," and may consist of a trouble-shooting flowchart located at the freezer device for quick reference and immediate response by the technical staff.

STANDARD:

D9.6.6.1 *Instructions shall include a procedure for notifying processing personnel.*

D9.6.7 *Storage devices of appropriate temperature shall be available for cellular therapy product storage if the primary storage device fails.*

Explanation:
Back-up storage devices (either internal or external) capable of maintaining cellular therapy products with an acceptable storage temperature range must be identified in advance in the event of interruption (D4) or mechanical failure of the storage device (e.g., rupture of liquid nitrogen storage tank), or the event of a disaster (D5.1). Instructions describing the actions to take must be in the form of an SOP (see D5.1). Records of temperatures during storage must be available, with notations made for action taken when temperatures fall outside of the designated range.

Example(s):
Failure of a primary storage device or a disaster may result in activating preplanned use of a backup device available either in the same or a different facility. The plan should factor in prioritization based on recipient status (e.g., imminent transplant).

STANDARD:

D9.7 *The storage device shall be located in a secure area and accessible only to personnel authorized by the Processing Facility.*

Explanation:
Cellular therapy products for administration must be in secure locations to prevent accidental or deliberate tampering with products or with storage devices that may result in failure to maintain the proper storage temperature.

Laboratories that do not have total control over personnel entering the facility must have a process in place to identify who has access and to prevent unauthorized access.

Example(s):
Security may include storage devices with locks, electromagnetic security capabilities, or an enclosed room with door locks.

STANDARD:

D9.8 The Processing Facility shall use an inventory control system to identify the location of each cellular therapy product and associated samples. The inventory control system records shall include:

D9.8.1 Cellular therapy product unique identifier.

D9.8.2 Recipient name or unique identifier.

D9.8.3 Storage device identifier.

D9.8.4 Location within the storage device.

Explanation:
There must be a mechanism by which cellular therapy products and sample vials from the products can be located in storage devices and a system to track remaining units. This is to prevent retrieval of the wrong product and minimize exposure of products to temperatures outside acceptable limits during the storage or the retrieval process. Audits must be performed periodically to confirm proper function.

The system shall include the elements described in this standard. These elements should allow tracing back to additional cellular therapy product information, such as the recipient name or unique identifier (if known), the date of collection or processing, the date of issue, and the disposition.

Evidence:
The inspector should ask for a demonstration of the system, including verification that the cellular therapy product can be located in the storage container. The inspector should also review the processes in place to make changes in inventory entries when products are added or removed to assure the integrity of the system is maintained.

Example(s):
The inventory control system may be in the form of an electronic database or may consist of log books or other manual systems.

D10: CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING

STANDARD:

D10.1 *Standard Operating Procedures for transportation and shipping of cellular therapy products shall be designed to protect the integrity of the product and the health and safety of individuals in the immediate area.*

Explanation:

The Processing Facility must have transportation and shipping SOPs in place to assess risks during distribution to cellular therapy product integrity and recipient status (i.e., imminent transplant). This process must include container validation and courier qualifications.

The Processing Facility shall have written policies and SOPs for the distribution of cellular therapy products to and from the facility. Such SOPs include transport or shipping from internal sites, such as from the Collection Facility to the Processing Facility, at release to internal clinical program sites, or to external facilities. These SOPs must include maintenance of optimal temperature during distribution. The product container and tubing must be securely sealed and packaged to protect it from potential harm during transit and to prevent exposure of individuals involved in its transport and/or shipping to potentially infectious agents.

Human tissue, regardless of infectious disease testing, must be considered potentially infectious. For non-cryopreserved products, absorbent material in the transport container is no longer required by the Standards, but is a recommended practice in the event of breakage.

Evidence:

The inspector must determine if the transport and shipping SOPs in use within the Processing Facility are adequate for the conditions. The inspector should review receipt records of both non-cryopreserved and cryopreserved cellular therapy products shipped and received by the facility for adherence to the Standards. Inspectors should verify a process and container validation is adequate to demonstrate maintenance of product security and integrity during expected transit time and ambient temperature conditions specific to the transport and shipping systems in use.

STANDARD:

D10.2 *The primary product container for non-frozen cellular therapy products shall be placed in a secondary container and sealed to prevent leakage.*

Explanation:

For non-cryopreserved products, a thermally insulated container should be used with appropriate temperature stabilizing material such as cold packs, temperature stabilizing packs, or phase-change materials specific to the validated container system(s) in use, which are necessary to maintain the required temperature. Containers utilizing TIC panels made of a hard plastic and that contain phase change material in liquid form may be considered the equivalent of thermal insulation, as product is protected from frozen material by the outer hard plastic. These types of containers require process validation.

STANDARD:

D10.3 *Cellular therapy products that require a temperature-controlled environment and that are transported or shipped over an extended period of time shall be transported or shipped in a container validated to maintain the appropriate temperature range.*

Explanation:

These SOPs must include maintenance of optimal temperature during distribution. The cellular therapy product temperature during transit is dependent upon a number of variables, including: the transport time, ambient temperature ranges, initial temperature, size of the product, and characteristics of the specific container system. The ideal transport temperature of non-cryopreserved products may range from 1-24°C. There must be a prospective agreement among the collecting, processing, and receiving facilities regarding transport and shipping conditions based on intended use of the product upon receipt, among other factors. Most products should not be transported or shipped at temperatures above 24°C. Non-cryopreserved products should never be allowed to cool to temperatures below freezing.

For cellular therapy products transported between sites of a single cellular therapy program, the distance between the facilities varies widely. Transport between facilities, where the product remains in the control of trained personnel, usually requires the use of an outer container that protects the product from adverse conditions encountered during transport (e.g., air pressure changes, rough handling, exposure to extremes of temperature, unexpected delays), and that has been validated to maintain the agreed transport temperature for the expected transit time and conditions.
For situations where transport to and from the Processing Facility requires only minutes, such as between adjacent facilities, a controlled temperature environment is optional, provided the product is transported securely, safely, and remains in the control of trained personnel. However, for extended periods of transport time within a facility or outside of a building, a controlled temperature environment should be maintained using a validated outer container and shall remain in the control of trained personnel.

Validation and periodic quality control must be performed on all dry shippers used for cryopreserved cellular therapy products and for containers used for non-cryopreserved products, specific to the transit conditions expected and the design and characteristics of the containers or shippers in use. Validation must be performed prior to use and when changes to the container system are made. Containers should be monitored to safeguard continued performance and verified or re-validated periodically per Processing Facility-defined SOPs. Calibration and verification of function of data loggers per manufacturer's recommendation is required.

Example(s):

Refrigerated cellular therapy products shall be insulated from direct contact with frozen materials during transportation and/or shipping. Frozen products may be placed in the dry shipper surrounded by material such as styrofoam to absorb impacts during shipping.

Total nucleated cell (TNC) count, viability of product, etc., are examples of data on which temperature ranges should be established.

STANDARD:

D10.4 *Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.*

D10.5 *Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.*

Explanation:

For transported or shipped cellular therapy products, an appropriate shipping container should be utilized whether product transport is internal or external. The shipping container must be validated for its intended purpose for all types of products transported (i.e., fresh unfrozen products or cryopreserved) and the temperature at receipt of the product should be documented. For cryopreserved products, the container should maintain the temperature at least 48 hours beyond the expected time of arrival at the receiving facility and be "charged" for use following the manufacturer's instructions.

STANDARD:

D10.5.1 *The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.*

D10.5.2 *The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transport or shipping.*

Explanation:

Containers for distribution of cryopreserved and non-cryopreserved products that leave the Processing Facility must be made of durable material and insulation that will withstand leakage of contents, shocks, pressure changes, and temperature extremes. Transport containers containing cellular therapy products should not be exposed for prolonged periods to extreme heat or cold. Since cryopreserved product primary containers are susceptible to breakage, they must be packaged so as to minimize movement during transit. At a minimum, the acceptability of all products must be verified at receipt. As a minimum, documentation of this inspection and container temperature at receipt is required for the processing records of the receiving facility for all products.

STANDARD:

D10.5.2.1 *The temperature of the shipping container shall be continuously monitored during shipment of cellular therapy products.*

Explanation:

When cryopreserved products are shipped to another facility, and are not in the control of the Processing Facility or receiving facility personnel, the temperature during shipment must be continuously monitored and that record must be maintained by the distributing facility. For cryopreserved products that are transported (hand carried) by knowledgeable personnel from the distributing or receiving facility, product temperature at the receiving facility should be documented regardless of the distance traveled.

STANDARD:

D10.5.2.2 The shipping facility shall maintain a record of the temperature over the period of travel.

Explanation:
Continuous monitoring that creates a record typically utilizes a thermometer with data logging capability. The frequency of data capture is not specified, but should be sufficient to confirm that the proper temperature was maintained. For external transportation, it is recommended that a copy of the data logger printout be shared with the receiving facility for their records; however, documentation from the distributing facility of the temperature conditions during transport would be acceptable.

STANDARD:

D10.5.3 The outer container shall be secured.

D10.5.4 The outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix III.

D10.5.5 There shall be a document inside the outer container that includes all the information required on the outer container, in conformity with the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix III.

D10.5.6 The outer container shall be labeled in accordance with applicable laws and regulations regarding the cryogenic material used and the transport or shipment of biological materials.

Explanation:
Labeling that must be affixed to the outer container or accompanying the cellular therapy product is specified in Appendix III.

Appropriate biohazard and warning statements must be present on the documentation inside the container. Outer containers bearing biohazard and warning statements on the exterior of the container will be refused by some carriers.

Information regarding shipping and receiving facilities and responsible individuals at those centers is required for contact in the event of delay or emergency during transit or questions about the cellular therapy product arise after it reaches its destination. Having this information attached to the container safeguards that the product can be delivered in the event that the accompanying paperwork is lost or destroyed. To safeguard anonymity of donors and recipients of unrelated transplants, neither the donor nor recipient name shall be on the transport or shipping label; however, unique identifiers are appropriate.

The Processing Facility personnel are responsible for verifying the labeling requirements of any courier services utilized.

The courier should be able to contact the receiving facility on a 24-hour basis in case of emergency or delay during transit. Shipping instructions, contact names, and phone numbers should be printed or, if handwritten, clearly legible.

Evidence:
The inspector should review transportation and shipping records and inspect outer containers to confirm that the elements in this section are met and documented.

Example(s):
EU regulations also require the time at the start of transportation or shipping, and require specification of the conditions of transportation or shipping relevant to the quality and safety of the tissues and cells, such as "Keep Cool," "DO NOT FREEZE," "Keep Upright," etc.

STANDARD:

D10.6 *The transit time shall be within time limits determined by the distributing facility in consultation with the receiving facility to maintain cellular therapy product safety.*

D10.7 *If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported.*

Explanation:
If a patient has undergone high-dose marrow ablative treatment in preparation for transplant, the cellular therapy product is essential for the patient's survival since it may not be possible to obtain additional marrow or blood from the original donor or a second donor in time to prevent complications from aplasia. For this reason, it is important that the product be entrusted to a knowledgeable individual who accompanies it from the distributing facility to the receiving facility.

STANDARD:

D10.8 *There shall be plans for alternative means of transport or shipping in an emergency.*

D10.9 *The cellular therapy products should not be passed through X-Ray irradiation devices designed to detect metal objects. If inspection is necessary, the contents of the container should be inspected manually.*

Explanation:
Outer containers should not be exposed to gamma irradiation or X-Ray devices designed to detect metal objects to prevent potential damage that may compromise progenitor cell repopulating capacity. Circumstances may require X-Ray by airport security personnel. Those situations should be avoided if possible, but complied with as required.

Evidence:
SOPs should address alternative emergency transport and provide direction to request a manual inspection of cellular therapy products rather than X-Ray exposure. Inspectors should review the process for qualification of courier appropriate to the transportation and/or shipping methods provided.

D11: DISTRIBUTION AND RECEIPT

STANDARD:

D11.1 DISTRIBUTION CRITERIA

D11.1.1 The processing, collection, and transport or shipping records for each cellular therapy product shall be reviewed by the Processing Facility Director or designee for compliance with Standard Operating Procedures and applicable laws and regulations prior to product release or distribution.

D11.1.1.1 Records shall demonstrate traceability from the donor to the recipient and from the recipient to the donor.

Explanation:

By definition, distribution is the time at which the cellular therapy product leaves the control of the Processing Facility. This includes both distribution of the product within the institution for administration and release of the product to an outside facility for additional processing or administration. In both cases, review of the product's processing and tracking records by the Processing Facility Director or designee is required to confirm that the product meets all predetermined criteria for release including those required by the Standards, the Processing Facility's own SOPs, and applicable regulations. Documentation of specific areas of review must include:

- Allogeneic donor test results to confirm that the relevant communicable disease agent tests were performed within the required time span.
- Confirmation that the unique product identifier on the label matches the identifier in the facility records and can be traced to the donor records. Tracking and tracing must be bi-directional from donor to recipient and from recipient to donor.
- Review that donor eligibility determination was completed. o
- Review of the entire processing record for completeness and accuracy per SOPs.

STANDARD:

D11.1.2 Each cellular therapy product shall meet pre-determined release criteria prior to distribution from the Processing Facility. The release criteria shall include donor eligibility determination for allogeneic products. D11.1.2.1 The Processing Facility Director or designee shall give specific authorization for release when the cellular therapy product does not meet technical release criteria.

D11.1.2.2 The Processing Facility Medical Director or designee shall give specific authorization for release when the cellular therapy product does not meet clinically relevant release criteria.

D11.1.2.3 Documentation of agreement between the Processing Facility Medical Director or designee and the recipient's physician to use any non-conforming product shall be retained in the processing record if such release is allowed by policies, Standard Operating Procedures, or package inserts of licensed products.

Explanation:
The Standards also require that there be predefined release criteria for distributed products and that there be provisions for exceptional release when a given cellular therapy product does not meet established criteria.

While the Processing Facility Director or designee may approve the release of products that meet all release criteria, the Processing Facility Medical Director or another suitable designee with the appropriate medical background must authorize exceptional release when the failed criteria might affect the clinical efficacy of the product. It is left to the Processing Facility to define who the "designee" would be that meets the knowledge requirement for approval for release of a product under exception, and this should be clearly defined in the facility SOP for product approval for release.

A designee is 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.

Evidence:
The inspector should review documentation that release criteria are defined and are met for given product types issued by the Processing Facility. Additionally, the inspector should specifically review records of products released under exception to confirm that the required documentation of Processing Facility Director, Processing Facility Medical Director, or designee approval and physician notification is present.

Example(s):

For failed release criteria that are technical or clerical in nature, the Processing Facility Director or designee may approve the product for release. Such examples may include a review of the processing record that shows a missing signature, or a product with an adequate cell dose but a below-expected cell recovery (assuming that cell recovery was considered to be a release criteria).

STANDARD:

D11.1.3 Each cellular therapy product issued for administration shall be visually inspected by two (2) trained personnel immediately before release to verify the integrity of the product container and appropriate labeling.

D11.1.3.1 A cellular therapy product shall not be released when the container is compromised and/or recipient or donor information is not verified unless the Processing Facility Director or designee gives specific authorization for the product's release.

Explanation:
The processing record of products issued under exceptional release must include documentation of consent from the recipient's physician. The release process includes the requirement for two trained individuals to inspect the final product to confirm that the product is properly labeled, is intact, and is normal in appearance. The individuals may be members of the patient care team, or the Processing Facility staff.

Evidence:
The inspector should review the release documentation to verify that all the requirements were met and the signatures of two trained individuals exist.

STANDARD:

D11.1.4 For each type of cellular therapy product, the Processing Facility shall maintain and distribute or make a document available to clinical staff containing the following:

D11.1.4.1 The use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

D11.1.4.2 Instructions for handling the cellular therapy product to minimize the risk of contamination or cross-contamination.

D11.1.4.3 Appropriate warnings related to the prevention of the transmission or spread of communicable diseases.

Explanation:
The frequency with which individuals are involved in administration of a given type of cellular therapy product may vary. Information regarding the product should be made available to the transplant medical staff within the Clinical Program to provide a full description of the product and the way in which the product should be handled and administered based on the current protocols and practices of the institution. Instructions for administration must include information to prevent the introduction, transmission, or spread of communicable diseases.

The instructions for administration may contain cell types that are not currently being used at the Processing Facility, but must include all cell types that are in use. The facility will need to generate instructions for administration for cellular therapy products not included in this document, and may create their own documents for all products as long as they meet the criteria specified in this section of the Standards. The facility may wish to issue a "Circular of Information" with each administration although this is not required by the Standards. The circular must be available to personnel at the sites where administrations are performed. However, EU regulations require that instructions for opening the container, package, and any required manipulation or reconstitution be included as a document accompanying the product. Like SOP manuals, these documents should be reviewed at least every two years and must reflect the current practices in the facility.

Evidence:
The inspector should review the current version of the instructions for administration and its availability at the sites of administration.

Example(s):
A "Circular of Information for the Use of Cellular Therapy Products" document has been prepared jointly by multiple organizations, including FACT and JACIE. This document provides the information listed in D11.1.4 for commonly used hematopoietic cellular therapy products and may be used to satisfy the requirements of this standard. A copy may be downloaded from the FACT website at http://factwebsite.org/Inner.aspx?id=691.

A method of circulating this information is via an SOP for administration that describes all elements listed in this standard.

STANDARD:

D11.2 DISTRIBUTION RECORDS

D11.2.1 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:

D11.2.1.1 The proper product name and identifier.

D11.2.1.2 Identifier of the intended recipient.

D11.2.1.3 Documentation of donor eligibility determination, as appropriate.

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D11.2.1.4 The distribution date and time.

D11.2.1.5 Identification of the facilities that requested and distributed the product.

D11.2.1.6 Identity of the receiving facility.

D11.2.1.7 Date and time cellular therapy product was distributed.

D11.2.1.8 Date and time cellular therapy product was received.

D11.2.1.9 Identity of the transporting or shipping facility.

D11.2.1.10 Identity of personnel responsible for cellular therapy product transportation or shipping and of personnel responsible for receiving the product.

D11.2.1.11 Identity of the courier.

D11.2.1.12 Documentation of any delay or problems incurred during transportation or shipping.

Explanation:

The distribution records must include, at a minimum, the distribution date and time, recipient name and identifier, product identifier(s), the proper product name(s) and any attributes of the product(s), the identity of the distribution facility, as well as documentation of allogeneic donor eligibility, if applicable. If the cellular therapy product is distributed for administration, the distribution records must also document receipt of the product by the medical staff responsible for administration, including the date and time of receipt. Clinical standards additionally require documentation in the recipient's medical record of the administered cellular therapy product unique identifier, initiation and completion times of administration, and any adverse events related to administration. This requirement may be met using a "product administration form," a copy of which can be maintained in the Processing Facility record. If

the product is distributed to an external facility the distribution records must include documentation of receipt by a responsible individual at that facility. Documentation of receipt can be by signature or initials. The recipient information in the distribution records must match that on the product label.

Transport and shipping records must be complete to allow tracking and tracing of the cellular therapy product from one facility to another. Records must document the identity of all responsible personnel including the courier and any delays or problems occurring during product transit. Key steps in receipt, quarantine, release, and return must be traceable to the product, including responsible staff and date and time, where applicable.

Evidence:
The inspector should verify the presence of product distribution records in the Processing Facility files for each product that is released for distribution. The inspector should confirm that identification checks and product receipt are documented in the distribution records. An SOP should state that the facility should keep signed product distribution and administration records in the processing record.

The inspector should ask to review transportation and shipping records for cellular therapy products distributed between facilities for compliance with this section of the Standards.

STANDARD:
D11.3. RECEIPT OF CELLULAR THERAPY PRODUCTS

D11.3.1 Standard Operating Procedures shall be established and maintained for acceptance, rejection, and quarantine of cellular therapy products.

Explanation:
Processing Facilities must have established SOPs for receipt to verify that the appropriate cellular therapy product has been received and that it is acceptable for administration to the intended recipient. This standard applies to the receipt of cellular therapy products from a Collection Facility within the Processing Facility's institution, from an external facility, or from the clinical unit that returned the product after it was distributed for administration.

The cellular therapy product receipt SOP must minimally describe the criteria for product acceptance, rejection, and quarantine. Documentation of the receipt process must include the integrity of the primary product container and confirmation that the label information meets the requirements specified in Appendix II. There must also be a visual examination of the appearance of the cellular therapy product for evidence of microbial contamination (excess hemolysis or inappropriate cloudiness, or other unusual appearance). Any samples that accompany the product must be labeled so as to be clearly identified with the donor and date of collection. In many cases donor screening and test results will have been received into the Processing Facility prior to product receipt. The minimum requirements for a summary of documents used to determine allogeneic donor eligibility, to which the facility shall have ready access, are defined in Appendix IV.

A process to store cellular therapy products in quarantine until they have been determined to meet all predetermined release criteria must be in place. Management of the return of products must be addressed in SOPs.

Evidence:
The inspector should review documentation of cellular therapy product receipt into the Processing Facility to confirm compliance with the facility's SOPs and the Standards, and should verify quarantine process is defined in SOPs and physical or electronic systems are in place to support quarantine functions.

Example(s):
EU requirements for documents that should be available to the Processing Facility that are not addressed by FACT-JACIE Standards are defined in EU 2006/17/EC and EU 2006/86/EC and include the identification of the person responsible for the procurement, the SOP that was used, a listing of batch numbers of reagents and solutions used. Other specified EU requirements are present on the label, including the collection date and time and identity of the Collection Facility; however, all of this required information may be part of the label or the accompanying documents that serve as an extension of the label. For inspections performed in EU member states, the access to such documentation containing the required information should be confirmed.

STANDARD:

D11.3.2 The receipt of each cellular therapy product shall include inspection to verify:

D11.3.2.1 The integrity of the cellular therapy product container.

D11.3.2.2 The appearance of the cellular therapy product for evidence of mishandling or microbial contamination.

D11.3.2.3 Appropriate labeling.

D11.3.3 There shall be Standard Operating Procedures to verify that the cellular therapy product was appropriately transported or shipped.

D11.3.3.1 The receiving facility shall document the temperature inside the container upon arrival if shipped or transported on public roads.

D11.3.3.2 For cryopreserved cellular therapy products, receiving facility records shall include documentation of the transport container temperature during shipping.

D11.3.4 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.

D11.3.5 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.

Explanation:
A Processing Facility is responsible for all activities performed by external facilities, especially the manufacture of cellular therapy products the facility will ultimately distribute for administration to a recipient. When the Processing Facility or external facility performs more than minimal manipulation, the external facility must be qualified to demonstrate that it follows current GMPs to protect product integrity, recipient safety, and regulatory compliance, including requirements of an IND or BLA.

In the Standards, "manufacturer" refers to whoever produced the cellular therapy product, such as a laboratory, a facility that banks biological products, etc. This standard does not require the receiving facility to establish cellular therapy product specifications for products received from a third-party; rather, if the manufacturer provides specifications the facility must verify the specifications are met. If not, this could be evidence of damage to the product's integrity.

STANDARD:

D11.3.6 *When cellular therapy products are returned to the Processing Facility after distribution for administration, there shall be documentation in the Processing Facility records of the events requiring return, the temporary storage temperature when at the clinical facility, the results of inspection upon return, and subsequent action taken to protect product safety and viability.*

D11.3.6.1 *The Processing Facility Director or designee shall consult with the recipient's physician regarding reissue or disposal of the returned product.*

Explanation:
The return of any cellular therapy product issued for administration is always a deviation from standard procedures, and requires a detailed report as to the cause and action taken by the Processing Facility to safeguard the product.

Should a product need to be returned to the facility, it should be stressed to the medical staff that this be done as soon after issue as possible. All events surrounding the release and return of the product must be documented in the facility records including the reason for return. The facility personnel are responsible for examination of the product and documentation of the outcome of that examination including the length of time the product was removed from a monitored temperature controlled environment and the temperature of the product upon return to the facility.

Products cannot be reissued or disposed of without authorization by a responsible individual such as the Processing Facility Director or Processing Facility Medical Director, and must always be done in collaboration with the recipient's physician. Records for both the initial distribution and any subsequent distribution must be maintained in the Processing Facility record. Return of products and conditions of re-storage, reissue or disposal shall be described in an SOP, logically as part of the facility's SOP for release and exceptional release SOP (see D5.1).

The FACT-JACIE Standards require a SOP for product recall (see D5.1), which may include elements of product return and reissue, but must additionally address situations in which the Processing Facility must recall a distributed product. For academic centers that primarily distribute products for direct administration, such an event would be very rare. For laboratories that process products for multiple centers and distribute products in advance of the administration day, such a situation may be more likely to occur.

Evidence:
The inspector should verify the Processing Facility SOP for product return and ask to review the records of one or more products that were returned and reissued, if this situation has occurred.

Example(s):
There are a variety of reasons why a product may be returned to the Processing Facility, such as cases in which a recipient has an anaphylactic reaction to DMSO or when a scheduled treatment is delayed.

D12: DISPOSAL

STANDARD:

D12.1 Disposal of cellular therapy products shall include the following requirements:

D12.1.1 A pre-collection written agreement between the storage facility and the designated recipient or the donor defining the length of storage and the circumstances for disposal of cellular therapy products.

Explanation:
The control of the disposal of cellular therapy products must be clearly defined to protect both the recipient from inadvertent destruction of potentially life-saving products and the need of the Processing Facility storage unit to operate efficiently. Written SOPs are required that detail the conditions under which product disposal may occur and the process to be followed for the disposal of products. The limits for storage and reasons for disposal must be defined prior to the collection of the product, and is usually contained in the consent for the collection of products.

In the case of autologous and/or related donations, donors, recipients, and associated clinical programs should be informed of the conditions of storage and storage duration, preferably before product collection.

The most common reasons for disposal are the following:

- Death of the recipient: Death of the recipient, identification of cellular therapy products for the recipient, or notification of the recipient's responsible physician, must be documented by the storage facility before the product can be discarded.
- No further need for the cellular therapy product: Under certain circumstances, the physician responsible for the recipient may determine there is no further need for the product. If the recipient is alive at the time, the recipient, or legal guardian, must be offered an opportunity to move the product to an alternative facility for storage. This situation has potential legal liability to the institution, and many institutions may decide to store products for the life of the intended recipient rather than expose themselves legally in disposing of potentially life-saving products.
- Discard to comply with written agreements with donor registries: Donor registries may have their own specific standards on product cryopreservation and disposal that will be agreed upon between the processing/storing facility and the registry. The processing/storing facility must adhere to these standards and/or to the FACT-JACIE Standards, whichever is more stringent.

For medical and legal reasons, it is essential to document that the conditions for disposal have been met and that the current processing procedures are not in contradiction with consent forms signed at the time of collection.

Processing Facilities are not required to directly contact the recipient; however, they must require that the transplant physician obtain an agreement on the length of storage and circumstances for disposal of cellular therapy products.

Evidence:
The inspector should ask to review records of cellular therapy products that have been disposed, and should be able to trace all steps of notification of product discard, method of destruction or transfer, and documentation of the action in the recipient's records.

Example(s):
FACT strongly advises that SOPs for disposal and consents for collection be reviewed by the institution's legal advisors, since the ownership of cellular therapy products vary depending on whether the product is autologous or allogeneic, and can also vary between nations, states, provinces, or other governmental units that regulate Processing Facilities.

STANDARD:

D12.1.2 The option to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.

D12.1.3 Documentation of no further need for the cellular therapy product before any product is discarded.

D12.1.3.1 For HPC products, this shall include documentation of the designated recipient's death, if applicable.

Explanation:
The clinical team does not have to write a specific note stating death; however, documentation must be a primary piece of evidence and should not conflict with others.

The institution should have a process for documentation of death that is entered into the recipient's medical record outside of the lab.

Example(s):
Proof of death includes an autopsy report, a dictated clinical note, or the Social Security index in the U.S. Secondary sources of information, such as newspaper articles, do not satisfy this requirement.

STANDARD:

D12.1.4 *Approval by the Processing Facility Medical Director in consultation with the recipient's physician for cellular therapy product discard or other disposition, and method of disposal.*

Example(s):
If the Medical Director of the storage facility approves of cellular therapy product disposal, it is recommended that he/she consults with the recipient's physician and the two parties are in agreement on the vital status of the patient, the disposition of the product, and method of disposal. This can be accomplished with an exchange of documents between the Processing Facility Medical Director and the recipient's physician. Documented approval to the Processing Facility for disposal by the recipient's physician is also acceptable.

STANDARD:

D12.1.5 *A method of disposal and decontamination that meets applicable laws and regulations for disposal of biohazardous materials and/or medical waste.*

Explanation:
Cellular therapy products derived from human tissue are considered to be a potential biohazard and adherence to universal precautions is required during the disposal process.

Evidence:
The applicant must present evidence to the inspector that the Processing Facility is in compliance with standards of biohazard waste disposal.

Example(s):
Disposal can be by ultra-high temperature incineration, autoclaving, or decontamination with freshly prepared hypochlorite solution followed by, if permitted by local law, discard in a landfill or other institutionally-approved method.

STANDARD:

D12.1.6 *Processing Facilities, in consultation with the Clinical Program, shall establish policies for the duration and conditions of storage and indications for disposal.*

D12.1.6.1 Recipients, donors, and associated Clinical Programs should be informed about policies for directed cellular therapy products as part of the informed consent process and before the cellular therapy product collection.

D12.1.7 If there is no pre-existing agreement describing conditions for cellular therapy product storage and/or discard or if the intended recipient is lost to follow-up, the storage facility shall make a documented effort to notify the donor, cellular therapy product manufacturer, or designated recipient's physician and facility about product disposition, including disposal or transfer.

Explanation:
Two problems faced by older cellular therapy programs are the disposition of cellular therapy products collected when there was no pre-existing agreement describing conditions for product storage and/or disposal, or when recipients are lost for follow-up and their survival cannot be confirmed. Each institution must establish its own policy on discarding such products. The definition of a good faith effort to contact the recipient or family likewise is a decision left to the individual center. The rights of the donor (whether related or unrelated) should be protected according to local laws and the standards of donor registries.

STANDARD:
D12.2 The records for discarded or transferred cellular therapy products shall indicate the product was discarded or transferred, date of discard or transfer, disposition, and method of disposal or transfer.

D13: RECORDS

STANDARD:
D13.1 There shall be a records management system for quality and cellular therapy product record creation, assembly, review, storage, archival, and retrieval.

Explanation:
A record is defined as documented evidence that activities have been performed or results have been achieved. A record does not exist until the activity has been performed. Each Processing Facility has the flexibility to develop an individualized system of organizing and maintaining records as long as certain objectives are achieved. The record keeping system must be documented and should include at a minimum:

- Location of new and completed forms.
- Method of error correction that prevents obscuring the original entry and indicates the identity and date of the individual modifying the record.
- Method to prevent destruction or loss of the record.
- Method of documenting modifications and distribution.

- Time of retention and proper storage location.
- System to secure confidentiality of records.
- Methods for filing and transfer of records to archival storage.

STANDARD:

D13.1.1 *The records management system shall facilitate the review of records pertaining to a particular cellular therapy product prior to distribution and for follow-up evaluation or investigation.*

Explanation:
The Processing Facility must make provisions for all records to be maintained for the required period of time in the event that the facility ceases operation. Records that allow the tracing of a product from the donor to the recipient or final disposition and from the recipient or final disposition to the donor must be maintained even when cellular therapy products are transferred to another facility.

Recipient and donor files (either electronic or hard copy) must be maintained with a secure system that guarantees absolute confidentiality and is in compliance with applicable laws and regulations on confidentiality and data protection.

The sponsor of the research, IRB, and/or governmental authorities may place specific requirements for long-term maintenance of research records.

Evidence:
The inspector should review the methods in place for record use and storage, with an eye to steps in the process that may compromise confidentiality.

STANDARD:

D13.1.2 *The records management system shall facilitate tracking of the cellular therapy product from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.*

D13.1.3 *For cellular therapy products that are to be distributed for use at another institution, the Processing Facility shall inform the receiving institution of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.*

D13.1.4 *Records shall be maintained in such a way as to secure their integrity, preservation, and retrieval.*

Explanation:
Records may be maintained in more than one location, provided that the records management system is designed to safeguard prompt identification, location, and retrieval of all records. The methods for filing and transfer of records to archival storage should be specified in a policy or in the SOP manual.

Evidence:
Records related to products processed in the Processing Facility under IRB-approved research protocols should be maintained in an orderly manner with sufficient organization to allow timely retrieval of information.

Example(s):
It is recommended that recent records be kept on-site and archived records are readily accessible within a reasonable time frame.
Records may be maintained as original paper records, electronic files, photocopies, digital images, or on microfiche or microfilm. Electronic records must be backed up on a regular basis and stored to prevent their loss when records are maintained in common electronic portable formats. Examples of common formats include but are not limited to, portable document format (PDF), extensible markup language (XML), or standard generalized markup language.

STANDARD:

D13.1.5 *Records shall be accurate, legible, and indelible.*

D13.1.6 *Safeguards to secure the confidentiality of all records and communications between the collection, processing, and clinical facilities, and their recipients and donors, shall be established and followed in compliance with applicable laws and regulations.*

Example(s):
Breaches in policy that might compromise confidentiality include: unsecured patient records; patient charts left unattended in areas where unauthorized personnel and/or visitors may have access, or unattended computer screens displaying patient information in such areas; indiscriminate discussion using patient-specific identifiers in the presence of unauthorized personnel or visitors; patient information posted on chalk or bulletin boards that is potentially visible to unauthorized personnel and/or visitors; and release of confidential information without appropriate consent and approval.
Confidential storage may consist of maintaining the records in a locked room with access restricted to authorized personnel and/or the use of locked file cabinets. The Processing Facility must have SOPs describing the maintenance of donor and recipient confidentiality (see D5.1).

STANDARD:

D13.2 *ELECTRONIC RECORDS*

D13.2.1 *The Processing Facility shall maintain a current listing of all critical electronic record systems. Critical electronic record systems shall include at a minimum systems under the control of the Processing Facility that are used as a substitute for paper, to make decisions, to perform calculations, or to create or store information used in critical procedures.*

Explanation:
The definition of an electronic record is, "A record or document consisting of any combination of text, graphics, or other data that is created, stored, modified, or transmitted in digital form by a computer." This Standard requires Processing Facilities to establish and maintain a current listing of all critical electronic record systems specific to cell processing. As facilities utilize more electronic systems, it is important that they maintain a list of which ones are critical.

Electronic records are considered critical when any one of the following points occurs:

- used as a substitute for paper.
- used to make decisions based upon the data stored and/or created by the electronic record system (including outcome analysis).
- used to make calculations via automated functions.
- used to create and/or store pieces of information that are inputs into critical processes (whether the electronic record system is used during critical processes or used as source data for critical procedures).

Critical procedures include processing techniques, cryopreservation procedures, labeling, storage conditions, and distribution.

It is not the intent of the Standards to include hospital-based systems and clinical medical records. These systems are typically inspected by hospital-based regulatory and accrediting organizations. Furthermore, Processing Facilities may not have the authority to direct validation studies on these systems.

Evidence:
Inspectors should assess the Processing Facility's list of critical electronic record systems to confirm it includes all electronic record systems used by the facility that meet the criteria in this standard.

Example(s):
Critical electronic record systems may include commercial software, custom-made software, or databases and spreadsheets.

When computers are used to generate paper printouts of electronic records, and the printouts are the "official" records used for the performance of further activities, the electronic records are not considered to be used as a substitute for paper records. For example, an electronic record of the location of a cellular therapy product in liquid nitrogen storage is printed for the processing chart and the information is verified by a signature or initials. This printed record is then used by personnel to retrieve the product at the time of administration. The electronic record is not considered to have been used in lieu of a paper record, and may not be critical based on that criterion. If, however, the electronic system performed one or more calculations on the entered data prior to making the final printout, then the system is critical, and the standards in this section would apply. Similarly, if the electronic system formats data that is entered into a specific format for printing for retention, then that data is also processed, and validation that the data is being correctly reproduced is necessary.

If a computerized system (word processor) is used to generate SOPs, validation is not required since the quality and safety of a cellular therapy product would not be directly affected. However, if a computerized system is used to make a critical calculation (i.e., T Cell dose, DMSO concentration, CD34 cell recovery) and the electronic calculation is the only calculation performed, validation is required to

assure that the calculation is always performed correctly under any circumstances. However, if the computerized calculation is used to confirm a manual calculation, and the manual calculation is used for manufacturing purposes, the extent of validation need not be as extensive as in the previous example.

In the U.S., when electronic records are used as a substitute for paper, the inspector should refer to the FDA document Part 11, Electronic Records; Electronic Signatures - Scope and Application, for guidance to assess the validation procedures (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072322.pdf).

STANDARD:

D13.2.2 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.

D13.2.2.1 There shall be a means by which access to electronic records is limited to authorized individuals.

D13.2.2.2 The critical electronic record system shall maintain unique identifiers.

D13.2.2.3 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

D13.2.3 For all critical electronic record systems, there shall be an alternative system for all electronic records to allow for continuous operation of the Processing Facility in the event that critical electronic record systems are not available. The alternative system shall be validated and Processing Facility staff shall be trained in its use.

D13.2.4 For all critical electronic record systems, there shall be written Standard Operating Procedures for record entry, verification, and revision.

D13.2.4.1 A method shall be established or the system shall provide for review of data before final acceptance.

Example(s):

Standards require that data is reviewed before final acceptance, but a second individual to verify the data is not required. Systems may be programmed to validate data (e.g., product numbers should only have a specified number of alphanumeric characters, date fields should follow a specific format).

STANDARD:

D13.2.4.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

Explanation:
In case of error or ambiguity, a method must exist to allow traceability of data entered into the electronic record system to the staff member who performed the entry. This may take the form of an audit trail maintained internally by software, or may take the simple form of a log-in sheet on which staff members record their session with the electronic record system and identify what data was entered in that session.

Example(s):
To identify individuals responsible for record entries, several options exist. Examples include using a sign-in sheet when using the system or using a worksheet to create an audit trail of each data element. More sophisticated systems usually have an automated system that tracks record entry based upon an individual's log-in credentials.

STANDARD:

D13.2.5 *For all critical electronic record systems, there shall be the ability to generate true copies of the records in both human readable and electronic format suitable for inspection and review.*

D13.2.6 *For all critical electronic record systems, there shall be validated procedures for and documentation of:*

Explanation:
Establishment of an electronic record keeping system that meets one or more of the criteria for a critical electronic record system requires validation. The extent of validation is somewhat dependent upon whether the computerized system was developed in-house, custom-built by an outside vendor or consultant, or developed from off-the-shelf software.

Validation procedures of critical electronic systems include, as appropriate, such things as:

- Documentation of development requirements and function.
- Verification that calculations are performed correctly.
- Evidence that records reproducibly contain the desired information.
- Tests of system functions under "worst case" scenarios such as system overloads (e.g., too many simultaneous users, too many simultaneous processes being performed [such as too many programs open on a Windows desktop]), power failures, etc.
- A method for data verification before final entry.
- Internal consistency checks to verify that values are within defined ranges.
- Restricted entry of data to match predefined value limits.
- Required entry of data with field information limited with choices for data consistency.
- Source data is derived from pre-defined sources such as fixed forms. "Monitoring for data integrity" means establishing assurances that data has not been changed either by accident or by intent, and requires access to original documents whenever possible along with a plan for verification of the electronic system data by comparison to original data.
- Evidence of a schedule of regular back-ups that include storage of back-up data in a site other than the point of primary entry to reduce the odds of destruction of both the primary database and the back-up copy.

- Documentation of the database system, including written methods for data entry and generation of printed reports that include all of the information entered into the database, acceptable sources of the entered data, and a description of system maintenance and development history.
- Formal and documented training in system use requirements for all personnel.
- Evidence of SOPs in place for computer record-keeping systems.
- Regular quality audit trails.
- A mechanism to report deviations to assure that problems are reported and resolved.
- Evidence that changes to records do not obscure previously entered information.
- Documentation that deleted electronic files have been converted to non-electronic media such as microfilm, microfiche, or paper in a manner that preserves the content and meaning of the record.

Evidence:
While details of the validation system may be located in an institutional department of information services or elsewhere, the Processing Facility shall have a summary of the validation available to the inspector.

If electronic records are used in addition to paper records, the inspector should evaluate the electronic record system to determine that:

- SOPs exist to describe the development, validation, testing, training, use, modifications, maintenance, and document control regarding the electronic system.
- The system has access limited to authorized individuals and that documentation is generated to identify which individuals have accessed the system and made record entries.
- Operational system checks are performed periodically.
- Authority checks are performed periodically.
- Device checks are performed periodically.
- Documentation that the individuals performing the development, maintenance or use of electronic systems have the education, training, and experience to perform the assigned tasks.
- Procedures are in place to provide for record keeping in the event of failure of the electronic record system, and that the staff members who may have to follow these procedures are trained in their use.
- A process for generating back-ups of records maintained electronically is in place.

STANDARD:

D13.2.6.1 Systems development.

D13.2.6.2 Numerical designation of system versions, if applicable.

D13.2.6.3 Prospective validation of systems, including hardware, software, and databases.

D13.2.6.4 Installation of the system.

D13.2.6.5 Training and continued competency of personnel in systems use.

Explanation:
As with all other cellular therapy processing activities, the staff members who utilize the electronic record system must be trained for such use. Moreover, just as SOPs are required for cell manipulations, SOPs must also be in place to describe how to enter, process, and retrieve data using the electronic record system. Competency of staff using the system must be documented on a regular basis (annually at a minimum), and must also be documented with changing versions of the systems in use.

STANDARD:

D13.2.6.6 Monitoring of data integrity.

D13.2.6.7 Back-up of the electronic records system on a regular schedule.

D13.2.6.8 System maintenance and operations.

D13.2.6.9 System assignment of unique identifiers.

D13.2.7 All system modifications shall be authorized, documented, and validated prior to implementation.

D13.3 RECORDS TO BE MAINTAINED

D13.3.1 Processing Facility records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained for a minimum of ten (10) years by the Processing Facility, or longer in accordance with applicable laws or regulations, or with a defined program or institution policy.

D13.3.1.1 Facility maintenance records pertaining to facility cleaning and sanitation shall be retained for at least three (3) years or longer in accordance with applicable laws or regulations, or with defined program or institution policy. All other facility maintenance records shall be retained as in D13.3.1.

D13.3.2 Records to allow tracing of cellular therapy products shall be maintained for a minimum of ten (10) years after final distribution of the product, or as required by applicable laws and regulations. These records shall include collection and processing facility identity, unique numeric or alphanumeric identifier, collection date and time, product identity, and donor and recipient information as found on the original container.

D13.3.3 All records pertaining to the processing, testing, storage, or distribution of cellular therapy products shall be maintained for a minimum of ten (10) years after the date of administration, or if the date of administration is not known, then a minimum of ten (10) years after the date of the cellular therapy product's distribution, disposition, or expiration, or the creation of the cellular therapy product record, whichever is most recent, or according to applicable laws and regulations or institutional policy, whichever requires the longest maintenance period.

Explanation:
The standards in this section detail what records must be maintained and the minimum time period of retention. Where institutional or governmental policies differ, the longer retention period must be observed. Records must be retrievable within a reasonable time frame, but need not be immediately available in the Processing Facility.

Records that are to be maintained for at least 10 years after their creation include:

- QM records: validation and qualification studies; equipment maintenance reports; the results of audits; errors, accidents and adverse reactions reports; and outcome analysis. Because QM documents provide evidence of compliance with the QM requirements, they should be maintained for as long as they are applicable to the processes, equipment, supplies, and reagents currently being used. For example, the validation study for a current processing procedure needs to be maintained regardless of how long ago the study was performed in order to demonstrate compliance with validation requirements.
- Personnel training and competency records: job qualification records; records of orientation; initial training; safety training for biological, chemical and radiation exposure and/or disposal; continuing education; and annual competency assessments.
- Processing Facility maintenance management and general facility issues: dates and extent of renovations and new construction; dates and extent of repairs on mechanical systems; preventive maintenance on equipment; agreements and/or contracts with any entity served by the facility; sterilization records; disposition of supplies and reagents; and the outcome of any building and/or facility inspections for safety and/or compliance with governmental and/or other agencies.
    - Processing Facility management records should include a list of responsible individuals with job titles and areas of oversight and resolution of facility problems.

General Processing Facility records may include global policies for the institution of which the facility is a part. Examples include disaster plans; fire response and safety; biological, chemical and radiation disposal policies; and confidentiality and data protection requirements.

An exception to the 10-year requirement for retention of Processing Facility maintenance records is for the documentation of cleaning and sanitation. These records need only be retained for at least 3 years after creation but should include cleaning schedules, methods, and identification of personnel responsible for cleaning. There should also be documentation of initial training and retraining of personnel as needed.

Evidence:
The inspector should look for evidence of 10-year retention of representative records, including some older and some more recent documents. Each Processing Facility should maintain a comprehensive list of all relevant faculty and support staff associated with that facility for the immediate previous 10-year period. The inspector may ask to review the personnel list and then ask to see dated training or competency records for a specific individual. Likewise, the inspector may ask to see the original records of validation of the controlled rate freezers, shipping containers, or cryopreservation technique, assuming the facility is less than 10 years old.

The inspector should take into account during the inspection that the Processing Facility is only responsible for compliance from the time of its initial FACT or JACIE accreditation. Some Processing Facilities have not been accredited by FACT or JACIE for a full 10 years. In these cases, the facilities are only held responsible for retaining records for as long as they have been accredited and required to comply with the Standards.

Example(s):
Cellular therapy products processed years ago for a recipient may have a complex history. It might be possible that some of the products could not be released because of out-of-specification parameters, some were administered, some are still stored, or some might have been discarded because they were no longer needed for the recipient.

NMDP requires that records from unrelated donor eligibility determination, and HPC, Apheresis product records pertaining to collection, processing, labeling, packaging, storage, distribution and final disposition be maintained indefinitely. NMDP further requires indefinite retention of records pertaining to the traceability and tracking of all aspects of the manufacture of the HPC product along with records of adverse reactions and post-donation complications, treatment interventions, and recovery.

STANDARD:
D13.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

D13.4.1 The Processing Facility shall maintain a listing of the names, addresses, and responsibilities of other facilities that perform manufacturing steps on a cellular therapy product.

D13.4.2 The Processing Facility shall furnish to the facility of final disposition a copy of all records relating to the collection, processing, and storage procedures performed in so far as the records concern the safety, purity, or potency of the cellular therapy product involved.

Explanation:
The Processing Facility shall have an applicable SOP or SLA that describes the dissemination to other collection and/or clinical facilities of data that concerns safety, purity, and potency of the cellular therapy product.

Evidence:
The inspector should determine if divided responsibility occurs regarding any aspect of the transplant process, and ask to review a relevant recipient file to confirm that an appropriate mechanism is in place to track the process from beginning to end and trace the process from the end to the beginning.

Example(s):
The processing and the storage of a cellular therapy product might be located in different departments of the same institution. There must be documents clearly defining the responsibilities of each department. It must be possible to identify these responsibilities when reviewing the documents. In addition, there should be a written policy or agreement between both departments that defines the responsibilities and the documents to be handed over between both departments.

STANDARD:

D13.4.3 *If two (2) or more facilities participate in the collection, processing, or distribution of the cellular therapy product, the records of the Processing Facility shall show plainly the extent of its responsibility.*

Explanation:

Most, but not all, Processing Facilities will have some of the activities or services covered by the Standards performed by another entity. In such cases, the conditions under which the activity or service is performed must be documented through written agreements.

These agreements should clearly define roles and responsibilities for critical tasks. All such agreements should be dated, should be reviewed and renewed on a regular basis, and include provision for the maintenance of records following termination of the agreement. How such agreements are executed is a function of the type of Processing Facility.

The agreements must clearly define the role and responsibility of the contracted facility to comply with all governmental regulations and FACT-JACIE Standards that are applicable to the performed services. The contracted facility must also adhere to critical processing, storage, and distribution standards defined by the contracting facility although the contracted facility does not have to be FACT-JACIE accredited. The contracting facility must have implemented a process to verify that regulated services are performed in compliance with all applicable regulations and standards.

In the event that two or more facilities participate in the collection, processing, storage or administration of a cellular therapy product, the records of each participating facility must clearly indicate the extent of each facility's responsibility. The Processing Facility's records should include relevant contracts and agreements and the Processing Facility is responsible for compliance with the relevant FACT-JACIE Standards. The entire record of the outside facility(ies) need not be duplicated for the facility record. However, the facility record should allow tracing and tracking of relevant information to the correct source. For example, the facility may manufacture products for multiple clinical programs. The facility record should indicate where the product was collected, stored, and/or administered but does not need to contain a record of the supply and reagent lot numbers used for steps performed at the collection or clinical facilities. The facility should verify that such relevant and appropriate records will be maintained by the facility that performs the work. Records of allogeneic donor eligibility screening and testing must be provided to the facility. Maintenance of records must be specified in the SOPs and it must be clear who is responsible for maintaining records. In general, records should be sufficiently detailed to enable tracking and tracing from a donor to a recipient or final disposition and vice versa.

Donor and recipient confidentiality must be maintained through the use of identifiers whenever the identity of the unrelated donor must remain anonymous. The location of each facility must be known to the relevant personnel at each facility, but should not be known to the recipient. To that end, the Processing Facility may not know the identification or location of the Collection Facility in the case of a product obtained through an unrelated donor registry. Facilities that participate in programs such as NMDP or other donor registries will have well-defined procedures for divided responsibility. Applicable rules and regulations regarding the sharing of confidential information must be followed.

QM Plans must include the concept of written agreements even if no agreements are currently in place at the Processing Facility. The purpose is to outline the general process for establishing agreements should the need arise. Extensive detail is not required, but the plan must minimally describe who is responsible for reviewing and approving agreements and require that agreements include the external facility's responsibility to comply with the Standards in their activities relating to the Processing Facility.

In the event the Processing Facility (or entities with which the facility has agreements) terminates its activities, it is essential that traceability data and material concerning the quality and safety of the cellular therapy products be provided to the relevant parties.

Evidence:
The inspector should review the process for establishing agreements or contracts with entities outside of the Processing Facility that participate in product collection, testing, storage, transport or other critical services that might affect the quality of the product. In the case of donor registries, they should be accredited by the World Marrow Donor Association (WMDA). If agreements exist, examples should be reviewed by the inspector for adherence to the facility's established process. In all cases a process must exist for the development and implementation of such agreements. The inspector should verify that there is a process in place to assess compliance with the requirements and that this process is effective. Copies of those agreements should be available to the inspector on the day of the inspection.

Example(s):
Written agreements should be reviewed every two years, similar to SOPs, although a greater or lesser time interval may be appropriate under some conditions. The effective dates of an agreement could be specified within the agreement itself. It would be helpful to have a list of written agreements to inventory whether each one is reviewed and renewed appropriately.

For services provided with the same institutions, shared policies or procedures that address expectations and performance quality can be interpreted as agreements. For Processing Facilities receiving products facilitated through donor registries, agreements may be through those registries.

Such agreements may include, but are not limited to: donor qualification, determination of donor suitability and eligibility (allogeneic donors only), collection of the product, donor or product testing, and long-term storage.

Stand-alone facilities may execute agreements directly with the service providers (or institutions for which they provide services), whereas agreements involving Processing Facilities in academic institutions may be between the institution and the service provider.

Audits of external facilities may be accomplished by reviewing the Processing Facility's internal and external audit reports, performing on-site inspections for compliance or receiving period performance reports from the facility. There may be other alternatives but the contracting facility must verify that their contracted services are meeting requirements.

APPENDIX I

MINIMUM NUMBER OF NEW PATIENTS FOR ACCREDITATION

Clinical Programs shall transplant at least the following number of new patients[1] before initial accreditation and annually thereafter:

Transplant Population	Clinical Site(s)	Type of Transplant	Twelve (12) Months Prior to Initial Accreditation	Average Per Year Within Accreditation Cycle
Adult OR Pediatric (only one of these two)	Single Clinical Site	Autologous only	5 autologous	5 autologous
		Allogeneic and Autologous	10 allogeneic recipients	10 allogeneic recipients
	Multiple Clinical Sites	Autologous only	5 autologous recipients at each site	5 autologous recipients at each site
		Allogeneic and Autologous	5 allogeneic recipients at each applicable site[2] 5 autologous at each applicable site[2]	5 allogeneic recipients at each applicable site[2] 5 autologous at applicable each applicable site[2]
Combined Adult AND Pediatric	Single Clinical Site	Autologous only	5 adult autologous And 5 pediatric autologous recipients	5 adult autologous and 5 pediatric autologous recipients
		Allogeneic and Autologous	5 adult allogeneic recipients 5 pediatric allogeneic recipients	5 adult allogeneic recipients 5 pediatric allogeneic recipients
	Multiple Clinical Sites	Autologous only	5 adult autologous at each applicable site 5 pediatric autologous recipients at each applicable site	5 adult autologous recipients at each applicable site 5 pediatric autologous recipients at each applicable site
		Allogeneic and Autologous	5 adult allogeneic recipients at each applicable site 5 pediatric allogeneic recipients at each applicable site 5 adult autologous at each applicable site[2] 5 pediatric autologous at each applicable site[2]	5 adult allogeneic recipients at each site 5 pediatric allogeneic recipients at each site 5 adult autologous at each applicable site[2] 5 pediatric autologous at each applicable site[2]

[1]The term "new allogeneic patient" or "new autologous patient" includes only a patient who received his/her first transplant of that type during the period of time in question.

[2]Programs performing allogeneic and autologous transplantation that have more than one clinical site may or may not perform both types of transplant at each site. The requirement for five autologous transplant recipients per site only applies to those sites that do not perform allogeneic transplant.

Explanation:
To demonstrate continuing proficiency in a Clinical Program, a minimum number of patients must be treated in the 12-month period preceding accreditation, and annually thereafter. (The number of patients between inspections is submitted to FACT and JACIE in the interim/annual report.) If the Clinical Program is requesting accreditation for allogeneic or allogeneic and autologous transplant, at least 10 new allogeneic patients must have been transplanted. The term "new allogeneic patient" or "new autologous patient" includes a patient who will be receiving their first transplant of each type. Patients receiving second or subsequent transplants of the same type will only be counted towards a Clinical Program's volume if there has been at least one year between transplants.

Donor lymphocyte infusions (DLI) are considered part of the initial transplant because they generally follow a transplant when a recipient does not demonstrate tri-lineage engraftment (i.e., red cells, neutrophils, and platelets) when engraftment would have been expected. The recipient may experience a relapse after transplant or rejection of the cellular therapy product. When a recipient does not receive enough viable stem cells, the DLI provides more cells from the same donor into what is conceived of as an "empty marrow space" to achieve engraftment.

There is no minimum requirement for autologous transplant for centers performing allogeneic transplants, as it is felt that proficiency in allogeneic transplant is a sufficient criterion for performing autologous transplant. If one site of a program that performs allogeneic and autologous transplants performs autologous transplants alone, it must meet the criteria of a minimum average of five autologous transplants per year.

The age definition for a pediatric patient varies in different countries but there would be general consensus that a child aged 12 or younger should be treated in a pediatric unit. A combined pediatric/adult Clinical Program should have a policy on how they distribute adolescents and young adults between the two components of the Clinical Program.

For a combined adult and pediatric Clinical Program or a Clinical Program using different sites, a minimum of five new allogeneic transplant patients at each site are required for the allogeneic accreditation, which will also accredit the units for autologous transplantation. Clinical Programs that are at risk for not meeting the minimum patient volumes may be notified by the FACT or JACIE office and may also be requested to submit a plan to meet minimum patient volumes. Accreditation will be removed if these requirements are not met.

If the Clinical Program is requesting accreditation for autologous transplant only, at least five new autologous patients must have been transplanted in the 12 months prior to accreditation, and an average of five new patients must be transplanted each year of the accreditation cycle as set by FACT or JACIE, as applicable, for renewal applications. The term "new autologous patient" refers to a patient who will be receiving their first autologous transplant or a subsequent autologous transplant more than a year after the previous one.

Five autologous patients at each site and for each population (adult and pediatric) transplanted are required in the 12 months preceding accreditation (and an average of five annually thereafter). A center performing autologous transplants alone would not be eligible for accreditation for allogeneic transplants until they met the requirement of 10 new allogeneic patients because of the specific competencies required for the care of these patients.

This standard allows Clinical Programs to apply for accreditation prior to meeting the minimum volume, but this is intended for exceptional circumstances. In this scenario, there must be adequate QM data to demonstrate compliance to the Standards, and the program's team must be experienced and mature (see B3 Personnel). Accreditation will not be awarded until the minimum volume is met. The Clinical

Program must decide if it is in a position to accept the risk of not meeting the minimum volume (and not becoming accredited) within the accreditation timeline.

Evidence:
The inspector will review the number of transplants in the previous year (initial accreditation) or the yearly average throughout the accreditation cycle (renewal accreditation) and may also ask how patients are allocated to each site if warranted.

Example(s):
The following examples illustrate the criteria used to determine if a given recipient would be considered to be a "new patient:"

- A patient on a tandem study (planned sequential transplants) who received two autologous transplants two months apart would count as one new autologous patient.
- A patient on a tandem study who received an autologous transplant and subsequently received an allogeneic transplant four months later would count as one new autologous patient and one new allogeneic patient.
- A patient receiving an allogeneic transplant who failed to engraft and received a second allogeneic transplant two months later would count as one new allogeneic patient.
- A patient who received an allogeneic transplant then relapsed and received a second allogeneic transplant from the same or a different donor 18 months later would count as one new allogeneic patient in each year.
- A patient who received an autologous transplant for myeloma with a good response who subsequently progressed and received a second transplant five years later would count as a new autologous transplant on each occasion.
- A "boost" for an aplastic patient 35 days after initial transplant is considered part of the initial transplant (one transplant).

FACT and JACIE will use the average number of transplants over the accreditation cycle to determine if a Clinical Program meets the minimum transplant volume per year. For example, if a program performs 8 allogeneic transplants in the first year, 15 in the second, and then 10 in the third, the program will have performed an average of 11 transplants per year during the accreditation cycle and be considered to have met the standard.

As an example, consider a Clinical Program that has two sites, an adult site where 10 autologous transplants were performed in 10 new patients with myeloma in the last year and a pediatric site where tandem transplants were performed in 3 patients with neuroblastoma who received 2 products each. Only the adult site meets the criteria of five patients per site.

APPENDIX II

CELLULAR THERAPY PRODUCT LABELING

Each label shall include at least the elements detailed in the following table[1]:

Element[2]	Partial label	Label at completion of collection	Label at completion of processing	Label at distribution for administration[4]	
				ISBT128	Eurocode
Unique numeric or alphanumeric identifier[3]	AF	AF	AF	AF	AF
Proper name of product[5]	AF	AF	AF	AF	AF
Product code[5]			AC	AF	AF
Recipient name and/or identifier		AT	AT	AF	AT
Identity and address of collection facility or donor registry		AT	AC	AF	AT
Date, time collection ends, and (if applicable) time zone		AT	AC	AF	AF
Approximate volume		AT	AT	AF	AF
Name and quantity of anticoagulant and other additives		AC	AC	AF	AF
Donor identifier and (if applicable) name		AT	AT	AF	AT
Recommended storage temperature range		AT	AT	AF	AF
Biohazard Legend (as applicable)		AT	AT	AF	AT
Warning Labels (as applicable, see CM7.4, C7.4, D7.4):					
• Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES"		AT	AT	AT	AT
• Statement "WARNING: Advise Patient of Communicable Disease Risks"		AT	AT	AT	AT
• Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"		AT	AT	AT	AT
Identity and address of processing and distribution facility(ies)			AC	AF	AC
Statement "Do Not Irradiate"			AT	AF	AF
Expiration Date (if applicable)			AC	AF	AF
Expiration Time (if applicable)			AC	AF	AF
ABO and Rh of donor (if applicable)			AC	AF	AF
RBC compatibility determination (if applicable)				AC	AC
Statement indicating that leukoreduction filters shall not be used.				AF	AF
Statement "FOR AUTOLOGOUS USE ONLY" (if applicable)		AT	AT	AF	AF
Date of distribution				AC	AC

AF=Affix, AT=Attach or Affix, AC=Accompany, Attach or Affix

[1]Container and full package labeling requirements for licensed products or products under Investigational New Drug (IND) application shall follow applicable laws and regulations. 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.

[3]Overlay labels for supplementary identifiers shall not obscure the original identifier.

[4]Products thawed at the bedside do not require a new label unless repackaged into a new container.

[5]Product proper names and attributes are listed in Chapter Three of the ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions. Available at: www.iccbba.org > Subject Area > Cellular Therapy > Standard Terminology.

APPENDIX III

CELLULAR THERAPY PRODUCT LABELS FOR SHIPPING AND TRANSPORT ON PUBLIC ROADS

Each container for shipping and transport on public roads shall include a document on the inside of the container and a label on the exterior of the container with at least the elements detailed in the following table:

Element	Inner container document	Outer container label
Date of distribution	AC	AC
Time[1] of distribution, if appropriate	AC	AC
Statement "Do Not X-Ray" and /or "Do Not Irradiate", if applicable	AC	AF
Statements "Human Cells for Administration" or equivalent and "Handle with Care"	AC	AF
Shipper handling instructions	AC	AF
Shipping facility name, street address, contact person, and phone number	AC	AF
Receiving facility name, street address, contact person, and phone number	AC	AF
Biohazard and/or Warning Labels (as applicable, see CM7.4.2, C7.4.2, D7.4.2).	AC	
If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES" Statement "WARNING: Advise Patient of Communicable Disease Risks" Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"	AC AC AC	

AC= Accompany, AF=Affix

[1]Time shall include the time zone when shipping or transport of the cellular therapy product involves crossing time zones.

APPENDIX IV

ACCOMPANYING DOCUMENTS AT DISTRIBUTION

Products collected in or designated for use in the U.S. shall be accompanied upon leaving the Collection or Processing Facility with at least the elements detailed in the following table[1]:

Documentation	Allogeneic 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 administered until completion of the donor-eligibility determination, except under condition of urgent medical need			X
Listing of any required screening or testing that has not yet been completed			X
Results of donor screening that has been performed			X
Documentation that the physician using the cellular therapy product was notified of incomplete testing or screening			X
Instructions for product use to prevent the introduction, transmission, or spread of communicable diseases[1]	X	X	X
Instructions for reporting serious adverse reactions or events to the distributing facility[1, 5]	X	X	X

[1]For autologous cellular therapy products, instructions for product use to prevent the introduction, transmission, or spread of communicable diseases and for reporting serious adverse reactions or events to the distributing facility are always required for autologous products. Furthermore, a donor eligibility determination is not required by FDA. However, if any donor screening or testing is performed and risk factors or reactive test results are identified, accompanying documentation shall be provided.

[2]May only be distributed after release by the Processing Facility Medical Director due to urgent medical need. For ineligible cellular therapy products or incomplete donor eligibility determination, the product shall be shipped in quarantine. For products distributed prior to completion of donor eligibility, determination shall be completed and the physician shall be informed of the results.

[3]Access (electronic or otherwise) to the source documents by the distributing facility and/or receiving facility is sufficient.

[4]This includes laboratories certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 or those laboratories that have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services, or those that have met equivalent non-U.S. requirements.

[5]Access to the Clinical Program SOPs and forms could suffice when the distributing and clinical facilities are within the same facility.