

The background of the cover features a microscopic view of red blood cells. The left side is a light gray field with many semi-transparent, white, biconcave disc-shaped cells. A diagonal black line separates this from a dark red field on the right, which contains more solid, dark red biconcave disc-shaped cells.

CELLULAR THERAPY

Accreditation Manual

FIFTH EDITION

fact FOUNDATION FOR THE
ACCREDITATION OF
CELLULAR THERAPY
AT THE UNIVERSITY OF NEBRASKA MEDICAL CENTER


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



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

Fifth Edition
Version 5.3

NOTICE

These Standards are designed to provide 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.

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INTRODUCTION

This Accreditation Manual is intended to accompany the *FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing, and Administration, Fifth Edition, 2012* (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 cellular therapy products, including 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.

PART A: TERMINOLOGY, ABBREVIATIONS, AND DEFINITIONS

- A1 Terminology
- A2 Abbreviations
- A3 Definitions

PART A: TERMINOLOGY, 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.

A2 ABBREVIATIONS

The following abbreviations cover terms used in these Standards:

Abbreviations

<i>ABO</i>	Major human blood group including erythrocyte antigens, A, B, O
<i>AC</i>	Accompany
<i>AF</i>	Affixed
<i>Anti-</i>	Antibody to the antigen designated
<i>ASBMT</i>	American Society for Blood and Marrow Transplantation
<i>ASHI</i>	American Society for Histocompatibility and Immunogenetics
<i>AT</i>	Attached
<i>CFR</i>	Code of Federal Regulations
<i>cGMP</i>	current Good Manufacturing Practices
<i>cGTP</i>	current Good Tissue Practices
<i>CIBMTR</i>	Center for International Blood and Marrow Transplant Research
<i>CME</i>	Continuing Medical Education
<i>CMS</i>	Centers for Medicare and Medicaid Services
<i>CLIA</i>	Clinical Laboratory Improvement Amendments
<i>CMV</i>	Cytomegalovirus
<i>CPD</i>	Continuing Professional Development
<i>CTP</i>	Cellular therapy product
<i>DNA</i>	Deoxyribonucleic acid
<i>EBMT</i>	European Group for Blood and Marrow Transplantation
<i>ECP</i>	Extracorporeal photopheresis
<i>EFI</i>	European Federation for Immunogenetics
<i>EU</i>	European Union
<i>FACT</i>	Foundation for the Accreditation of Cellular Therapy
<i>FDA</i>	U. S. Food and Drug Administration
<i>HCT/Ps</i>	Human cells, tissues, or cellular or tissue-based products
<i>HLA</i>	Human leukocyte antigen
<i>HPC</i>	Hematopoietic progenitor cells
<i>IDE</i>	Investigational device exemption
<i>IND</i>	Investigational new drug
<i>ISCT</i>	International Society for Cellular Therapy
<i>JACIE</i>	Joint Accreditation Committee – ISCT and EBMT
<i>OSHA</i>	Occupational Safety and Health Administration
<i>NMDP</i>	National Marrow Donor Program
<i>QM</i>	Quality management
<i>RBC</i>	Red blood cell
<i>Rh</i>	Rhesus systems of human red cell antigens; used in this document to refer to the Rh(D) antigen only, unless otherwise specified
<i>SCTOD</i>	Stem Cell Therapeutics Outcomes Database
<i>SOP</i>	Standard operating procedures

<i>TC</i>	Therapeutic cells
<i>US</i>	United States
<i>USDA</i>	United States Department of Agriculture
<i>WMDA</i>	World Marrow Donor Association

A3 DEFINITIONS

The definitions in this section are descriptive only. In the event of a conflict with the Standards, the Standards shall prevail.

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 Practitioner: Advanced Practitioner of Nursing; includes certified nurse anesthetist, nurse practitioner, certified nurse midwife, and clinical nurse specialist.

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 infusion 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.

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.

Audit: Documented, systematic evaluation to determine whether approved policies or 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, therapeutic cells, cord blood cells, mesenchymal stromal cells) that is procured from a donor and intended for processing and administration.

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

Clinical Program: An integrated medical team housed in geographically contiguous or proximate space with a single Clinical Program Director and common staff training programs, protocols, and quality management systems. The Clinical Program shall use cell collection and processing facilities that meet FACT-JACIE Standards with respect to their interactions with the Clinical Program. Clinical Programs that include non-contiguous institutions shall demonstrate evidence of regular interaction and common protocols, staff training procedures, quality management systems, and review of clinical results.

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. A Collection Facility may be part of the same institution as the Clinical Program or may be part of another institution and perform cellular therapy product collection services through contractual agreement.

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 causes of an existing discrepancy or other undesirable situation to prevent recurrence.

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 facility. For example, DMSO is a critical reagent because omitting it from the freezing medium will cause loss of cells during freezing and thawing.

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-autologous purposes are controlled under cGMP regulations. Similar requirements are enforced 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.

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 or accepted standard.

Unplanned Deviation: Occurred without intent.

Planned Deviation: Was allowed to occur with documented approval as the best course of action when adherence to the established course or accepted standard was not feasible or possible.

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 transplant recipient’s primary treating physician whose primary obligation is to help the donor understand the process, the procedures, and the risks and benefits of donation. The advocate should protect and promote the interests, well-being, and safety of the donor.

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.

Eligible: An allogeneic cellular therapy product donor who meets all donor screening and testing requirements related to transmission of infectious disease as defined by applicable laws and regulations.

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. Requires documented approval.

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. Such activities include determination of donor eligibility or suitability, product collection, processing, storage, distribution, issue, and administration.

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 infusion 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.

Ineligible: An allogeneic cellular therapy product donor who does not meet all donor screening and testing requirements related to transmission of infectious disease as defined by applicable laws and regulations.

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:* The international information technology standard for transfusion medicine and transplantation.

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

Labeling: Steps taken to identify the original cellular therapy product collection and any products or product modifications, to complete the required reviews, and to attach the appropriate labels.

Licensed health care professional: An individual who has completed a prescribed program of health-care related study and has been certified 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 or license.

Manipulation: An ex vivo procedure(s) that selectively removes, enriches, expands, or functionally alters HPC products.

Minimally Manipulated: Processing that does not alter the relevant biological characteristics of cells or tissues.

More than minimally manipulated: Processing that does alter the relevant biological characteristics of cells or tissues.

Unmanipulated hematopoietic progenitor cells: HPC as obtained at collection and not subjected to any form of processing.

Manufacturing: 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 the screening and testing of a cell or tissue donor.

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.

Mid-Level Practitioner: Physician Assistant, Nurse Practitioner, or other Advanced Practitioner who provides primary patient care with physician oversight.

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

Nurse Practitioner: A nurse with a graduate degree in advanced practice nursing who is licensed or certified by the applicable authority to provide patient services in defined areas of practice in collaboration with other health professionals.

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, activity, or the like.

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 Assistant: A person formally trained and licensed or certified by the applicable authority to provide diagnostic, therapeutic, and preventive health care services with physician supervision.

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.

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

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

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

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

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

Processing: All aspects of manipulation, 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 sample: A representative quantity of product removed from the cellular therapy product; an aliquot.

**Products:* The proper name for each class (broad descriptions of products) is as follows:

Concurrent Plasma, Apheresis: Plasma collected from the donor as part of an apheresis cell collection procedure for use by the laboratory in further processing of that donor's product.

HPC, Apheresis: Peripheral blood collected by apheresis as a source of hematopoietic progenitor cells. Mobilized unless otherwise stated in modifier.

HPC, Cord Blood: Umbilical cord blood and/or placental blood collected as a source of hematopoietic progenitor cells.

HPC, Marrow: Bone marrow collected as a source of hematopoietic progenitor cells.

HPC, Whole Blood: Whole blood collected as a source of hematopoietic progenitor cells. Mobilized unless otherwise stated in modifier.

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.

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 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 handbook: A document describing the application of general principles of quality management in cellular therapy programs using templates, scenarios, and sample

documentation. It is an adjunct to help cellular therapy programs prepare for and maintain FACT or JACIE accreditation. May also be referred to as a quality guide.

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

Quality management: An integrated program of quality assessment, assurance, control, and improvement.

Quality management plan: A written document that describes the systems in place to implement the quality management program. May also be referred to as the quality management manual or handbook.

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 as the quality management system.

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.

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

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

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

Standard Operating Procedures (SOP) Manual: A compilation of policies and 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 Cellular Therapy Product Collection, Processing, and Administration*, which may be referred to herein as "Standards" or "FACT-JACIE Standards."

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

Syngeneic: The biologic relationship between identical twins.

Therapeutic cells: Nucleated cells from any source (marrow, peripheral blood, or umbilical cord and/or placental blood) intended for therapeutic use other than as HPC.

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.

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

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

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

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

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

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

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

Variance: A planned deviation from recommended practice or standard operating procedure.

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

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

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

Written: Documentation in human readable form.

**These definitions are as of 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.*

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PART B: CLINICAL PROGRAM STANDARDS

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- B2 Clinical Unit
- B3 Personnel
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- B6 Allogeneic and Autologous Donor Selection, Evaluation,
and Management
- B7 Therapy Administration
- B8 Clinical Research
- B9 Data Management
- B10 Records

PART B: CLINICAL PROGRAM STANDARDS

STANDARD:

B1 GENERAL

B1.1 The Clinical Program consists of an integrated medical team housed in geographically contiguous or proximate space with a Clinical Program Director(s) and common staff training, programs, protocols, and quality management systems.

Explanation:

This standard is the definition of a Clinical Program, an entity that can be inspected and independently accredited. This standard will be interpreted as meaning that the different clinical units that make up a single program must be geographically contiguous or proximate enough to allow for close and regular interaction.

It is possible to have one or more than one Clinical Program in a defined network and/or within a single metropolitan area. Each could be separately accredited 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 metropolitan area. Only those programs that truly function as a single integrated program may apply as one Clinical Program.

Evidence:

The questions on the inspection application and checklist are designed to elicit the information necessary to determine if a single Clinical Program exists. Individual clinical sites will be inspected as appropriate units should be no more than one hour travelling distance in each direction, and they should exist within a single metropolitan area.

Example(s):

A Clinical Program may have one or more clinical sites. In some cases, some, but not necessarily all, of the components of a single program may be present at a single site. The Accreditation Committee will individually evaluate situations such as these after the inspection report has been submitted.

STANDARD:

B1.1.1 Clinical Programs that include non-contiguous institutions shall demonstrate common protocols, procedures, quality management systems, and review of clinical results and evidence of regular interaction.

Explanation:

This standard means that clinicians accredited together as a Clinical Program must work together in readily demonstrable ways on a daily basis, and have a single director or co-directors (the Program Director(s)), each of whom is responsible for these clinical transplant activities. Programs that include non-contiguous sites must be sites within the same defined network.

A Clinical Program may undertake transplants at more than one site. In most cases, each site would be located at a different hospital. Several clinical sites, particularly with different directors or outside a defined network, joining together for the purpose of meeting criteria to qualify as a Clinical Program do not fulfill the intent of these Standards. By itself, the presence of one or more of the characteristics in this standard does not necessarily define a single program nor

meet the intent of 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.

Evidence:

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

It is incumbent on the applicant to demonstrate with evidence that there is sufficient integration. In evaluating whether several noncontiguous sites constitute a Clinical Program, the inspector will expect to find the following if a single Clinical Program exists:

- Common or equivalent staff training programs, especially for nurses. This would include in-service training and competency testing in the same topics.
- Common clinical protocols, whether local, regional, or national. This could include clinical treatment protocols and high-dose therapy regimens as well as protocols for the management of fever, prophylactic antibiotics, antiviral and antifungal prophylactic regimens, and administration guidelines for medications and blood components. Common forms, flow sheets, and patient databases would typically be found.
- Regular interaction: This should include regularly scheduled conferences such as Morbidity and Mortality, quality assessment and improvement, protocol development, journal clubs, patient assessment and evaluation, tumor boards, multidisciplinary teams, processing facility meetings, etc. The inspector should check attendance to confirm that all sites are represented. Regular interaction should involve physicians, nurses, coordinators, social workers, education consultants, processing staff, and others. Clinical results may be reviewed at these meetings; such results could also be reported in joint manuscripts. Such regular interaction should be documented in minutes of meetings.
- A common database of all patients treated by the Clinical Program, including a single statistical support group and/or data managers.

Example(s):

Examples of a single clinical Program within a defined network 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, or
- Any other robust organizational structure involving center and satellite units.

For example, 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 transplant units at two hospitals. In addition, if a large general hospital had both a pediatric unit and an adult unit, which were staffed by either specialist pediatric or adult nurses, this would be considered two sites. In contrast, a large adult unit that transplanted patients on two wards, but where nursing staff and physician coverage were 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 contiguous or under one roof. 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.

Evidence:

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

Example(s):

A hematopoietic progenitor cell (HPC) Collection Facility may be accredited independently, or in conjunction with a Clinical Program and/or with a cell Processing Facility. A Clinical Program and the Collection Facility could be joint facilities, with the cells processed and stored at a distant site. A Processing Facility may process and store cells for several Clinical Programs.

An example of a situation where a Clinical Program may not be able to collect a cellular therapy product at an accredited Collection Facility is a pediatric program in a city where there is no FACT or JACIE-accredited adult program. The program may elect to collect an adult donor in a collection center of a registry operating in accordance with WMDA guidelines.

While it is expected that the Clinical Program will use cell collection facilities that meet FACT-JACIE Standards, it is accepted that the center will not always know where an unrelated product procured through the National Marrow Donor Program (NMDP) or other donor registries has been collected. In this setting, a collection center used by a registry operating in accordance with World Marrow Donor Association (WMDA) guidelines may be a criterion.

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 of 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 these 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 from outside of its immediate jurisdiction.

Although many of the existing standards may be applicable to cellular therapy products not obtained from living humans, a Clinical Program cannot be cited for not following standards in cases where a deviation is recognized as limited to products not covered by the scope of these Standards.

Compliance with any of the numerous national and international regulations should indicate that the Clinical Program is safely run. However, compliance with other organizations' standards or governmental regulations does not imply that FACT-JACIE Standards have been met. In all cases, governmental regulations supersede any organization's standards if the standards are inconsistent with a specific regulation. However, a FACT-JACIE standard that is more rigorous than a governmental regulation must be followed.

Clinical Programs that are not in compliance with applicable governmental law cannot be accredited by FACT or JACIE. Non-compliance with B1.3 may jeopardize that accreditation.

Evidence:

Current certifications will demonstrate what areas of facility function have been certified by other organizations and/or competent authorities. While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with applicable laws and regulations.

Example(s):

Documentation of evidence may include facility registration or licensure. In the U.S., minimally manipulated HPC, Marrow is currently not regulated under either of these federal regulations. Both minimally manipulated HPC, Apheresis and TC 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). If these products are extensively manipulated, from an unrelated donor, 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 are regulated under the Public Health Service Act 351 and therefore are referred to as 351 products.

In the Member States of the Europe Union (EU), both HPC and TC fall under the European Directive (EUD) 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 EUD 2006/17/EC and EUD 2006/86/EC. The EUD 2001/83/EC regulates products that are classified as medicinal products (MP). This includes somatic cell therapy MPs and gene therapy MPs. The ATMP Regulation 1394/2007 entered into force on December 30, 2008 to include tissue engineered products as well. The consequence of classification as an MP is that a GMP environment is required for the production of these cells. Furthermore, each Member State in the EU may add on additional regulations to the EUDs, which have to be followed, but Member State-specific regulations will not be specified in the guidance to these Standards.

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, acceptable Occupational Safety and Health Administration (OSHA) inspections, or accreditation by the AABB, American Society for Histocompatibility and Immunogenetics/European Foundation for Immunogenetics (ASHI/EFI), the College of American Pathologists (CAP), or any other applicable accreditation body.

STANDARD:

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

Explanation:

Clinical Programs must be appropriately licensed, registered, and/or accredited as required by applicable laws and regulations. National 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.

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 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 (also known as the Joint Commission on Accreditation of Healthcare Organizations or JCAHO), the Healthcare Facilities Accreditation Program (HFAP) of the American Osteopathic Association, or Det Norske Veritas Healthcare, Inc (DNV). 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 For initial accreditation, a dedicated transplant team including a Clinical Program Director(s) and at least one other physician trained and/or experienced in cellular therapy and/or HPC transplantation shall have been in place for at least twelve (12) months preceding accreditation.

Explanation:

The standard requires that a Clinical Program have sufficient experience as a team in caring for transplant patients. A dedicated transplant team does not necessarily mean that all of the individual members of this team do nothing but transplantation. It is likely that individuals may do basic research, clinical research, other non-transplant clinical care, or administrative work during the time they are not actively attending to transplant patients. That is the concept of the transplant team.

If an experienced team relocates and develops a new Clinical Program, that new program must have been in place a year and the team must perform a minimum number of transplants (per B1.5 and B1.6) at the new location prior to accreditation. 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 FACT or JACIE, as appropriate, and may require reinspection in accordance with FACT or JACIE policies. The applicable Accreditation Committee will make the final decision on whether a reinspection is required.

Evidence:

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

Example(s):

Changes in a Program Director would not necessarily require reinspection, especially if the majority of faculty and staff remained unchanged and the scope of transplant activities also

remain the same. However, if the Clinical Program has only one or two physicians who relocate, reinspection may be required when new physicians are appointed. Likewise, if the entire collection or processing facility personnel left the Clinical Program and were replaced by new employees or if the service was contracted out 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 FACT-JACIE Standards).

STANDARD:

B1.5 If the Clinical Program requests accreditation for allogeneic HPC transplantation, a minimum of ten (10) new allogeneic patients shall have been transplanted during the twelve (12) month period immediately preceding program accreditation and a minimum average of ten (10) new allogeneic patients shall be transplanted per year within the accreditation cycle. A Clinical Program that is accredited for allogeneic transplantation will be considered to have met the numeric requirement for autologous transplantation.

B1.5.1 For Clinical Programs utilizing more than one clinical site and requesting accreditation for allogeneic HPC transplantation, a minimum of five (5) new allogeneic patients shall have been transplanted at each site performing allogeneic transplants during the twelve (12) month period immediately preceding accreditation and a minimum average of five (5) new allogeneic patients shall be transplanted at each site performing allogeneic transplants per year within the accreditation cycle. A site that is accredited for allogeneic transplantation will be considered to have met the numeric requirement for autologous transplantation.

B1.5.1.1 For clinical sites performing only autologous transplants, a minimum of five (5) new autologous patients shall have been transplanted at each site during the twelve (12) month period immediately preceding accreditation and a minimum average of five (5) new autologous patients shall be transplanted at each site per year within the accreditation cycle.

B1.5.2 A combined Clinical Program caring for pediatric and adult patients at the same site shall perform a minimum average of five (5) allogeneic HPC transplants for each population per year within the accreditation cycle.

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.) Note in this standard, the 10 per year for the 12 months prior to accreditation is "shall" (required). 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. 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.

For a combined adult and pediatric Clinical Program at a single site, a minimum of five new adult and five new pediatric allogeneic transplant patients are required for allogeneic accreditation; sites accredited for allogeneic transplantation will also be accredited for autologous transplantation.

Because of the mix of patients and transplant types in a particular Clinical Program, some components of care, such as cryopreservation or mobilization of a heavily pretreated donor, may not be practiced frequently. Issues related to proficiency for care or procedures that a center does not perform frequently are covered in the relevant standard for that procedure or type of care.

This standard allows Clinical Programs to apply for accreditation prior to meeting the minimum transplant volume, but this is intended for exceptional circumstances. In this scenario, there must be adequate quality management 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 transplant volume is met. The Clinical Program must decide if it is in a position to accept the risk of not meeting the minimum transplant volume (and not becoming accredited) within the accreditation timeline set by FACT or JACIE as applicable.

Evidence:

For a combined adult and pediatric Clinical Program, the inspector will review the number of adult and pediatric transplants in the last year (initial accreditation) or the yearly average throughout the accreditation cycle (renewal accreditation) and may also ask how patients are allocated to each program 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.

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.

STANDARD:

B1.6 If the Clinical Program requests accreditation for only autologous HPC transplantation, a minimum of five (5) new recipients of autologous transplantation shall have been transplanted during the twelve (12) month period immediately preceding accreditation and a minimum average of five (5) new recipients of autologous transplantation shall be transplanted per year within the accreditation cycle.

B1.6.1 For Clinical Programs utilizing more than one clinical site and requesting accreditation for autologous HPC transplantation only, a minimum of five (5) new patients shall have been transplanted at each site during the twelve (12) month period immediately preceding accreditation and a minimum average of five (5) new patients shall be transplanted at each site per year within the accreditation cycle.

B1.6.2 A combined Clinical Program requesting accreditation for autologous HPC transplantation only and caring for pediatric and adult patients at the same site shall perform a minimum average of five (5) transplants for each population per year within the accreditation cycle.

Explanation:

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 quality management 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 adult and pediatric transplant volumes in the last year (initial accreditation) or throughout the accreditation cycle (renewal accreditation) and may also ask how patients are allocated to each site if warranted.

Example(s):

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.

FACT and JACIE will use the average number of transplants over the accreditation cycle to determine if a Clinical Program meets the minimum volume per year. For example, if a program performs three autologous transplants in the first year, eight in the second, and then four in the third, the program will have performed an average of five transplants per year during the accreditation cycle and be considered to have met the standard.

STANDARD:

B2 CLINICAL UNIT

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

Explanation:

Inspectors will recognize that the unit facilities may vary between centers. Variation in facilities may be reasonably based on a number of factors, including the numbers and case mix of transplants performed, epidemiological factors influencing the prevalence of opportunistic infections, and potential economic factors. There is also recognition of an increasing use of ambulatory approaches to transplantation.

The manner in which various units meet this requirement may vary depending on the type of patient being treated (e.g., unrelated allogeneic recipient; autologous recipient; or recipient with mismatched or T-cell depleted, nonmyeloablative, or cord blood transplantation).

The standard is not meant to imply that every unit must have laminar airflow available, 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 prevention and control (see B5.1.6) should indicate how allocation of rooms are 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 procedures 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 details regarding monitoring airborne infections will provide evidence of compliance.

Signs posted around the unit and the behavior of the staff during the visit consistent with what would be expected for the type of infection control that is required in the policies and procedures demonstrates compliance. If there are renovation or construction projects underway the appropriate environmental controls must be present.

Reasonable documentation and plans regarding the minimization of microbial contamination needs to exist for those units where patients could reasonably be expected to be cared for (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 HPC patients.

When an accredited Clinical Program is to be relocated, qualification and validation must be performed to ensure the new space meets the Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT Policy 6.1.001 Inspection Process. This includes a description and floor plan of the new facility, QM documents, and relocation date. The policy can be found on the FACT website. 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. Rooms should be sited on a single unit where infection control policies can be implemented. Portable, industrial-grade HEPA filters may be used in non-Protective Environment rooms to accommodate vulnerable patients in case of a shortage of rooms.

Visitors should receive information concerning communicable infections. At a minimum, signs should be posted to inform the public about visitation restrictions. This 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:

B2.1.1 The inpatient program shall have an intensive care unit or equivalent coverage available.

B2.1.1.1 There shall be written guidelines for clear communication and prompt transfer during and ongoing monitoring of the transfer of patients to an intensive care unit or equivalent coverage.

Explanation:

There shall be ready access to an Intensive Care Unit (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

but contractual arrangements with another institution may be considered if transfer procedures are in place to assure patient safety.

Clinical Programs must have written guidelines for the transfer of patients to an intensive care unit or equivalent coverage. The purpose of these guidelines is to facilitate clear communication between the program and any other departments and health care professionals, prompt transfer, and ongoing monitoring. It is not intent to require guidelines regarding the selection of patients for transfer to an ICU. Such decisions are made on a case-by-case basis based on clinical assessment.

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 sites as the clinical unit(s) and the SOP for transfer of patients to the ICU must be available. Discussion about shared decision-making about the patients and how the specific cellular therapy patient care needs are met will illustrate that patients receive appropriate intensive care when needed. An interview may be requested with a representative from the ICU team.

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 in which the inpatient program and the other institution have a good working relationship and the ICU meets these Standards.

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 neighboring pediatric hospital's ICU. This is acceptable so long as the arrangement is well established and monitored.

STANDARD:

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

B2.2.1 Outpatient facilities shall have a plan for providing access to an intensive care unit or equivalent coverage for patients who may become critically ill.

Explanation:

This standard is meant to address the minimal requirements for the space where outpatients can be evaluated and treated. The standard does not imply that a specifically designed or designated outpatient treatment unit must be used. Given the interchange between inpatient and outpatient units, close organizational relationships should exist, particularly with respect to infection control.

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. Outpatient facilities need to document a plan for immediate transfer to an ICU, emergency department (ED), or inpatient unit if clinically warranted.

Evidence:

Relationships between outpatient and inpatient facilities, including steps taken to minimize transplant infection, must be documented within policies, procedures, and/or the organizational chart. An SOP should also describe the admissions process.

Where patients are managed in an outpatient setting prior to engraftment, the unit should be able to demonstrate appropriate policies and procedures for patient management including availability of immediate admission to appropriate facilities when required.

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, infusions, and transfusions may also comply with this standard. The Clinical Program should provide a plan for the outpatient unit to provide, as necessary, provisions for isolation of patients, administration of fluids, and blood products.

Signs should be posted to inform patients and relatives about communicable infections. This could also include information about incubation periods and risks of live vaccines.

A protocol for outpatient facilities to contact emergency medical services (911 in the U.S. or 112 in the EU) and a plan for prompt care is adequate.

STANDARD:

B2.3 Facilities used by the Clinical Program shall be maintained in a clean, sanitary, and orderly manner.

Evidence:

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

STANDARD:

B2.4 The following shall apply to both inpatient and outpatient care:

B2.4.1 There shall be provisions for prompt evaluation and treatment by a transplant attending physician available on a 24-hour basis.

B2.4.1.1 If general medical physicians provide inpatient-based care to transplant patients, there shall be a policy for their scope of care and afterhours coverage.

Explanation:

There must always be a transplant attending physician available to evaluate and treat cellular therapy patients, whether available on-site or on-call. It is acceptable to allow hematologists, oncologists, hospitalists, general internists, and physicians of other specialties to provide general patient care during afterhours; however, there must be criteria for distinguishing when evaluation and treatment must be performed by a transplant attending physician. There are patient care issues unique to cellular therapy that must be addressed by a physician with specific training for these events.

Evidence:

There should be guidelines describing the outpatient clinic and afterhours care of the patients that describe the role of the transplant attending physician. This must include criteria for when evaluation and treatment must be performed by a transplant attending physician.

Example(s):

One example of a situation in which prompt evaluation and treatment is needed by a transplant attending physician is bacterial sepsis, which needs to be treated with antibiotics immediately.

The Emergency Department (ED) may be acceptable when other outpatient facilities are unavailable, if the physician coverage is adequate to ensure that the HPC recipients are evaluated promptly (i.e., not caught in the middle of a busy trauma center) and not exposed to risk of infectious disease transmission, including respiratory spread.

STANDARD:

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

Explanation:

In addition to having medications available, the pharmacy must have mechanisms to prevent dosing errors in the administration of high-dose therapies.

STANDARD:

B2.4.3 There shall be access to renal support under the direction of nephrologists and trained personnel.

Evidence:

The Clinical Program must have documentation that there is ready access for its patients to receive renal support, such as dialysis, if the need arises.

Example(s):

The need for dialysis may be fulfilled by provision of dialysis on the transplant unit, as an outpatient service, or in an intensive care unit, as deemed appropriate by clinical staff under the direction of appropriate personnel. The requirement may also be achieved through a dialysis unit within the institution or through a well-documented arrangement with a neighboring institution's dialysis unit if the inpatient program and the other institution have a good working relationship.

STANDARD:

B2.4.4 There shall be 24-hour availability of autologous and/or CMV-appropriate and irradiated blood products needed for the care of transplant patients.

Explanation:

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

Example(s):

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

STANDARD:

B2.4.5 The Clinical Program shall refer planned discharges to facilities and health care professionals adequate for post-transplant care.

B2.4.5.1 The Clinical Program shall provide or secure oversight of care that meets applicable standards.

Explanation:

Discharges should normally take place after patients have achieved clinical and hematological stability. In exceptional cases, a Clinical Program may adopt a policy of discharging patients 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 procedures which should be made available to the inspection team.

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. Programs should provide a thorough justification for the necessity of the shared care arrangement within their Quality 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 these 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:

B2.4.6 Clinical Programs performing allogeneic cell transplants shall use HLA testing laboratories appropriately accredited by the American Society for Histocompatibility and Immunogenetics (ASHI), European Federation for Immunogenetics (EFI), or equivalent, with the capability of carrying out deoxyribonucleic acid (DNA)-based HLA-typing.

Explanation:

ASHI, EFI, and equivalent organizations are the recognized authorities in histocompatibility. The laboratory results upon which donor selection for allogeneic transplant is made must meet these requirements.

ASHI accreditation consists of two parts: technologies/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.

Evidence:

A copy of the current (in-date) ASHI or EFI certificate for the laboratory is required, to include at least the competencies listed above. If ASHI accreditation is not for HSC/BM Transplantation, the Clinical Program must describe the role the HLA testing laboratory fulfills in donor selection and the HLA expertise in the program.

Example(s):

If the HLA testing laboratory is accredited for the appropriate technologies/methods, but not in HSC/BM Transplantation, the Clinical Program must have sufficient expertise to select the best matched donor for the recipient.

STANDARD:**B2.5 SAFETY REQUIREMENTS**

B2.5.1 The Clinical Program shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.

B2.5.2 The Clinical Program shall have a written safety manual that includes instructions for action in case of exposure to communicable disease or to chemical, biological, or radiological hazards, where applicable.

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 Clinical Program's policies and procedures, 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 program must be covered in the program'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 reviewed this information.

Facilities should post warning signs wherever radioactive materials are in use. All persons who may be exposed to blood or body fluids must have appropriate personal protective equipment available to them. This includes those exposed to HPC 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 provided. Gloves must be provided whenever potential infectious exposure exists and when sterile procedures are required to protect the product and/or patient.

In case of exposure either to communicable disease or other hazards such as chemical, biological, or radiological hazards, the response and action taken might be time sensitive and thus could affect the outcome of the exposure. Therefore, it is critical that the Clinical Program has a safety manual and the staff members have access to instructions regarding the best method to respond to a specific incident as outlined in the safety manual.

Evidence:

If a clinical procedure is underway during the day of inspection, the inspector should observe personnel for use of protective clothing and other biosafety precautions. Employee files for compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures must exist. The presence of unused equipment, excessive traffic from unauthorized personnel, and inappropriate storage of reagents and supplies may also contribute to an unsafe environment and will be noted by the inspector.

The inspector should examine how cellular therapy products are being handled and discarded (e.g., incinerator, waste field, etc.) and compare his/her observations with the written protocols. The inspector should examine selected employee files for compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures. Compliance with applicable regulations should be addressed by the Clinical Program and verified by the inspector.

The inspector can also review training documentation for infection control and OSHA regulations and safety procedures.

Example(s):

Safety training, including standard 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 via computer. 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. A Standard Operating Procedure (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 safety manual is kept updated with institutional 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:

B3 PERSONNEL

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 program is located who has achieved specialist certification in one or more of the following specialties: Hematology, Medical Oncology, Pediatric Immunology, or Pediatric Hematology/Oncology. Physicians trained prior to requirements for specialty training may serve as Clinical Program Director if they have documented experience in the field of HPC transplantation extending over ten (10) years.

Explanation:

The Clinical Program Director must be licensed or registered to practice medicine in the location and country where the Clinical Program is located. Appropriately licensed means that the Clinical Program Director must be licensed or registered according to applicable laws and regulations to practice medicine in the state, province, or country where the 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 Europe Union or North America, the Accreditation Committee will assess their documentation of training and the Board

will make the final determination. Specialist certification can be obtained from jurisdictions other than where the Clinical Program Director practices.

It is recognized that board exams and higher training in hematology/oncology do not extensively cover cellular therapy and HPC transplantation and there may be circumstances when expiration of board certification or specialist registration can be allowed. For example, if a significant portion of a Clinical Program Director's duties includes the direct care of transplant patients, he/she will have the experience to maintain the knowledge obtained during the board certification process. However, if applicable laws and regulations require current specialist certification, the Clinical Program Director must maintain his/her certification as required.

Those physicians who completed their medical training prior to the availability of specific training in transplantation may be qualified 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 FACT-JACIE Standards require that only one person be named the Clinical Program Director for compliance with these Standards and to serve as the point of contact for communication from 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 or specialist certification as appropriate. 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. or Europe Union.

Individuals with specialist certification/registration in other areas who consider that they have equivalent training and experience must submit their qualifications for consideration by the appropriate Accreditation Committee and approval by the FACT or JACIE Board of Directors, as appropriate.

Physicians who completed their training prior to the availability of specific training in transplantation must document 10 years of experience in the form of a work history, including the size and complexity of the programs in which the applicant Clinical Program Director has worked (e.g., autologous transplant only, autologous and allogeneic, unrelated donors, allogeneic with T-Cell depletion, etc.) and the approximate number of transplant patients the individual has managed. Documentation must be in the form of one or more letters from the supervisor or professional colleague of the applicant and can also include evidence in the literature of this person's contributions to transplantation. These contributions should extend over the entire 10-year time frame to demonstrate continuous activity in the field of transplantation medicine by the applicant. Both a Curriculum Vitae (CV) and photocopies of representative publications must be included.

Example(s):

Specialist certification in the U.S. is board certification, and 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.

Those physicians who received all or part of their medical and specialty training outside of the U.S. may be ineligible to become Board-certified in the U.S. on this basis alone. In addition, 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/board exams.

For programs seeking FACT accreditation, physicians who received all or part of the medical and 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. Letters from the directors of the referenced training programs should be obtained and should describe the specifics of the training received. The FACT Accreditation Committee will assess this documentation to determine if it is “equivalent” to U.S. board certification. The FACT Board of Directors will make the final determination.

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 achieving specialist certification, the Clinical Program Director must have two (2) years of experience providing direct patient care in HPC transplantation. Clinical training often includes a significant portion of time with research studies rather than the care of patients. These trainings and/or fellowships, while valuable, do not count towards the requirement for two years of direct clinical management of HPC transplant patients.

Evidence:

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 following information: 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 if both autologous and allogeneic transplant recipients were represented and in what proportion, and an estimate of the actual number of weeks committed to this experience. 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 patients and donors, 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 process functions may assume some of these duties. Similarly, a quality officer may facilitate the execution of a process improvement program. The ultimate responsibility for performance of the quality plan and monitoring of Clinical Program elements, internal or contracted, will fall to the Clinical Program Director. Review of external elements of the program may be accomplished by contract review or review of pre-selected indicators as part of a Quality Management (QM) Plan. Because cell collection and processing services play a major role in patient outcomes, the Clinical Program Director must monitor whether these services meet these Standards and contractual requirements (see B4).

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

Example(s):

For example, individual transplant physicians may accept patients or donors for entry into the Clinical Program according to institutional standards, but it is the responsibility of the Clinical Program Director (or his/her designee) to review and comply with those standards.

STANDARD:

B3.1.5 The Clinical Program Director shall have oversight of the medical care provided by all members of the Clinical Program including medical care provided by the physicians on the transplant team.

B3.1.5.1 The Clinical Program Director shall be responsible for verifying the knowledge and skills of the physicians and mid-level practitioners of the transplant team.

Explanation:

This standard is not meant to imply that the Clinical Program Director is directly responsible for the medical activity of another physician or a mid-level practitioner. The Clinical Program Director is responsible for reviewing the knowledge and skills of the transplant physicians and mid-level practitioners. 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 patients was specifically addressed, etc.

Physicians not directly affiliated with the transplant program, including hematologists, oncologists, hospitalists, and other physicians and mid-level practitioners involved in the care of the patient must be credentialed and are responsible for maintaining their credentials for their own departments.

STANDARD:

B3.1.6 The Clinical Program Director shall participate regularly in educational activities related to the field of HPC transplantation.

Explanation:

The field of transplant medicine continues to evolve rapidly. Clinical Program Directors should participate regularly in educational activities related to the field. The purpose of this requirement is for key personnel to keep up with current advancements in the field. The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation

should be in an activity that includes substantive information related to the field of HPC transplantation.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not a Clinical Program Director meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material. Recognized educational activities include those for which certified continuing education credits are offered, examples included in this Accreditation Manual, and internal training programs that are specific to HPC transplantation 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 the accreditation cycle:

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

Example(s):

Evidence of compliance may include either formal or informal study, such as meeting the requirements of applicable national or international continuing education programs. Presentation of CME/CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. A Clinical Program Director may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and/or publication of a manuscript related to HPC transplantation).

Grand Rounds may meet the standard as long as they are related to the field of HPC transplantation and/or cellular therapy and the individual is in attendance. If Grand Rounds are to be considered for meeting this standard, it is incumbent on the Clinical Program to clearly outline the subject, location, and date of these activities.

STANDARD:

B3.2 ATTENDING PHYSICIANS

B3.2.1 Clinical Program 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, Adult or Pediatric Immunology, or Pediatric Hematology/Oncology.

Explanation:

This standard is parallel to the requirements for the Clinical Program Director; however, it allows specialist training rather than requiring specialist certification for physicians. It also allows for attending physicians certified in Adult Immunology in adult programs, though this does not meet the requirements for the Clinical Program Director.

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 board certification/eligibility or equivalent, a copy of the current certificate or documentation of completion of the requisite fellowship and primary board certification in Hematology, Medical Oncology, Adult or Pediatric Immunology, or Pediatric Hematology/Oncology is required.

Example(s):

In the U.S., this includes physicians who are eligible to complete specialist Board examinations. In the Europe 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 attending physician practices.

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

The equivalent European requirements include specialist registration or completion of higher specialist training in one of the specialties listed in B3.2.1. For Australia and New Zealand, the equivalent requirements include specialist registration or completion of higher specialist training in one of the specialties listed in B3.2.1.

STANDARD:

B3.2.2 Clinical Program attending physicians shall participate regularly in educational activities related to the field of HPC transplantation.

Explanation:

The field of transplant medicine continues to evolve rapidly. Attending physicians should participate regularly in educational activities related to the field. The purpose of this requirement is for key personnel to keep up with current advancements in the field. The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation should be in an activity that includes substantive information related to the field of HPC transplantation and/or cellular therapy.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not an attending physician meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material. Recognized educational activities include those for which certified continuing education credits are offered, examples included in this Accreditation Manual, and internal training programs that are specific to HPC transplantation and/or diseases in which cellular therapy is a therapeutic option.

The Clinical Program Director should evaluate the continuing education obtained by attending physicians during the annual performance review as required in B4.3.

Evidence:

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

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

Example(s):

Evidence of compliance may include either formal or informal study, such as meeting the requirements of applicable national or international continuing education programs. Presentation of CME/CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. An attending physician may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and/or publication of a manuscript related to HPC transplantation).

Grand Rounds may meet the standard as long as they are related to the field of HPC transplantation and/or cellular therapy and the physician is in attendance. If Grand Rounds are to be considered for meeting this standard, it is incumbent on the Clinical Program to clearly outline the subject, location, and date of these activities.

STANDARD:

B3.3 CLINICAL TRANSPLANT TEAM

B3.3.1 Clinical Programs performing pediatric transplantation shall have a transplant team trained in the management of pediatric patients.

B3.3.2 Clinical Programs performing pediatric transplantation shall have at least one attending physician who has achieved specialist certification in Pediatric Hematology or Oncology or Pediatric Immunology. An attending physician may also serve as the Clinical Program Director, if appropriately credentialed.

B3.3.3 For Clinical Programs performing adult transplantation, there shall be at least one attending physician who has achieved specialist certification in Hematology, Medical Oncology, or Immunology. An attending physician may also serve as the Clinical Program Director, if appropriately credentialed.

Explanation:

The standards require that transplant teams be trained in the management of children or adults as appropriate for the age ranges of patients being treated. These Standards do not define pediatric age limits as these vary by institution.

Teams treating children must include an attending physician who has achieved specialist certification in Pediatric Hematology/Oncology or Pediatric Immunology. Teams treating adults must include an attending physician who has achieved specialist certification in Hematology, Medical Oncology, or Immunology. After achieving specialist certification, re-certification is not required.

The Clinical Program Director can fulfill the requirements in B3.3.2 or B3.3.3 if he/she is appropriately qualified.

Evidence:

Physicians who completed their medical training prior to the availability of specific training in transplantation must document 10 years of experience in the form of a work history, including the size and complexity of the programs in which the individual has worked (e.g., autologous transplant only, autologous and allogeneic transplant, unrelated donors, allogeneic with T-Cell depletion, etc.) and the approximate number of transplant patients the individual has managed. Documentation must be in the form of one or more letters from the supervisor or professional colleague of the applicant and may include evidence in the literature of this person's contributions to transplantation. These contributions should extend over the entire 10-year time frame to demonstrate continuous activity in the field of transplantation medicine by the applicant. Both a CV and photocopies of representative publications must be included.

Example(s):

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

In the U.S., specialist certification is the equivalent of board certification/eligibility. In Europe and Australasia (Australia, New Zealand, and the neighboring Pacific Islands), the equivalent requirements include specialist registration or completion of higher specialist training in one of the aforementioned specialties. Specialist certification can be obtained in a jurisdiction other than where the physicians practice.

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 and published contributions in the field of HPC transplantation.

STANDARD:

B3.3.4 The Clinical Program shall have access to licensed physicians who are trained and competent in marrow collection and 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 facility to provide marrow collection services from trained and competent physician(s). If a program's SOPs state that marrow collection will be performed in the event apheresis collection is no longer an option (e.g., if a donor fails to mobilize), the program must comply with this standard and document a contingency plan if mobilization fails or a sufficient volume cannot be collected. Whether or not the cellular therapy program is requesting accreditation for marrow collection, the clinical transplant team must be able to recognize when a marrow harvest is needed and act accordingly.

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 accreditation or an average of one procedure per year in an accreditation cycle, as defined in CM1.4.1 and CM1.5. Clinical Programs collecting marrow must document compliance with all requirements of Part CM of these Standards.

Example(s):

Evidence of training may include documentation by a letter of 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 surgical procedures.

In the case of autologous donors, some Clinical Programs may consider a failed mobilization as cause for the patient to no longer be a candidate for transplant. If marrow collection is not considered an option for the program, then this standard would not be applicable.

STANDARD:

B3.3.5 The Clinical Program shall have access to personnel who are trained and competent in cellular therapy product collection by apheresis and an apheresis collection facility that meets these Standards.

B3.4 TRAINING FOR CLINICAL PROGRAM DIRECTORS AND ATTENDING PHYSICIANS

B3.4.1 Attending physicians shall each have a total of one year of supervised training in the management of transplant patients in both inpatient and outpatient settings.

B3.4.2 Clinical training and competency shall include the management of:

B3.4.2.1 Autologous transplant patients for physicians in Clinical Programs requesting accreditation for autologous transplantation.

B3.4.2.2 Allogeneic transplant patients for physicians in Clinical Programs requesting accreditation for allogeneic transplantation.

B3.4.2.3 Both allogeneic and autologous transplant patients for physicians in Clinical Programs requesting accreditation for allogeneic and autologous transplantation.

B3.4.3 Clinical Program Directors and attending physicians in all Clinical Programs shall have received specific training and maintain competency in each of the following areas:

- B3.4.3.1 Indications for HPC transplantation.*
- B3.4.3.2 Selection of appropriate patients and preparative regimens.*
- B3.4.3.3 Pre-transplant patient evaluation, including assessment of appropriate patient suitability and HPC adequacy with respect to collection.*
- B3.4.3.4 Donor and recipient informed consent.*
- B3.4.3.5 Administration of preparative regimens.*
- B3.4.3.6 Donor evaluation and management.*
- B3.4.3.7 Administration of growth factors for HPC mobilization and for post-transplant hematopoietic cell reconstitution.*
- B3.4.3.8 HPC product infusion and patient management.*
- B3.4.3.9 Management of neutropenic fever.*
- B3.4.3.10 Diagnosis and management of infectious and non-infectious pulmonary complications of transplantation.*
- B3.4.3.11 Diagnosis and management of fungal disease.*
- B3.4.3.12 Diagnosis and management of veno-occlusive disease of the liver.*
- B3.4.3.13 Management of thrombocytopenia and bleeding.*
- B3.4.3.14 Management of hemorrhagic cystitis.*
- B3.4.3.15 Management of mucositis, nausea, and vomiting.*
- B3.4.3.16 Management of pain.*
- B3.4.3.17 Palliative and end of life care.*
- B3.4.3.18 Diagnosis and management of HPC graft failure.*
- B3.4.3.19 Evaluation of post-transplant cellular therapy outcomes.*
- B3.4.3.20 Evaluation of late effects of allogeneic and autologous transplants, including cellular, pharmacologic, and radiation therapy.*

Example(s):

Possible late effects of transplants include second malignancies, renal failure, decline in cognitive function, and others.

STANDARD:

B3.4.3.21 Documentation and reporting for patients on investigational protocols.

B3.4.3.22 Applicable regulations and reporting responsibilities for adverse events.

B3.4.4 Additional specific clinical training and competency required for physicians in Clinical Programs requesting accreditation for allogeneic HPC transplantation shall include:

B3.4.4.1 Identification, evaluation, and selection of HPC source, including use of donor registries.

B3.4.4.2 Donor eligibility determination.

B3.4.4.3 Methodology and implications of human leukocyte antigen (HLA) typing.

B3.4.4.4 Management of patients receiving ABO incompatible HPC products.

B3.4.4.5 Diagnosis and management of cytomegalovirus (CMV) infection and disease.

B3.4.4.6 Diagnosis and management of other viral infections in immunocompromised hosts.

B3.4.4.7 Diagnosis and management of acute and chronic graft versus host disease.

B3.4.4.8 Diagnosis and management of post-transplant immunodeficiencies.

Evidence:

Clinical Program Directors and attending physicians must have written confirmation of their training or experience and documentation of competency. Specialist certification is fulfillment of this requirement. Other documentation as evidence of compliance with this standard includes 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 if both autologous and allogeneic transplant recipients were represented and in what proportion, and an estimate of the actual number of weeks committed to this training and/or experience. In addition, the letter should document the applicant's training, competency, and/or knowledge (as required) in each of the subjects and procedural skills listed in B3.4.2 - B3.4.5.

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. Evaluation of competency for each area does not have to be performed every year; rather, the Clinical Program may wish to address different areas at different times during the accreditation cycle.

The Clinical Program Director and attending physicians must have training and competency in evaluating post-transplant cellular therapy outcomes (including in clinical trials) and in evaluating the late effects of cellular therapy.

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.

Example(s):

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, 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.

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

STANDARD:

B3.4.5 The attending physicians shall be knowledgeable in the following procedures:

B3.4.5.1 HPC processing.

B3.4.5.2 HPC cryopreservation.

B3.4.5.3 Bone marrow harvest procedures.

B3.4.5.4 Apheresis collection procedures.

B3.4.5.5 Extracorporeal photopheresis for allogeneic transplants, if applicable.

Explanation:

Cell processing, cryopreservation, and progenitor cell collection by apheresis are procedures that must be familiar to every transplant physician; however, it is not necessary for every physician to be specifically trained or competent to collect, process, and/or cryopreserve the cells. Each physician should know, for example, the indications and limitations for some common cell processing procedures (e.g., red cell depletion, T-cell depletion, or volume reduction), reasons to cryopreserve or not to cryopreserve a progenitor cell product, some consequences of cryopreservation, and some 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. Accordingly, it is not necessary for every physician to be specifically trained or competent to collect marrow (although each Clinical

Program must have access to at least one physician who is trained and competent in bone marrow harvesting (B3.3.4 applies). Every physician must be knowledgeable about the procedure and its risks and benefits in order to best counsel patients and donors regarding the best selection of stem cell source.

Extracorporeal photopheresis/photochemotherapy (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. 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.

Example(s):

That each physician is knowledgeable needs to be documented, using a letter from the Clinical Program Director, evidence of CME/CPD, or a copy of a publication authored by the physician.

STANDARD:

B3.5 MID-LEVEL PRACTITIONERS (Physician Assistants, Nurse Practitioners, Advanced Practitioners)

B3.5.1 Mid-level practitioners shall be licensed to practice in the jurisdiction of the Clinical Program and shall be limited to the scope of practice of their licenses and within parameters of their training.

Evidence:

Evidence of current licensure to practice in the jurisdiction of the Clinical Program as well as a written description of responsibilities with description of supervision must be presented. Note that the role of mid-level practitioner is not found in all countries, nor do all Clinical Programs have mid-level practitioners.

STANDARD:

B3.5.2 Mid-level practitioners shall have received specific training and maintain competency in the transplant-related cognitive and procedural skills that they routinely practice. These skills shall be documented and may include but are not limited to those listed in B3.4.3.

Evidence:

Competency in each of the areas described in B3.4.3 as applicable to the cognitive and procedural skills they routinely practice must be documented for each mid-level practitioner by the Clinical Program Director. Pediatric mid-level practitioners must have training in pediatrics as specified by B3.3.1.

Example(s):

This documentation can be in the form of a letter, checklist, or competency evaluation. When conferences or courses attended cover the subjects in B3.4.3 or other relevant aspects of cellular therapy, documentation of such continuing education could be used to support training and competency.

STANDARD:

B3.5.3 Mid-level practitioners shall participate regularly in educational activities related to the field of HPC transplantation.

Explanation:

The field of transplant medicine continues to evolve rapidly. Mid-level practitioners should participate regularly in educational activities related to the field. The purpose of this requirement is for key personnel to keep up with current advancements in the field. All mid-level practitioners should have documentable annual continuing education. The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation should be in an activity that includes substantive information related to the field of HPC transplantation and/or cellular therapy.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not a mid-level practitioner meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material. Recognized educational activities include those for which certified continuing education credits are offered, examples included in this Accreditation Manual, and internal training programs that are specific to HPC transplantation and/or diseases in which cellular therapy is a therapeutic option.

The Clinical Program Director should evaluate the continuing education obtained by mid-level practitioners during the annual performance review as required in B3.5.

Evidence:

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

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

Example(s):

Evidence of compliance may include either formal or informal study, such as meets the requirements of applicable national or international continuing education programs. Presentation of CME/CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. A mid-level practitioner may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and publication of a manuscript related to HPC transplantation).

Grand Rounds may meet the standard as long as they are related to the field of HPC transplantation and the practitioner is in attendance. If Grand Rounds are to be considered for meeting this standard, it is incumbent on the Clinical Program to clearly outline the subject, location, and date of these activities.

STANDARD:

B3.6 NURSES

B3.6.1 The Clinical Program shall have nurses formally trained and experienced in the management of patients receiving cellular therapy.

B3.6.2 A Clinical Program treating pediatric patients shall have nurses formally trained and experienced in the management of pediatric patients receiving cellular therapy.

B3.6.3 Training shall include:

B3.6.3.1 Hematology/oncology patient care, including an overview of the cellular therapy process.

B3.6.3.2 Administration of preparative regimens.

B3.6.3.3 Administration of blood products, growth factors, cellular therapy products, and other supportive therapies.

B3.6.3.4 Care interventions to manage transplant complications, including, but not limited to, neutropenic fever, infectious and noninfectious processes, mucositis, nausea and vomiting, and pain management.

B3.6.3.5 Recognition of cellular therapy complications and emergencies requiring rapid notification of the clinical transplant team.

B3.6.3.6 Palliative and end of life care.

B3.6.4 There shall be written policies for all relevant nursing procedures, including, but not limited to:

B3.6.4.1 Care of immunocompromised patients.

B3.6.4.2 Administration of preparative regimens.

B3.6.4.3 Administration of cellular therapy products.

B3.6.4.4 Central venous access device care.

B3.6.4.5 Administration of blood products.

Explanation:

These are core competencies for nurses in HPC transplantation and cellular therapy. It is important for nurses in units that care for patients to be oriented to the special needs of these patients.

Nurses in intensive care units may not have the degree of training or 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 patient. How these issues are addressed when the patient must be treated on a unit other than the transplant unit must also be defined.

The Standards also require that nurses be trained in the management of children or adults as appropriate for the age ranges of patients being treated. The Standards do not define pediatric age limits as these vary by institution.

Specific transplantation training does not need to be a part of the formal job orientation for all nurses. Specific training may be obtained through agreements with another established transplant institution for specific training. Nurse competencies should be evaluated according to a defined process on an annual basis at a minimum. Nursing personnel must be able to recognize when rapid notification of a transplant team member is required. The Clinical Program is responsible for identifying what situations would constitute a need for rapid notification.

Evidence:

Evidence of training in these core competencies must be documented. Because on-going education and documentation of continued competency are required, review documentation of in-service training and/or attendance at conferences is necessary.

Evidence of compliance with these Standards may include age-specific competencies and proficiencies, age specific orientation for new employees, attendance of age-specific continuing educational activities, and age-specific preceptorships.

Example(s):

Formal training can include in-service and annual review classes that address the relevant transplant-related topics as well as through conference attendance or on-the-job training. All of these training experiences should be documentable through conference attendance documents, a list of attendees at an internal class, a checklist for training of new employees, an individual employee's continuing education record, and/or similar documents.

STANDARD:

B3.6.5 There shall be an adequate number of nurses experienced in the care of transplant patients.

B3.6.6 There shall be a nurse/patient ratio satisfactory to manage the severity of the patients' clinical status.

Explanation:

The intent of this standard is to acknowledge that nursing needs of patients vary based upon the severity, or acuity, of patients' clinical status. The unit should be staffed so that if several patients require periods of >1 nurse/patient, there will be adequate numbers of trained staff. Similarly, if no patient requires this intensity of care, fewer staff should be able to care for the patients. Thus, there is no specific number or ratio sought, but some demonstration that sufficient flexibility exists within the pool of trained staff to meet intensive patient 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. Documentation and interviews of the staff are ways to determine that the nurse staffing is adequate.

STANDARD:**B3.7 CONSULTING SPECIALISTS**

B3.7.1 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 patients requiring medical care, including but not limited to:

B3.7.1.1 Surgery.

B3.7.1.2 Pulmonary medicine.

B3.7.1.3 Intensive care.

B3.7.1.4 Gastroenterology.

B3.7.1.5 Nephrology.

B3.7.1.6 Infectious diseases.

B3.7.1.7 Cardiology.

B3.7.1.8 Pathology.

B3.7.1.9 Psychiatry.

B3.7.1.10 Radiology.

B3.7.1.11 Radiation oncology with experience in large-field (e.g., total body or total lymphoid) irradiation treatment protocols, if radiation therapy is administered.

B3.7.1.12 Transfusion medicine.

B3.7.1.13 Neurology.

B3.7.1.14 Palliative and end of life care.

B3.7.2 A Clinical Program treating pediatric patients shall have consultants, as defined in B3.7.1, qualified to manage pediatric patients.

Explanation:

The standard requires that consulting specialists (e.g., specialist physicians, surgeons, and psychiatrists) be available. There must be at least one for each specialty; however, Clinical Programs often have access to a specialty group in which the individual consultants rotate schedule. Consulting specialists' qualifications are typically managed by a credentialing or medical personnel office within the hospital; however, the program can also verify that the

specialists' qualifications are appropriate. These consultants or specialty groups shall have

physicians on the team who demonstrate age-specific expertise in the age ranges transplanted by the program.

There must be the ability to perform both anatomical pathology and histopathology. Histopathology includes a wide range of clinical and laboratory support needed for the care of transplant patients, such as managing complex infectious diseases and graft versus host disease. Histopathology may include specialization, with hematopathology being usually the most relevant specialization. Pathologists do not have to be on-site, but the Clinical Program must have access to this specialty.

Infectious diseases specialization includes both the clinical and laboratory aspects of infection and medical microbiology and may be provided by dually certified specialists or by teams comprised of clinical and laboratory specialists.

Evidence:

The Clinical Program must provide documentation of appropriate credentialing of the consulting specialists and/or specialist groups. Clinical Programs are not required to submit documentation for individual consultants unless requested by the inspector if needed to verify the appropriateness of the credentialing guidelines.

Evidence that the consultants are available to the Clinical Program for assistance when needed should be prepared for inspector review.

Example(s):

Documentation of appropriate credentialing may include the guidelines utilized by the credentialing office or specific documentation regarding individual consultants' qualifications. Such evidence may include medical staff credentialing, photocopies of documents that demonstrate board eligibility/certification in the U.S. or evidence of higher specialist registration/training in Europe or Australasia, as well as letters from division/department heads.

Examples of palliative and end of life care include hospice care and symptom management.

STANDARD:

B3.8 QUALITY MANAGEMENT SUPERVISOR

B3.8.1 There should be a Clinical Program Quality Management Supervisor approved by the Program Director to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Clinical Program.

B3.8.2 The Clinical Program Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular therapy, and/or quality management.

Explanation:

The Clinical Program should identify at least one person with responsibility for quality management (QM) supervision. This individual can be the Program Director or a qualified designee. Delegation of a qualified designee should be documented, either in the QM plan or in

a procedure related to it. The QM Supervisor may be shared with other portions of the cellular therapy program and/or the institution.

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 QM Supervisor should be an individual with at least 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 Clinical Program, or it could be a member of the program who has additional responsibilities within the facility.

The QM Supervisor should have an active role in preparing, reviewing, approving, or implementing QM policy procedures and must ensure that the procedures are in compliance with these Standards and all applicable state and government laws and regulations before implementation. A key role of the QM supervisor is to develop systems for auditing Clinical Program activities to ensure compliance with the written SOPs and policies.

Clinical Program QM Supervisors are required to participate regularly in educational activities related to cellular therapy and/or QM.

Evidence:

The inspector should look for documentation that a QM Supervisor is in place and performs or oversees the functions covered in the QM section of the Standards.

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

- Title of activity.
- Type of activity (for example, webinar, meeting, grand round, etc.).
- Topic of activity (for example, hematology, cell transplantation, etc.).
- 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 QM Supervisor'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 QM Supervisor 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 supervisory responsibilities as long as there is documentation of who is assigned the supervisor role.

STANDARD:**B3.9 SUPPORT SERVICES STAFF**

B3.9.1 The Clinical Program shall have one or more designated staff with appropriate training and education to assist in the provision of pre-transplant patient evaluation, treatment, and post-transplant follow-up and care. Designated staff shall include:

B3.9.1.1 Pharmacy staff knowledgeable in the use and monitoring of pharmaceuticals used by the Clinical Program.

B3.9.1.2 Dietary staff capable of providing dietary consultation regarding the nutritional needs of the transplant recipient, including enteral and parenteral support, and appropriate dietary advice to avoid food-borne illness.

B3.9.1.3 Social Services staff.

B3.9.1.4 Psychology Services staff.

B3.9.1.5 Physical Therapy staff.

B3.9.1.6 Data Management staff sufficient to comply with B9.

Explanation:

The standards require that other staff, as listed above, is available to support the Clinical Program. The staff does not need to be completely dedicated to the program but sufficient Full Time Equivalent (FTE) employees must be available to meet patient needs. Outpatient facilities need access to support services staff. Staff must have sufficient training to allow them to meet specific needs of transplant patients. Clinical Programs handling pediatric patients should have a staff member that is proficient in dealing with pediatric patients.

While a physical therapist is an essential member of the transplant team, it is also recommended that the Clinical Program have access to rehabilitation services including occupational therapists.

Evidence:

Adequacy of data management personnel could be assessed based on how current registry reporting is and the existence of significant backlogs and/or errors.

STANDARD:**B4 QUALITY MANAGEMENT**

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

B4.1.1 The Clinical Program shall establish and maintain a written Quality Management Plan.

Explanation:

Development of a comprehensive Quality Management (QM) Program is often the most challenging and time-consuming exercise that a Clinical Program encounters when preparing for a FACT or JACIE inspection. The QM Program consists of a description of the strategy (QM Plan) and the associated policies and procedures, which drive the operation of the QM Program.

The QM Plan is the written document that outlines how a Clinical Program will implement its QM Program (quality assurance, control, assessment, and improvement activities). The specific procedure to be followed for each of the required elements does not have to be fully described in the QM Plan, but must at a minimum be summarized in the plan with a reference to the appropriate document with the details. The QM Plan does not necessarily need to be stand-alone, serving only the program. In such a case, the written QM Plan should include all elements required by the Standards and clarify the nature of participation by other areas and/or institutions.

An integrated Clinical Program may 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 between the quality programs of the Clinical, Collection, and Processing Facilities. Relationships and interactions between Quality Managers/representatives in the different organizations should be explicit to underpin cohesion within the overall cellular therapy program. There should also be a provision for communication of information between key elements of the program, including vendors and collaborators.

Free-standing facilities will have individual QM Plans, but all elements listed are required.

Evidence:

The QM Plan must be submitted to FACT or JACIE prior to inspection. To assist the inspection, the structure and relationships within the QM Program should be summarized in the presentation to the inspectors early in the course of the inspection.

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.

Some Clinical Programs call their QM Plan a Quality Manual or Quality Handbook. Varying names such as these are acceptable as long as all of the applicable requirements are met.

STANDARD:

B4.2 The Quality Management Plan shall include an organizational chart of key personnel and functions within the cellular therapy program, including clinical, collection, and processing.

B4.2.1 The Quality Management Plan shall include a description of how these key personnel interact to implement the quality management activities.

Explanation:

The organizational chart should include the reporting structure for the Clinical Program.

The description of the operation of the QM Program should include the processes in place to accomplish the goals, e.g., meetings, participants, schedule, and documentation.

Some institutions may choose to have an overall Transplant Program Director that oversees the Clinical Program, Collection Facility, and Processing Facility. If so, this position must be included in the organizational chart required in the QM Plan.

Evidence:

The minutes and attendance list of regularly scheduled QM meetings are an effective way to document communication of quality assessments to key individuals within participating facilities in the Clinical Program.

Example(s):

If a Clinical Program contracts its processing service to an outside entity, the organizational chart must include the contracted service.

STANDARD:

B4.2.2 The Clinical Program Director or designee shall be responsible for the Quality Management Plan.

B4.2.2.1 The Clinical Program Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

B4.2.2.2 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.

B4.2.2.3 The Clinical Program Director or designee shall report on quality management activities, at a minimum, quarterly.

B4.2.2.4 The Clinical Program Director shall report on the performance of the Quality Management Plan, at a minimum, annually.

Explanation:

There must be a designated person to oversee the QM Program. The ultimate responsibility for performance of the QM Plan and monitoring of all QM Program elements, internal or contracted, is that of the Clinical Program Director. This includes reviewing key performance data across clinical, collection, and processing.

The day-to-day tasks of the QM Program, however, may be delegated to an individual within the Clinical Program with sufficient expertise. The designated person must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff.

QM activities shall be reported, at a minimum, quarterly to review the performance of the QM Plan. 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 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 to effect 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.

In addition, an annual report on the overall performance of the QM Plan will be provided to the directorship. The annual report will provide a year-long view of the overall function of the QM Plan, its effect on and interactions with the Collection and Processing Facilities, and provide clues on areas for improvement. There should be documentation of measurement results, analysis, improvement activities, and follow-up measurement as indicated. Review by the Clinical Program Director is to be documented.

Evidence:

Quality program meeting records should provide evidence of the Clinical Program Director's (or designee's) involvement.

Example(s):

A designee can be a member of another department, such as an institutional Quality Assessment and Improvement Department, who devotes some time to the quality management activities of the Clinical Program, or he/she could be a member of the transplant team. The staff conducting the quality assessment audits may be the designated supervisor or another staff member, but it must not be the staff member who performed the work under review, unless performed in a retrospective fashion with enough delay between the time the work was performed and the time it is audited to mitigate bias. The same person may be responsible for QM of all components of the Clinical Program or each component may have a distinct individual responsible for QM, as long as there is a mechanism for disbursement of information to all participating entities.

Quarterly reports can be based around 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 procedures introduced or amended.

Clinical Program 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.

STANDARD:

B4.3 The Quality Management Plan shall include, or summarize and reference, personnel education, experience, and training requirements for each key position in the Clinical Program. Personnel requirements shall include at a minimum:

B4.3.1 A system to document the following for all medical and nursing staff:

B4.3.1.1 Initial qualifications and training.

B4.3.1.2 Competency for each critical function performed.

B4.3.1.3 Continued competency at least annually.

B4.3.1.4 Annual performance review.

B4.3.1.5 Provisions for continuing education.

B4.3.2 A policy and/or procedure for personnel training and competency assessment.

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 should include all individuals with primary patient care responsibilities and others responsible for critical elements of the Clinical Program. Documentation of training should include all cognitive (i.e., intellectual knowledge) and procedural skills dictated by these Standards as is relevant to each individual. These requirements are detailed in B3.

Initial qualifications generally include minimal educational requirements, for example, Registered Nurse (RN) or formal training or education that is preferred but not required. Initial training documentation must include all specific procedures that a specific 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.

Competency, as defined, 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 personnel member (see Part A for the definition of “critical”). They must also have a system to document annual performance reviews, during which a personnel member’s collective competencies and behaviors are evaluated to determine whether or not the individual is meeting job duties and to identify needed areas of improvement.

Procedures for personnel training and competency assessment must be defined by an SOP. The training plan SOP should also define the minimal qualifications of any designated trainers.

Evidence:

The inspector will review the records of one or more employees to determine whether all of the required elements are documented. Documentation of annual competency assessment and continuing education should be verified. The inspector should find evidence of ongoing documentation of suitable educational activities for staff related to their duties, such as quality-related meetings, webinars, and/or FACT or JACIE training sessions.

Example(s):

Initial competency and annual continued 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.

STANDARD:

B4.4 The Quality Management Plan shall include, or summarize and reference, policies and procedures for development, approval, implementation, review, revision, and archival of all critical processes, policies, and procedures.

Explanation:

Documents serve multiple purposes for the QM Program. Documents provide the structure needed for quality assurance through policies and procedures, 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 needs to identify the documents critical to the Clinical Program and describe how they are conceived, generated, implemented, distributed, reviewed, and stored.

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 policies, procedures, and forms to determine if an operational change is the cause.

Evidence:

The inspector will look to see how the Clinical Program controls modifications of documents and whether retrospective review is possible.

STANDARD:

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

Explanation:

The QM Plan must provide details on how the Clinical Program deals with document control. It must list which documents are considered critical and fall under the purview of the document control system. This list must include all critical documents that are currently in effect. For example, B5.1 requires the Clinical Program to have an SOP for administration of HPCs and other cellular therapy products, so this would be considered a critical document. It is recognized that the practice of medicine may require some flexibility and the Clinical Program may choose to have guidelines rather than SOPs for clinical care issues such as antibiotic therapy that would not be considered critical documents.

Standardization of SOPs should include a system for numbering and titling that allows for unambiguous identification of procedures. The numbering system should allow for identification of revisions of the procedure with the same title. The Clinical Program should be consistent in the design of reports, worksheets, and forms. Like SOPs, these are considered to be controlled documents and require a numbering and titling system. Every worksheet is not required to look alike, but the same worksheet format must be used to document a specific function each time the function is performed. Similarly, as processes for performing functions change over time, the worksheets must be controlled so that they comply with updated procedures.

Archiving is an important element of the QM Program. 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 policies, procedures, and forms to determine if an operational change is the cause.

Evidence:

The inspector will look to see how the Clinical Program controls modifications of documents, whether retrospective review is possible, and whether previous policies and procedures can be identified.

Example(s):

Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software to lock specific areas, the whole document, or to prevent printing or have printed copies indicated as copies. Control over the location and number of SOP manuals and the photocopying of documents is another method. The intention is to make sure that only the currently approved document is available for use.

STANDARD:

B4.5.1 Listing of all active critical documents that shall adhere to the document control system requirements.

B4.5.2 A procedure for preparation, approval, implementation, review, revision, and archival of all policies and procedures.

Explanation:

The Clinical Program must have an SOP outlining the method by which the Clinical Program creates, approves, implements, reviews, and updates its SOPs (the “SOP for SOPs”). Personnel are required to adhere to the approved SOPs in their manual. Although formal review is required only every two years, when conditions require that a procedure or practice be modified, SOP review and revision must occur in a timely fashion. Indeed, the change should not occur until the appropriate procedure and/or policy is created or revised. This process must include a description of who may make changes and how these changes are reviewed, approved, documented and implemented by authorized personnel.

Example(s):

It is recommended that there be a specific signoff sheet for every policy and procedure 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:

B4.5.2.1 Archived policies and procedures, 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:

Archiving is specifically mentioned in this standard and is an important element of the QM Program. 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 policies, procedures, and forms to determine if an operational change is the cause. Procedures must be archived minimally for 10 years and the

inclusive dates of use for each version documented. Institutional or governmental regulations may require a longer period of retention; if so, the longer period applies.

Example(s):

The archived system may contain items such as date removed, version number, reason for removal, and person who performed removal.

STANDARD:

B4.5.3 A standardized format for policies, procedures, worksheets, and forms.

B4.5.4 Assignment of numeric or alphanumeric identifier and title to each document and document version regulated within the system.

B4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the clinical care of the patient and/or donor.

B4.6.1 Agreements shall include the responsibility of the third-party facility performing any step in collection, processing, or testing to comply with applicable laws and regulations and these Standards.

B4.6.2 Agreements shall be dated, reviewed, and renewed on a regular basis.

Explanation:

This standard is more likely to apply to Collection or Processing Facilities. However, if the Clinical Program interacts with third parties for provision or testing of cellular therapy products, it must have policies and procedures for developing and completing written agreements or contracts. These agreements should clearly define roles and responsibilities for critical tasks. All such agreements should be dated, reviewed and renewed on a regular basis as defined by the program, and include provision for the maintenance of records following termination of the agreement. If there are any changes in the substance of a written agreement by either party, the agreements must be renewed and only need to be sent to legal departments if there are changes requiring legal review as determined by the Clinical Program.

This standard does not apply to entities within the Clinical Program's own program or institution. For example, a complete transplant program within a single institution is not required to have written agreements as described in B4.6 for the Collection and Processing Facilities within the institution.

Evidence:

Written agreements must match current practices, which would signify that the agreements have been kept current.

Example(s):

Written agreements should be reviewed every two years, similar to SOPs although greater or lesser time intervals may be appropriate under some conditions. The effective dates of an agreement could be specified within the agreement itself. It would be helpful to have a list of written agreements to check whether each one is reviewed and renewed appropriately. Examples of written agreements include service level agreements and agreements with the NMDP or other registries.

STANDARD:

B4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of outcome analysis and product efficacy, as appropriate.

B4.7.1 Review of outcome analysis and product efficacy shall include at a minimum:

B4.7.1.1 For HPC products intended for hematopoietic reconstitution, a process for documentation and review of time to engraftment following product administration.

B4.7.1.2 For HPC products, overall and treatment-related morbidity and mortality at 100 days and 1 year after transplantation.

B4.7.1.3 For other cellular therapy products, the criteria for product efficacy and/or the clinical outcome shall be determined and shall be reviewed at regular time intervals.

B4.7.2 The Clinical Program shall provide data on outcome analysis and product efficacy, including adverse events related to the patient and/or product, in a timely manner to entities involved in the collection, processing, and/or distribution of the cellular therapy product.

Explanation:

Outcome analysis involves the collection, evaluation, and analysis of therapeutic outcomes, including engraftment data. Ordinarily, engraftment is assessed by time to recovery of neutrophils and platelets in the peripheral blood. Each Clinical Program shall define acceptable engraftment criteria for its patients. If products are sent from one facility to another, there should be a mechanism in place for the sending facility to obtain engraftment data from the receiving facility.

The analysis should include the average (or median) and observed ranges of engraftment for the various products and transplant procedures performed by the Clinical Program. Overall and treatment-related morbidity and mortality at both 100 days and 1 year post transplant are also required. Product characteristics, especially CD34 cell dose, should also be considered in such analysis. 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.

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. 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.

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

Evidence:

The Clinical Program should be prepared to present the engraftment data, the methods used to evaluate consistency in engraftment, and the documentation of review of the analyses. 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 its mere collection.

Example(s):

Performance measures may include survival, treatment-related mortality, specific complication rates, and other clinical outcomes, as well as adherence to selected policies or procedures. 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 patients, which may be compared to existing data either internally or, for example, in the International Bone Marrow Transplant Registry, European Blood and Marrow Transplant Registry, or equivalent. Additional activities influencing positive program outcomes include policy and procedure review, staff training and education, competency evaluations, proficiency testing, data and records management, and the review of all errors, accident reports, adverse reactions, and complaints.

Additional data Clinical Programs should provide to cord blood banks include 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 infusion, 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.

STANDARD:

B4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a timetable for conducting, reviewing, and reporting audits of the Clinical Program's activities to verify compliance with elements of the Quality Management Program and operational policies and procedures.

Explanation:

There is an emphasis on audits in Part B of the FACT-JACIE Standards because of the recognition of the difficulty of validating clinical processes. Audits are conducted to evaluate whether the QM plan is operating effectively and to identify trends and recurring problems. Processes to be audited should include those for which lack of compliance would potentially result in an adverse event as identified and documented by the Clinical Program Director.

Required audits are listed in B4.8.3. The audit process should be performed throughout the year in accordance with the Clinical Program's QM Plan and timetable (i.e., schedule), including reporting of the results of this activity. 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.

Evidence:

The Clinical Program may wish to facilitate the inspection with review of evidence through a concise audit presentation. Compliance is verified by examination of objective evidence. The

inspector may review audit schedules and results, but it is not the intent to use a facility's audits to identify deficiencies during an inspection.

The inspector should expect to find a written plan, assessment and audit results, actions taken, and follow-up assessments and audits. Documentation of the results and review of these audits will be requested by the inspector. The inspector shall maintain the confidentiality of the information.

Example(s):

Examples of audits in the Clinical Program include:

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

STANDARD:

B4.8.1 Audits shall be conducted on a regular basis 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 audits does not need to be external to the Program, but he/she should not have performed the actions being audited.

Example(s):

Some larger Clinical Programs may have a designated position for an individual who performs such audits, but in smaller Clinical Programs it is possible to use a team member with other responsibilities who also has sufficient expertise. For example:

- If the Clinical Program audits donor eligibility determinations and that task is normally performed by outpatient clinic staff, the audit could be performed by an inpatient nurse.
- In a joint adult and pediatric Clinical Program, pediatric staff could audit functions performed by the adult team and vice versa.

STANDARD:

B4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, and implement corrective actions when necessary.

Explanation:

Audit results should be used to identify trends. 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, etc).

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:

B4.8.3 The Clinical Program shall periodically audit at a minimum:

B4.8.3.1 Accuracy of data contained in the Transplant Essential Data Forms of the CIBMTR or the Minimum Essential Data-A Forms of the EBMT.

B4.8.3.2 Donor screening and testing.

B4.8.3.3 Verification of chemotherapy drug and dose against the orders and the protocol.

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

B4.8.4 Collection and analysis of data related to the audit shall be reviewed, reported, and documented, at a minimum, on an annual basis.

B4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on the management of cellular therapy products with positive microbial culture results that address at a minimum:

B4.9.1 Notification of the recipient.

B4.9.2 Recipient follow-up and outcome analysis.

B4.9.3 Follow-up of the donor, if relevant.

B4.9.4 Reporting to regulatory agencies if appropriate.

B4.9.5 Criteria for the administration of cellular therapy products with positive microbial culture results.

Explanation:

The Clinical Program 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 infused. Policies and procedures are required in all three areas of a cellular therapy program – clinical, collection, and processing – to deal with elements for which that areas of the program is responsible, and this requirement may be satisfied with a single policy or procedure or there may be separate documents. This standard lists the topics that must be addressed in policies and procedures, but does not dictate a single policy or procedure that must be followed.

The Clinical Program should have policies that address how it will manage cellular therapy products with positive microbial culture results. These should cover investigation of the cause and how positive cultures are reported in accordance with applicable government regulations.

The Clinical Program should have policies that cover responsibility for reporting. In some cases a positive result will be detected prior to infusion. There should be a policy for disposition of such a product, criteria for release, and notification to recipient and labeling if it were released. In other cases a positive result may only become available after the product has been infused. The Clinical Program should have policies that cover timely notification of the transplant physician caring for the patient as well as the Collection and Processing Facilities.

The Clinical Program must have criteria for when a cellular therapy product with a positive microbial culture can be used and if and/or when another collection should be pursued. If a positive product is used, the Clinical Program should document the expectations for outcome. For example, if the contamination is likely to jeopardize engraftment, there should be guidelines for monitoring the patient and pursuing another collection when necessary.

Evidence:

The chart of a patient or donor where the cellular therapy product was contaminated provides evidence of how the Clinical Program managed the process. 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, there may be an over-arching policy for the management of cellular therapy products with positive cultures. If there is such a policy, the procedure(s) that is followed must be referenced.

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., regulations for 351 and 361 products should be followed.

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

STANDARD:

B4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, adverse events, biological product deviations, and complaints.

B4.10.1 Policies and procedures shall include methods for:

B4.10.1.1 Detection.

B4.10.1.2 Investigation.

B4.10.1.3 Evaluation.

B4.10.1.4 Documentation.

B4.10.1.5 Reporting.

B4.10.1.6 Corrective action.

B4.10.1.7 Follow-up for effectiveness of corrective action.

B4.10.2 Documentation of each adverse event that occurs in the Clinical Program shall be reviewed in a timely manner by the Clinical Program Director.

B4.10.3 A written description of an adverse event shall be made available to the recipient's and/or donor's physician and the Collection and Processing Facilities, if appropriate.

B4.10.4 When applicable, adverse events shall be reported to the appropriate regulatory agencies within the required timeframes.

B4.10.5 Deviations from the following key Standard Operating Procedures, B5.1.1, B5.1.5, and B5.1.6, shall be documented.

B4.10.5.1 Planned deviations shall be pre-approved by the Clinical Program Director or designee.

B4.10.5.2 Unplanned deviations and associated corrective actions shall be reviewed by the Clinical Program Director or designee.

B4.10.6 There shall be a defined process improvement plan that includes policies or procedures for the recognition and investigation of the cause of all issues that require corrective action.

B4.10.6.1 Follow-up activities shall be conducted to determine if the corrective actions were effective.

Explanation:

There must be a process to detect, evaluate, document, and report errors, accidents, adverse reactions, and complaints 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 reactions, and complaints in an SOP along with when and how each is reported. Programs can use the definitions stated by applicable regulatory agencies. See the definitions of each of these types of incidents in Part A Definitions.

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

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

If an adverse reaction occurs to any human cellular product for which there is a reasonable possibility that the response may have been caused by the product, reporting of the adverse reaction must be done to all facilities associated with collecting, processing, and/or infusing the product. This includes graft failure. Usually the Clinical Program is responsible for making the initial report; however, all involved facilities must participate in the investigation and evaluation of what caused the reaction.

A biological product deviation (see definition in A3) is an event that represents a deviation from applicable regulations or established specifications that relate to the prevention of communicable disease transmission or HCT/P 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 HCT/P contamination. Such products are used by Clinical Programs 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 infusion has occurred.

The QM Program should address how the Clinical Program manages biological product deviations in general. The most common biological product deviations encountered by Clinical Programs involve 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.

QM involves ongoing assessment of the stability, reproducibility, and effectiveness of critical processes in order to continually improve program efficiency and patient outcomes. QM assessment findings are compared to pre-established specifications. When pre-established specifications are not met, implementation of corrective or improvement strategies is undertaken and monitored with follow-up assessment to determine the effectiveness of the change.

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

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 to effect 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.

Errors, accidents, adverse events, biological product deviations, and complaints 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.

Evidence:

There must be documentation describing how adverse reactions are investigated and reported, files of adverse reactions, and evidence that adverse reactions are reviewed by the Clinical Program Director and reported to the collection facility, processing facility, and appropriate governmental agencies.

The inspector should expect to find a written plan, results and discussion of prospective indicators, actions taken, and follow-up assessments. Review by the Clinical Program Director is to be documented.

Example(s):

Communication of adverse reaction 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.

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.

The following are examples of adverse events that must be reported according to the FDA's definition of an adverse reaction:

- 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:

B4.10.7 There shall be a defined process to obtain feedback from patients and patient representatives.

Example(s):

Feedback from patients and patient 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 program is included.

STANDARD:

B4.11 The Quality Management Plan shall include, or summarize and reference, policies and 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:

One of the most important paper trails in the Clinical Program allows for tracking of information about the cellular therapy product at all steps between the donor and the patient. Documentation in the medical record should include the identity and content of the cellular therapy product as well as the eligibility status of the allogeneic donor. There should also be a means, direct or indirect, that will allow for outcome information to be related back to the other facilities involved in collection, processing, and distribution of the product.

STANDARD:

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

Explanation:

Clinical Programs 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 procedure is required for addressing emergencies and disasters (see B5.1), the program must have a plan for how to handle interruptions that do not rise to the disaster level. It is appreciated that it is difficult to anticipate every possible situation that may occur. Therefore, the Standards do not require the program to outline actions for specific events; rather, the program is required to describe actions to take when an interruption presents, including who needs to be contacted, how to prioritize cases, and key personnel to be involved in identifying alternative steps to continue functions.

As more and more of the Clinical Program's documents exist on an electronic platform, there is increasing risk of temporary or permanent document loss. The institutional Information Technology Department generally ensures that software in use is validated for its function when installed, and that there is a regular schedule of back up to allow for retrieval of information when necessary. Freestanding facilities, as well as Clinical Programs utilizing desktop storage, should have a plan to create a similar level of security. In either case, the Clinical 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.

Example(s):

Previous editions of these Standards specifically required a plan for when electronic record systems cease to function, and this is one example of a situation that would interrupt Clinical Programs. Other examples include drug shortages, power outages, equipment failures, etc.

STANDARD:

B4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical reagents, supplies, equipment, and facilities used for the marrow collection procedure.

Explanation:

The rationale for requiring Clinical Programs that perform marrow collections to include qualification in their QM Plans is because the clinician is responsible for the marrow collection procedure. Marrow Collection Facilities are only required to establish and maintain QM Plans if they operate independently of a Clinical Program that is accredited or has applied for accreditation.

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 harvest. The program may choose to perform qualification for additional materials used in other clinical procedures if it wishes to do so.

STANDARD:

B4.14 The Quality Management Plan shall include, or summarize and reference, policies and procedures for validation and/or verification of the marrow collection procedure.

B4.14.1 Changes to the marrow collection procedure shall be verified or validated to determine whether they create an adverse impact anywhere in the operation.

Explanation:

The rationale for requiring Clinical Programs that perform marrow collections to include validation in their QM Plans is because the clinician is responsible for the marrow collection procedure. Marrow Collection Facilities are only required to establish and maintain QM Plans if they operate independently of a Clinical Program that is accredited or has applied for accreditation.

Validation is confirmation by examination and provision of objective evidence that particular requirements can be consistently fulfilled. A process (or procedure) is validated by establishing, by objective evidence, that the process consistently produces a cellular therapy product meeting its predetermined specifications. 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. Qualification is another term commonly used in this setting and is most similar to verification in that it is the part of the process that confirms functional performance.

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.

Validations can be performed prospectively, concurrently or retrospectively. Validations should be performed on processes and the use of equipment, reagent, and supplies.

Validation studies should be performed according to a validation procedure, utilizing a consistent format for conducting the studies, analyzing the data, drawing conclusions, and documenting the implementation of changes resulting from the investigation. The design of the study should be adequate to determine if the process achieves the purpose for which it is intended. The validation or verification plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. There should be an explanation, follow-up, and/or repeat of any test that fails to meet the expected outcome. Reports of these activities should be complete, legible, and organized for review.

The validation studies must include documented review by the QM Supervisor and/or other appropriate individuals from Quality Management.

Plans of validation studies shall be reviewed and approved by the Clinical Program Director or designee prior to execution of the plan.

Evidence:

The validation study must be executed according to the SOP. The inspector will note poorly designed or inadequately performed validation studies during the review process.

Example(s):

It is acceptable, but not required, for the Clinical Program to utilize validation plans, formats, and personnel from the Apheresis or Marrow Collection Facility or Processing Facility to perform validation studies, or to contract these validation services to a contract vendor.

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

The JACIE *Quality Management Guide* (see www.jacie.org/document-centre) includes further definitions and examples of validation.

STANDARD:

B5 POLICIES AND PROCEDURES

B5.1 The Clinical Program shall establish and maintain policies and/or procedures addressing critical aspects of operations and management in addition to those required in B4. These documents shall include all elements required by these Standards and shall address at a minimum:

B5.1.1 Donor and recipient evaluation, selection, and treatment.

B5.1.2 Donor and recipient consent.

B5.1.3 Donor and recipient confidentiality.

B5.1.4 Infection prevention and control.

B5.1.5 Administration of the preparative regimen.

B5.1.6 Administration of HPC and other cellular therapy products, including exceptional release.

B5.1.7 Administration of blood products.

Explanation:

The policies and/or procedures required in B4 pertain to the QM Program, whereas those required in this section are operational in nature. It is recognized that the practice of medicine requires some flexibility and that the Clinical Program may choose to designate policies for some clinical care practices as practice guidelines rather than as SOPs to allow this.

Alternatively, these can be formalized into individual SOPs or can be incorporated into other related SOPs and still meet the intent of the Standards.

The Clinical Program must have guidelines on the selection of cell source. 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 plans for how a physician may choose the best source of cells for a recipient and how those cells should be sought (for example, which registries are available for searching).

Evidence:

A document(s) addressing the elements listed in B5.1.1 to B5.1.10 must be present. When multiple topics are covered by a single SOP, it will aid the inspection process if the Clinical Program prepares a crosswalk between the list of required procedures in B5.1 and the program's own SOP Manual.

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.

STANDARD:

B5.1.8 Facility management and monitoring.

Example(s):

Examples of issues to be addressed with policies and procedures on facility management and monitoring include:

- Periodic testing and documentation of water for microbial contamination, specifically Legionella, of HEPA filtration units for adequacy of filtration and number of air exchanges in the room and in the hallways,
- Testing of positive pressure and negative pressure rooms for adequacy,
- Monitoring of temperature on the units,
- Frequency of cleaning of patient rooms, hallways, and ductwork,
- Examination under sinks for leakage on a periodic basis, and
- Examination of the ice machine and kitchen for mold.

STANDARD:

B5.1.9 Disposal of medical and biohazard waste.

B5.1.10 Emergency and disaster plan, including the Clinical Program response.

Explanation:

The standard requires that each Clinical Program have written policies and procedures that address all important aspects of the Clinical Program. The Clinical Program is not required to have an SOP titled for every item on the list, as long as each item is addressed within an SOP (or other acceptable document (e.g., practice guideline). The items in the checklist include the minimum requirements. In those circumstances where program or institution standards vary from these minimal requirements, the Clinical Program will be held to the higher standards.

The policies and procedures must be detailed, unambiguous, and adequately define all operational aspects of the Clinical Program.

A written copy or electronic version (with provision of hardcopy as necessary) of the Clinical Program's policies and procedures 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 procedures manual must be identical to the source document and must not be used to alter, modify, extend, delete, or otherwise edit any SOP.

It is recognized that the practice of medicine requires some flexibility and that the Clinical Program may choose to designate policies for some clinical care practices as practice guidelines rather than as critical SOPs to allow this.

Evidence:

Policies and procedures must be immediately available to personnel and the inspector. The manual should be organized in such a manner for the inspector to ascertain that the policies and procedures are comprehensive and define all aspects of the Clinical Program.

There will not be time to read all policies and procedures during the on-site inspection. The inspector is provided a Table of Contents for the procedure manual with the pre-inspection material. The Table of Contents should be examined 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 activities that can only be verified in person at the inspection site. When necessary, specific SOPs may be requested and read in their entirety by the inspector.

Example(s):

The policies and procedures 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 procedures are inadequate to meet standards or where there are issues that are specific to the Clinical Program, the facility must develop its own policies and procedures. In situations where institutional policies and procedures are utilized, there must be a defined mechanism for review and approval of revisions within the Clinical Program initially and two years thereafter.

For the emergency and disaster plan, the Clinical Program may use institutional policies for the general responses; however, specific procedures relating to the chain of command and necessary procedures to address the safety of stored stem cell units is 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. In cases where institutional policies and procedures are inadequate to meet these Standards or where there are issues that are specific to the Clinical Program, the program must develop its own policies and procedures. 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 individual Clinical Programs (available at <http://asbmt.affiniscape.com/associations/11741/files/EmergencyPreparednessGuidelines.pdf>).

STANDARD:

B5.2 The Clinical Program shall maintain a detailed Standard Operating Procedures Manual.

B5.2.1 The Standard Operating Procedures Manual shall include a listing of all current Standard Operating Procedures.

Explanation:

The SOP Manual is a compilation of policies and procedures containing written detailed instructions required to perform procedures. The purpose of the SOP Manual is to maintain the policies and procedures in an organized fashion so that all current documents can be found. Many Clinical Programs have adopted an electronic method of compiling its policies and procedures, which is acceptable. Hard-copy, bound manuals also meet the intent of the standard.

The language in the SOPs should be clear and allow an appropriately trained individual to achieve the goals of the procedures.

Evidence:

The SOP Manual should be organized in such a manner for the inspector to ascertain that the policies and procedures are comprehensive and define all aspects of the Clinical Program.

The inspector must verify that all elements of an SOP are present as defined in the “SOP for SOPs,” and that there is consistency in format from one SOP to another. The inspector must also confirm that the SOPs adhere to the requirements for all controlled documents as specified in B4.5.

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 inspection for compliance.

Example(s):

A Clinical Program may choose to have one SOP Manual or divide policies and procedures 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. Each procedure 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 program desires.

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 procedure shall include:

B5.3.1 A clearly written description of the objectives.

B5.3.2 A description of equipment and supplies used.

B5.3.3 Acceptable end-points and the range of expected results, where applicable.

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 A reference section listing appropriate literature, if applicable.

B5.3.7 Documented approval of each procedure by the Clinical Program Director or designated physician prior to implementation and every two years thereafter.

B5.3.8 Documented approval of each procedural modification by the Clinical Program Director or designated physician prior to implementation.

B5.3.9 A current version of orders, worksheets, reports, labels, and forms, where applicable.

Explanation:

This standard defines the minimum elements required in each SOP. SOPs are also controlled documents and must comply with the requirements in B4.5. Although the FACT-JACIE Standards indicate that an individual designated by the Clinical Program Director may review procedures 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 procedure must be updated at that time and reviewed before the changes are implemented; unchanged procedures must be reviewed at a minimum every two years.

Copies of current versions of worksheets, reports, labels, and forms, where applicable, must become a part of each SOP, whether as paper copies or via electronic links. 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.

Evidence:

SOPs must follow the indicated format and be approved and reviewed by the Clinical Program Director or appropriate designee. 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 and presented to the inspector on request.

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 quality documents.

The CLSI (Clinical and Laboratory Standards Institute) standard format can be useful in preparing these SOPs. [*Laboratory Documents: Development and Control; Approved Guideline— Fifth Edition*. CLSI document GP2-A5 (ISBN 1-56238-600-X), Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006.] Order at the CLSI Website at www.clsi.org. The CLSI format is not required. Some Clinical Programs may utilize a format consistent with ISO 9000 in which all documents, policies, procedures, and work instructions exist in a specific hierarchy. In this case, the inspector must be certain to review all relevant documents. Guidelines for this format are available from the American National Standards Institute website (www.ansi.org), the Canadian Standards Association website (www.csa-international.org), or the International Organization for Standardization (www.iso.org). The Clinical Program may use the format of its choice, as long as all listed elements are present.

Expected endpoints and range of results should be included where applicable. For clinical SOPs this might include acceptable 100 day treatment related mortality or specific infection rates.

It may be prudent to attach one or more completed forms to illustrate possible real life scenarios. Although not required by the Standards, 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.

Review of procedures can be documented in several ways, including but not limited to:

- Signature and date on each individual procedure,
- Signature and date for each title and version of individual procedures listed on a master document, and
- Electronic approval via an authenticated electronic document management system.

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

STANDARD:

B5.4 Copies of Standard Operating Procedures 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 procedures 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 procedures into different SOP Manuals, programs may choose to only have necessary procedures to perform specified processes at a workstation. However, all procedures 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 to the staff at all times (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 All personnel in the facility shall follow the Standard Operating Procedures related to their positions.

B5.6 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.

Explanation:

Before a staff member is allowed to perform new and revised policies and procedures, 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 procedure, but must document an individual's review and/or training before that person uses the revised policy or procedure.

Example(s):

Sometimes a revision to a policy or procedure is minor, such as an update to a referenced regulation or grammatical corrections. In these cases, full training may not be necessary. Review by the staff members is sufficient. For example, an email describing the change with a return receipt may be acceptable.

STANDARD:

B5.7 There shall be a process to address age-specific issues in the Standard Operating Procedures, as appropriate.

Explanation:

Pediatric transplant patients and donors require specific policies and procedures that address issues of age and size of the donor. The Clinical Program may use the format of its choice, as long as all listed elements are present. A 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.

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 parent or legal guardian. Specific consent is required for the use of growth factors, if utilized, in a minor, allogeneic donor.

Depending on the age range of patients 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. Elderly patients (greater than 65 years of age) should have appropriate access to rehabilitation and social support.

Evidence:

These policies and procedures should be reviewed by the inspector; an indication of the presence of such procedures should be apparent from review of the Table of Contents of the Clinical Program's SOP Manuals.

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 parents or legal guardians 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 ALLOGENEIC AND AUTOLOGOUS DONOR SELECTION, EVALUATION, AND MANAGEMENT****Explanation:**

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, all the requirements in B6 apply, including standards to safeguard appropriate confidentiality, confirm histocompatibility matching, and help 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 these Standards even in the autologous setting because considerations for informed consent and suitability (i.e., safety) of the individual include issues above and beyond the individual’s status as a transplant patient. 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	
B6.3 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	B6.3.5.1
	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:

These standards cover the requirements for allogeneic and autologous donor identification, evaluation, selection, and management. 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. Each aspect of donor selection, evaluation, and management must be performed according to written SOPs and the results of the evaluation are to be documented. Donor acceptability should be documented within the medical record in the Program and the results of that determination must be provided in writing to the Collection and Processing Facilities.

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.

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:

Policies and SOPs for donor selection must be written, clearly defined, and unambiguous. The inspector may ask to verify compliance with these SOPs by reviewing a specific donor evaluation.

Example(s):

Examples of written criteria for allogeneic donors include:

- Infectious disease markers obtained within the appropriate time frame before collection for a donor.
- Criteria for an ineligible but acceptable donor (for example, 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.

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 time frame for the product. It is the responsibility of the Clinical Program to document that donor evaluation procedures are in place to protect the recipient from the risk of disease transmission from the donor.

STANDARD:

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

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 so as to protect the potential donor from undue pressure should he/she be the only suitable donor.

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.marlow.org/JOIN/index.html?src=home>) and the Anthony Nolan Trust (<http://www.anthonynolan.org/What-you-can-do/save-a-life.aspx>).

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:

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 and parent of the donor who is a minor 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 The donor shall have an opportunity to ask questions.

B6.2.3 The donor shall have the right to refuse to donate.

B6.2.3.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.

B6.2.4 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.

B6.2.4.1 Informed consent from the allogeneic donor should be obtained by a licensed health care professional other than the intended recipient's primary transplant physician.

B6.2.5 In the case of a minor donor, informed consent shall be obtained from the donor's parent or legal guardian in accordance with applicable laws and regulations and shall be documented.

Explanation:

The informed consent substance and process is determined by the law in the jurisdiction of the Clinical Program. The essential elements of informed consent are that donors are told, in terms they can reasonably be expected to understand, 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 these 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.

Informed consent from the donors for the collection of the cellular therapy product with variances to these Standards must be clearly documented. The procedure for obtaining consent from donors must comply with applicable laws and regulations. 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.

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 should be consented by a member of the team other than the primary physician of the intended recipient or a clinician who is not a member of the BMT team but is knowledgeable with the collection procedures.

Evidence:

If the informed consent process is performed verbally, the clinic note must detail discussion of the protocol, including the required elements.

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 for cellular therapy product donation, even outside of a research protocol, be provided to the donor.

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:

B6.2.6 The allogeneic donor shall give informed consent and authorization in advance to release the donor's health information to the transplant physician and/or the recipient as appropriate.

Explanation:

The purpose of this standard is to protect donor confidentiality regarding his or her health information. The consent procedure should inform the recipient that he/she has the right to review his/her HLA typing and that of the donor only. The recipient does not have the right to review all 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:

B6.2.7 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 procedures in place to protect the safety of donors during the process of cellular therapy product collection.

B6.3.1.1 Any abnormal finding shall be reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

Explanation:

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

Abnormal findings in a donor, including, but not limited to, the 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 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.

STANDARD:

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

Explanation:

It is highly recommended that an independent physician or health care professional be utilized for evaluating donor suitability to reduce potential bias of the recipient's physician(s) or health

care professional(s). This individual should not be the primary transplant physician of the patient 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 transplant 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.

As discussed in the guidance for B6.2, in the allogeneic setting, donors should be consented and evaluated by a licensed physician or other licensed health care professional other than the primary transplant physician or health care professional of the intended recipient, or a clinician who is not a member of the BMT team but is knowledgeable with the collection procedures.

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 transplant physician or licensed health care professional evaluates the donor for suitability.

Example(s):

A potential donor could be evaluated by another member of the BMT program or by a clinician who is not a member of the team, 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 Clinical Program.

STANDARD:

B6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

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

B6.3.2.1 Possible need for central venous access.

B6.3.2.2 Mobilization therapy for collection of HPC, Apheresis.

B6.3.2.3 Anesthesia for collection of HPC, Marrow.

Explanation:

Communicable testing or screening of autologous donors in connection with product collection is no longer required by these Standards. However, consistent with B1.3, testing required by local laws or regulations is required.

The Clinical Program is required to evaluate the donor for potential risks of the collection procedure and should address how to mitigate and manage those risks for the donor’s and the recipient’s (if applicable) well-being.

Donors need to be assessed for the risks of central venous catheters, including significant complications such as hematomas, pneumothorax, hemothorax, and bacterial infections.

Evidence:

The donor pre-collection medical records for pre-collection workup results will contain evidence of compliance.

Example(s):

For example, a donor should be assessed for the risk of mobilization therapy and if he/she has a risk of failure to mobilize. If this risk is present, the Clinical Program should also evaluate the donor for fitness to undergo a marrow collection if necessary to protect the recipient who has already begun the preparative regimen.

STANDARD:

B6.3.3 The donor should be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen.

B6.3.4 A pregnancy assessment shall be performed for all female donors with childbearing potential within seven (7) days preceding donor mobilization, cellular therapy product collection, or initiation of the recipient's preparative regimen, whichever occurs earliest.

Explanation:

Hemoglobinopathy assessment is recommended since administration of mobilization agents such as G-CSF may pose a risk to the donor as it was associated with morbidity and mortality in donors with Sickle cell disease (HbSS), HbSC, and with compound hemoglobinopathies such as sickle-beta-thalassemia.

Pregnancy assessment is required since the donation of HPC from marrow or peripheral blood and anesthesia may pose a risk to the fetus. A female donor should undergo pregnancy testing within 7 days prior to donor mobilization, collection, or initiation of the recipient's preparative regimen, whichever occurs earlier. The intent is to confirm she is not pregnant before the initiation of the mobilization agent or administration of anesthesia and before the recipient starts the conditioning regimen. There should be documentation in the medical record of these results prior to initiating the collection process. 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., hysterectomy).

The purpose of this standard is to prevent donor mobilization and recipient conditioning occurring before finding out that the donor is pregnant. There are some obvious situations in which a pregnancy assessment would not occur within seven days prior to recipient conditioning. For example, if an HPC product is collected from the donor and subsequently cryopreserved for infusion weeks later, the donor does not have to be reassessed for pregnancy. Also, if a recipient is on a 21-day conditioning regimen, a pregnancy assessment must be performed within seven days prior to beginning that regimen.

Evidence:

Donor records will provide information on results and timing of pregnancy assessments.

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.

Pregnancy assessment may include a written questionnaire, documented verbal questionnaire, or a pregnancy test. A pregnancy test is not required, but if a test is performed, serologic assays should be used.

STANDARD:

B6.3.5 Laboratory testing of all donors shall be performed by a laboratory accredited, registered, or licensed in accordance with applicable laws and regulations using one or more donor screening tests approved or cleared by the governmental authority.

B6.3.5.1 The Clinical Program shall inform the Collection Facility and Processing Facility of donor test results or if any testing was not performed.

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 for cell products and within seven days prior to or after collection of leukocyte-rich products as required by the FDA or as required by non-U.S. equivalent regulations.

Example(s):

Examples of relevant accreditation organizations include CLIA, CAP, ASHI, AABB, JCAHO, HCFA, EFI, CPA (Clinical Pathology Accreditation (UK)), Australasian College of Pathologists.

STANDARD:

B6.3.6 A donor advocate should 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 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 should be utilized to appropriately counsel the donors and protect them from unsafe or futile donation procedures. Allogeneic donors who are minors or who are mentally incapacitated should have their best interests represented by a parent or another authorized medical decision-maker for that donor. 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 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](#)," (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:

B6.3.7 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the transplant physician.

Explanation:

The decision to collect a cellular therapy product from a donor who does not meet Clinical Program safety criteria must be made by the transplant physician. However, a designee may actually document the decision. These Standards also require that if donors who are ineligible according to applicable laws and regulations, or do not meet the institutional medical criteria for donation, are chosen, the rationale for use of that donor and the informed consent of both the donor and recipient (if applicable) must be documented.

Evidence:

The rationale and informed consent for a specific donor who did not meet the institution's donor criteria can be requested to verify compliance.

Example(s):

For example, the best matched allogeneic donor for a patient lives in a country where there is a risk of Creutzfeldt-Jakob disease (CJD). The risks of transmitting CJD are considered to be much lower than performing the transplant using a less well-matched donor; therefore, the attending physician may approve collection from this donor.

STANDARD:

B6.3.8 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff.

B6.3.9 There shall be a policy for follow-up of donors that includes routine management and the management of collection-associated adverse events.

Explanation:

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.

Collection-associated adverse events should be addressed in accordance with the Clinical Program's QM Plan (see B4.10).

Evidence:

The inspector can review the method in use to convey to the Collection Facility Staff the health status of the donor and ask for evidence of donor follow-up.

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.

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:

B6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

B6.4.1 Allogeneic donors and allogeneic recipients shall be tested for ABO group and Rh type using two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

B6.4.2 A red cell antibody screen shall be performed on allogeneic recipients.

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 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 be established.

If HPC, Cord Blood products are selected for transplantation, two independent ABO tests can only be performed when additional CB samples are available for testing.

Evidence:

Records of ABO and Rh typing results and antibody screening in the clinical records provide documentation of compliance.

Example:

Allogeneic donors may be tested at the time they are initially evaluated for donor suitability and eligibility and a second test performed at the time of cellular therapy product collection.

Alternatively, both tests may be performed prior to collection. Tests can also 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:

B6.4.3 Allogeneic donors shall be evaluated for risk factors that might result in disease transmission from the cellular therapy product by medical history, physical examination, examination of relevant medical records, and laboratory testing.

B6.4.4 The medical history for allogeneic donors shall include at least the following:

B6.4.4.1 Vaccination history.

B6.4.4.2 Travel history.

B6.4.4.3 Blood transfusion history.

B6.4.4.4 Questions to identify persons at high risk for transmission of communicable disease as defined by the applicable governmental authority.

B6.4.4.5 Questions to identify persons at risk of transmitting inherited conditions.

B6.4.4.6 Questions to identify persons at risk of transmitting a hematological or immunological disease.

B6.4.4.7 Questions to identify a past history of malignant disease.

B6.4.4.8 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 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, such as national or international health agencies' websites or publications.

Evaluation of risk factors for disease transmission by medical history, physical examination, 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.

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 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, 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 should be a process 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.

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 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 (www.factwebsite.org).

Additional FDA requirements can be found at:

<http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/tissue/ucm073964.htm>.

STANDARD:

B6.4.5 Within thirty (30) days prior to collection, allogeneic HPC donors shall be tested for evidence of clinically relevant infection by the following communicable disease agents using tests as required by applicable laws and regulations:

Explanation:

The Standards require that infectious disease testing for allogeneic donors be performed within 30 days prior to collection. Some governmental authorities, such as the U.S. FDA, allow for testing up to seven days after collection; however, this is intended only for rare occasions. To be compliant with these Standards, cellular therapy 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 B4.10.

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. Personnel should treat all biological products as potentially hazardous, whether or not testing is performed.

Evidence:

One or more completed allogeneic donor history questionnaires can be audited for the required elements in this standard.

Example(s):

Some Clinical Programs adopt the donor history questionnaire used by an unrelated donor registry to use for related donors.

STANDARD:

B6.4.5.1 Human immunodeficiency virus, type 1.

B6.4.5.2 Human immunodeficiency virus, type 2.

B6.4.5.3 Hepatitis B virus.

B6.4.5.4 Hepatitis C virus.

B6.4.5.5 Treponema pallidum (syphilis).

B6.4.6 If required by applicable laws and regulations, allogeneic HPC donors shall also be tested within thirty (30) days prior to collection for evidence of clinically relevant infection by the following disease agents:

B6.4.6.1 Human T cell lymphotropic virus I.

B6.4.6.2 Human T cell lymphotropic virus II.

B6.4.6.3 West Nile Virus.

B6.4.6.4 Trypanosoma cruzi (Chagas' Disease).

B6.4.7 Additional tests shall be performed as required to assess the possibility of transmission of other infectious or non-infectious diseases.

B6.4.8 For viable, lymphocyte rich cells, including therapeutic cells and other cellular therapy products, each allogeneic donor shall be tested for communicable disease agents listed in B6.4.5 and B6.4.6 within seven (7) days prior to or after collection in the U.S. or 30 days prior to collection in Europe, or in accordance with applicable laws and regulations.

Explanation:

Standards included under B6.4 define the minimal evaluation for infectious agents. Assessment of allogeneic donors is required to minimize the risk of transmitting infection to the recipients and for proper labeling and storage of cellular therapy products. These Standards require testing to be within 30 days before collection; any testing performed on or after the day of collection must follow the Clinical Program's policies and procedures for biological product deviations (see B4.10). 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.

These Standards detail minimal laboratory testing. All laboratory tests must be performed by a laboratory that is accredited for the relevant test. Testing may be performed at any time prior to the initiation of the preparative regimen except for infectious disease tests, which must be done on a sample obtained within 30 days prior to the collection of the peripheral blood stem/progenitor cell product or within seven days prior to or after collection of other leukocyte-rich cellular products or as required by applicable regulations.

Autologous patients are not required by this edition of the Standards to be tested for infectious disease agents in conjunction with cellular therapy product collection. However, as part of the process to determine autologous donor suitability, some or all of the infectious disease agent testing may be desired. Products from autologous patients known to be positive for agents listed in B6.4.5 or B6.4.6 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 standard 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 transplant procedure. Donor eligibility determination must be recorded.

The rationale and informed consent from the donor and recipient should be documented for donors with positive results. The Clinical Program should document within the medical record that the abnormal results have been discussed with the donor, and where applicable, with the recipient prior to initiation of the preparative regimen. The potential risk to the recipient should be discussed and documented in the medical record.

West Nile Virus transmission, from infected donors, has been confirmed in recipients of blood components and solid organs. This transmission has resulted in subsequent infection and death of the recipient. 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):

The FDA intends to notify the transplant industry through published guidance from time to time of 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 the 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 HCT/P.
- 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.

Relevant communicable diseases not specifically listed in the regulation as of August 2007 but later published in FDA guidance are:

- Sepsis (screening available)
- Vaccinia (screening available)

STANDARD:

B6.4.9 Allogeneic donors shall be tested for CMV (unless previously documented to be positive).

Explanation:

Cytomegalovirus (CMV) is not a relevant communicable agent or disease. However allogeneic donors 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 procedure 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 agents listed in B6.4.3 or B6.4.4. However, there must be a procedure 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 infusion form or other information available at product release.

STANDARD:

B6.4.10 Allogeneic donors and recipients shall be tested at a minimum for HLA-A, B, DRB1 type by a laboratory accredited by ASHI, EFI, or

equivalent. HLA-C testing shall be performed for unrelated allogeneic donors and related allogeneic donors other than siblings.

B6.4.10.1 DNA high resolution molecular typing shall be used for DRB1 typing.

B6.4.10.2 Verification typing shall be performed using an independently collected sample prior to allogeneic donor selection.

Explanation:

The Standards require testing for HLA-A, B, DRB1 type at a minimum and HLA-C testing for unrelated donors and related donors other than siblings. These are minimum requirements, and a Clinical Program may choose to use high resolution typing for Class I and Class II genes other than DRB1 also.

Verification typing shall be performed on the recipient and selected donor prior to final donor selection/clearance to donate. Verification typing should be done according to ASHI or EFI standards. The same resolution is not required for the verification typing.

For cord blood transplants, some cord blood banks may not test for all HLA loci or at the level of resolution required by these Standards. In this situation, the Clinical Program must test for these requirements using a cord blood unit sample if one is available.

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):

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:

B6.4.11 Allogeneic donors shall be tested for red cell compatibility with the recipient where appropriate.

B6.4.12 Allogeneic donor eligibility, as defined by applicable laws and regulations, shall be determined by a physician after history, exam, medical record review, and testing, and shall be documented in the recipient's medical record before the recipient's preparative regimen is initiated and before the allogeneic donor begins mobilization regimen.

B6.4.13 The use of an ineligible allogeneic donor shall require documentation of the rationale for his/her selection and suitability by the transplant physician, urgent medical need documentation, and the documented informed consent of the donor and the recipient.

Explanation:

These Standards also require that 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. 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.

The regulation requires labeling with a biohazard legend for cellular therapy products collected from ineligible donors with the statement “Warning: Advise patient of communicable disease risk” or 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 I of these 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>.

STANDARD:

B6.4.14 Allogeneic donor eligibility and suitability shall be communicated in writing to the Collection and Processing Facilities.

Explanation:

These standards are meant to require the Clinical Program Director or designee to review all donor data prior to collection of HPC or TC from marrow or peripheral blood, and to document in the record that the donor is appropriate for the intended recipient and is suitable to undergo the collection procedure (“in writing” also includes electronic documentation). The health care professional responsible for obtaining the health history must determine whether the donor has confirmed that all the information provided is true to the best of his/her knowledge.

STANDARD:

B6.4.15 There shall be a policy covering the creation, regular review, and retention of allogeneic donor records.

B6.4.15.1 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 the exclusion criteria, where required).
 - Consent / authorization form(s), where applicable.
 - Clinical data, laboratory test results, and the results of other tests performed.
 - For HPC donors, the donor's suitability for the chosen recipient must be documented. For unrelated donations, when the organization responsible for procurement has limited access to recipient data, the transplanting organization must be provided with donor data relevant for confirming suitability.
- 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. For donors with abnormal test results, it is recommended that appropriate follow-up evaluations be completed by either the transplant physician or a referral be made to an appropriate alternative physician.

STANDARD:**B7 THERAPY ADMINISTRATION**

B7.1 The attending physician shall verify the availability and suitability of a donor or cellular therapy product prior to initiating the recipient's preparative regimen.

Explanation:

Due to the toxicity of chemotherapy, especially high-dose chemotherapy, Clinical Programs must verify that cryopreserved cellular therapy products or suitable donors are available prior to administering preparative regimens.

There are risks involved in the distribution of products, such as damage to the product container and significant warming events. Loss of a product intended for a recipient who has already undergone chemotherapy in preparation for a transplant adversely 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.

STANDARD:

B7.1.1 The clinical service shall notify the Processing Facility prior to requesting a cryopreserved cellular therapy product from a cord blood bank or registry.

Explanation:

Cellular therapy products obtained from registries and/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.

Keeping the Processing Facility informed is especially important when a Clinical Program plans to request a cryopreserved cellular therapy product, such as a cord blood unit. A Processing Facility should not be expected to perform processing, (e.g., thawing or thawing and washing) for the first time on a particular type of cellular therapy product using a product intended for administration. The Clinical Program should make a good faith effort to request practice units from the registry and/or third party manufacturer (such as a cord blood bank) to allow the Processing Facility to validate processing procedures and train personnel.

Example(s):

When a cellular therapy product is selected from a registry, it is recommended that a copy of the product's registry report be given to the Processing Facility.

STANDARD:

B7.2 There shall be a policy addressing safe administration of the preparative regimen.

B7.2.1 There shall be a policy addressing safe administration of chemotherapy.

Explanation:

Timing of chemotherapy administration is essential for some chemotherapy drugs. It is recommended that a tracking system regarding mixture, delivery, and completed administration be instituted for all regimens based upon these drugs.

If there are differences between inpatient and outpatient processes, these should be addressed in applicable SOPs.

Example(s):

Melphalan is an example of a chemotherapy drug that requires careful timing of administration and for which there should be a written policy for administration.

STANDARD:

B7.2.1.1 The treatment orders shall include the patient height and weight, specific dates, 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 weight should be measured and recorded within an appropriate timeframe of the chemotherapy administration. The Clinical Program should also have a policy regarding when it is more appropriate to use Body Mass Index (BMI) or ideal body weight on the treatment orders.

STANDARD:

B7.2.1.2 Preprinted orders or electronic equivalents shall be used for protocols and standardized regimens. These orders shall be verified and documented by an attending physician.

Explanation:

The transplant regimen is critical to the success of the cellular therapy. As such, these Standards include steps that are designed to promote accuracy and safe delivery. Having a protocol or standard of care-specific set of orders that are preprinted and readily available in written or electronic form is a step in this process, but even then it is critical that the chemotherapy doses are verified by an attending physician prior to transmitting the order to the pharmacy.

Autologous products or allogeneic products cryopreserved after collection should be assessed to ensure adequacy of dose.

For products to be given without cryopreservation, a responsible member of the clinical transplant team should review donor information to ensure HLA typing, consent, eligibility, and any other issues are correct and documented.

STANDARD:

B7.2.1.3 The pharmacist preparing the chemotherapy shall verify and document the doses against the protocol or standardized regimen listed on the orders.

B7.2.1.4 Prior to administration of chemotherapy, two (2) persons qualified to administer chemotherapy shall verify and document the drug and dose in the bag or pill against the orders and the protocol, and the identity of the patient to receive the chemotherapy.

Explanation:

Even if an electronic system is used, there must be a method to document the verification of the drug and dose in the bag or pill against the orders and the protocol, and the identity of the patient to receive the chemotherapy by two people at the bedside in addition to the pharmacist.

Evidence:

Copies of standard treatment or research protocols in areas of patient 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 nursing staff that they have verified the pharmacist's notation of the drug and dose against the orders and the protocol, as well as the patient's identity.

While touring patient care areas, the inspector may also ask the pharmacist about their normal practice and if he/she retains ultimate responsibility for verification against the protocol or standard regimen listed on the orders. He/she may also ask staff members about their training in administering chemotherapy. Nurses may be asked about the normal procedures for chemotherapy administration to confirm this.

STANDARD:

B7.2.2 There shall be a policy addressing safe administration of radiation therapy.

B7.2.2.1 There shall be a consultation with a radiation oncologist prior to initiation of therapy if radiation treatment is used in the preparative regimen.

B7.2.2.2 The patient's diagnosis, pre-existing co-morbid conditions, and proposed preparative regimen shall be made available to the consulting radiation oncologist in writing.

B7.2.2.3 A documented consultation by a radiation oncologist shall at a minimum address any prior radiation treatment the patient may have received and any other factors that may increase the toxicity of the radiation.

B7.2.2.4 The consultation shall also include radiation planning.

B7.2.2.5 Prior to administration of each dose of radiation therapy, the dose shall be verified and documented as per radiation therapy standards.

B7.2.2.6 A final report of the details of the radiation therapy administered shall be documented in the patient medical record.

Explanation:

"In writing" as used in these 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.

Evidence:

Upon reviewing patients' charts, the written information available to the radiation oncologist, the radiation oncology consult, and radiation report at the end of treatment can be reviewed. 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:

B7.3 There shall be a policy addressing safe administration of extracorporeal photopheresis (ECP).

B7.3.1 There shall be a consultation with the facility that performs ECP prior to initiation of therapy.

B7.3.2 Before ECP is undertaken, there shall be a written order from a physician specifying, at a minimum, the patient's diagnosis, proposed regimen, timing of the procedure, and any other factors that may affect the safe administration of ECP.

B7.3.3 A final report of the details of ECP administered, including an assessment of the response, shall be documented in the patient's medical record.

B7.3.4 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.

B7.3.5 Outcomes, including adverse events, related to the administration of ECP to patients within the Clinical Program shall be analyzed annually.

Explanation:

Extracorporeal photopheresis/photochemotherapy (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 a 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.

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 Clinical Program aside from the provision of ECP. If ECP is performed at a site not applying for accreditation, then the Clinical Program must be able to demonstrate a robust written agreement that meets the requirements in B7.3.

STANDARD:

B7.4 There shall be a policy addressing safe administration of cellular therapy products.

Explanation:

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 (marrow, peripheral blood, and cord blood), cell counts, etc. should be taken into consideration. Programs should work with their Processing Facilities to ensure appropriate processing and preparation of the product for administration.

Non-cryopreserved hematopoietic stem cell infusion must be administered within the time specified by Clinical Program policies, registry requirements, and applicable laws and regulations. Thawed HPC administration should be completed as soon as possible. It may be optimal to thaw individual bags to reduce the time thawed products sit before infusion.

Programs must identify appropriate timeframes between the end of the preparative regimen (radiation or chemotherapy) and administration of the cellular therapy product to ensure that the infused product is not affected by the preparative regimen. The program must verify that the preparative regimens were given at the scheduled time and delay administration of the cells if required. Clinical Programs are responsible for communicating with the Processing Facility regarding any delayed administration.

Example(s):

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 infusion. If plans change, updated information is provided to the laboratory prior to the planned day of infusion.

Monitoring of vital signs is generally part of routine hospital policy for blood products; however, given the potential for infusion reactions (hypoxia, bradycardia, hypertension, etc.), the Clinical Program should monitor vital signs at least one hour after infusion.

For cord blood units, the NMDP recommends the washing procedure in Appendix F of the 0501 protocol, available at www.bmtctn.net, and requires washing of red cell replete CB units due to unexpected adverse events.

STANDARD:

B7.4.1 There shall be a policy for determining the appropriate volume and the appropriate dose of red blood cells, cryoprotectants, and other additives.

B7.4.1.1 Cord blood units that have not been red cell reduced shall be diluted and/or washed.

B7.4.1.2 Cord blood units that have been red cell reduced should be diluted and/or washed.

B7.4.1.3 For double cord blood transplants, the first unit shall be administered safely prior to administration of the second unit.

Explanation:

There have been documented adverse events related to the administration of cord blood units containing red blood cells. Clinical Programs need to determine the appropriate volume, DMSO (and other additives), and red cell load for recipients. These Standards require dilution and/or washing of cellular therapy products that have not been red cell reduced, and this practice is also recommended for products that have been red cell reduced. In the case of double cord blood transplants, the Clinical Program must wait to administer the second unit until it is determined that the first unit was administered safely with no adverse events.

Example(s):

For double cord blood transplants, the second unit should not be thawed until administration of the first unit begins and the Clinical Program is reasonably certain that no adverse reactions are occurring.

STANDARD:

B7.4.2 Two (2) qualified persons shall verify the identity of the recipient and the product and the order for administration prior to the administration of the cellular therapy product.

B7.4.2.1 Verification of the identity and the order shall be documented.

B7.4.3 There shall be documentation in the patient medical record of the unit identifier and a copy of the distribution record.

B7.4.4 A circular of information for cellular therapy products shall be available to staff.

Explanation:

If the clinical transplant team performs the infusion, then the clinical staff should fill in the appropriate sections of the infusion form. A copy of the infusion form will be available in the Processing Facility.

General instructions on handling cellular therapy should be established by the Clinical Program and circulated.

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 infusion 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):

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:

B8 CLINICAL RESEARCH

B8.1 If required by applicable laws and regulations, Clinical Programs shall have formal review of investigational treatment protocols and patient consent forms by a process that is approved by the appropriate governmental authority.

B8.1.1 Those Clinical Programs utilizing applicable 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.

B8.2 Documentation for all research protocols performed by the Clinical Program shall be maintained in accordance with institutional policies and applicable laws and regulations, including all audits; documentation of approval by the Institutional Review Board, Ethics Committee, or equivalent; correspondence with regulatory agencies; and any adverse outcomes.

Explanation:

The purpose of these standards is to confirm that the Clinical Program is obtaining appropriate review of clinical research protocols.

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) application or non-U.S. equivalent, the regulatory binder for such studies need to be available.

Example(s):

A Clinical Program in a cancer center may use the cancer center'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.

In the U.S., the appropriate governmental authorities include the Office for Human Research Protections under the Department of Health and Human Services and/or the FDA. In Europe, the Research Ethics Committee (REC) is the equivalent of the IRB 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 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 experimental 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 or 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.

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, as appropriate, the disclosure of any issues that may represent a conflict of interest in clinical research.

Explanation:

The purpose of this standard is to require that the Clinical Program has a conflict of interest policy. Examples of conflicts include financial, academic, or any other incentive that would unduly influence the clinical investigator to enroll patients on clinical research protocols.

Evidence:

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.

Example(s):

The Clinical Program may follow its institution's policy on conflicts of interest or develop its own policy.

In the U.S., CFR Part 54 applies.

STANDARD:

B9 DATA MANAGEMENT

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:

Data management obviously is an important element of good clinical care as well as clinical investigation. It is not the purpose of this standard to assess patient outcome. The inspection will be made against the Standards only. There is no FACT-JACIE Standard for outcome, thus outcome will not influence the accreditation decision.

The Clinical Program must furnish evidence of its own periodic data audits to determine if data are accurate for evaluation of patient outcomes as specified in B4.7. The choice of data to be audited is a decision for the program but should include those listed in B4.7. Programs should also benchmark their outcomes against published data when possible. If a program's outcomes fall below the expected range, there should be evidence that it has analyzed outcomes and developed a corrective action plan.

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. 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 Clinical Program.

In the event that the Clinical Program does not submit data to these registries, it should provide reasonable explanations for not submitting the data. Standard B4.7, as written, does require that, as part of the complete and accurate patient records, data of the type found in the databases of the CIBMTR or EBMT must be collected. 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.

Evidence:

To be consistent in the inspection and accreditation process, FACT and JACIE developed standardized Inspection Report Forms to be utilized to determine if the Clinical Program is maintaining complete and accurate medical records. In order to include the type of data required by the CIBMTR and EBMT, the actual registry TED or MED-A Forms are included in the on-site inspection process to eliminate any ambiguity regarding the data elements to be collected. Although at least 10 consecutive allogeneic and 5 consecutive autologous transplant recipients will be reviewed, the minimum number of data points to verify is 30. However, the records and data points will be selected randomly to determine the quality of completeness and accuracy of the records reviewed, and additional data points may be reviewed as applicable.

The purpose of selecting the 30 random data points and five required elements from appropriately selected patient records is to verify that:

- The appropriate number of patients was actually transplanted during the prior year.
- Data are readily available.
- Data are accurate.

The Clinical Program Director or designee will choose the patient records to be reviewed, and list them on the inspection checklist. The 10 consecutive allogeneic and 5 consecutive autologous transplant recipients do not need to be from the exact same time frame. However, they should be selected so that enough follow-up data is available to complete the TED/Comprehensive Report/MED-A Forms. The Clinical Program Director or designee should also mark the location of primary records required to verify the data to facilitate the inspection process.

Data management will be evaluated during the on-site inspection by a review of representative patient records. The Clinical Program will choose the format of the record to provide to the inspection team. It could be the primary patient record if this is the main way in which the program keeps its records. Alternatively, a "shadow chart" or a series of flow sheets could be prepared. If shadow charts or flow sheets are utilized, the inspector must verify at least some data points from the primary source record. If the program utilizes electronic records, it is incumbent upon the inspected site to provide the information to the inspector, i.e., hard copies of the primary source data must be assembled for the inspector to review. Records will be assessed for completeness by documenting the presence in the records of, at least, the five key pieces of transplant-related data represented on the Inspection Report Form. However, any or all of the data points on the TED/Comprehensive Report/MED-A Forms may be audited. Records will be assessed for accuracy by comparing the TED/Comprehensive Report/MED-A Form to the source document. The data points will be verified against a primary pathology report, a laboratory record, or similar data from another source.

The inspector will examine the patient records and forms selected by the Clinical Program for key data elements. Only in rare circumstances should the inspector request a record for review from a patient not selected by the Clinical Program. Instead, the inspector should ask for documentation of periodic audits of patient outcomes, donor screening and testing, and recipient day 100 treatment related mortality. These documents can be requested from the previous 10 years or from the initiation of the audit process.

The audit of these data is limited by the ability of the inspector to review information in a timely manner. Not every data point or every patient record can reasonably be reviewed. The 30 data points constitute an arbitrary subset of information to be reviewed. If many errors are found among these 30 data points, it is likely that additional problems with record keeping exist at that facility. Likewise, if there are no errors in the data set inspected, it is likely that the records are basically complete and accurate.

As Clinical Programs may have had more thorough data audits from other entities such as CIBMTR, CTN, EBMT, or co-operative groups, the inspector should ask the program to provide results of all external audits since the last FACT or JACIE inspection. An excellent recent audit by the CIBMTR or EBMT would allow the inspector to spend less time inspecting charts. Conversely, identification of a particular problem in a previous audit would focus the inspector on checking that the problem was remedied in the FACT or JACIE charts.

Example(s):

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.

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. FACT requests certain comprehensive report forms for patients without post-TED forms to be submitted prior to the inspection to verify compliance with B9.1.

In the UK, the British Society of Blood and Marrow Transplantation (BSBMT) produces transplant outcome data for national benchmarking purposes. This type of information should be made available to inspectors where available.

STANDARD:

B10 RECORDS

B10.1 Clinical Program records related to quality control, personnel training and competency, facility maintenance, facility management, complaints, or other general facility issues shall be retained in accordance with applicable laws and regulations, or a defined program or institution policy, unless otherwise specified in these Standards.

B10.1.1 Employee records shall be maintained in a confidential manner and as required by applicable laws and regulations.

B10.2 Patient 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 is latest.

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 Clinical Program ceases operation.

Clinical Program records include quality control, personnel training and competency, facility maintenance, facility management, and other general facility records. There should be a defined policy for retention of these records. Some types of records need to be kept for longer than others; for example, records of quality control would normally be kept for at least three years while records of facility maintenance may only need to be kept for a short time.

If government laws or regulations require longer retention periods, records shall be maintained for the period required by such laws or regulations.

Quality control records include all of the items referred to in B4 (Quality Management) including the results of audits; errors, accidents and adverse reactions reports; 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 mid-level practitioners, all letters documenting initial training, all competencies for cognitive and procedural skills, 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; preventative 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 infusion, 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.

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 procedure 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 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 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

B10.4.1 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.

B10.4.2 The Clinical Program shall furnish to other facilities involved in the collection or processing of the cellular therapy product outcome data in so far as they concern the safety, purity, or potency of the cellular therapy product involved.

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. 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 Clinical 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 patient 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 procedure 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):

For example, 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 infused 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.

Minutes of Clinical Program team meetings and QM meetings provide one method of partial compliance with the standards as outlined in B10.

PART CM: MARROW COLLECTION FACILITY STANDARDS

- CM1 General
- CM2 Marrow Collection Facility
- CM3 Personnel
- CM4 Quality Management
- CM5 Policies and 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

STANDARD:

CM1 GENERAL

CM1.1 These Standards apply to the Marrow Collection Facility for collection activities of all cellular therapy products collected from living donors.

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:

Parts C and CM describe the collection of HPCs and TCs from living donors for autologous, syngeneic, and allogeneic transplantation and/or from living donors for research. Part C applies to peripheral blood as the source for those cells. Part CM applies to bone marrow as the source for those cells. Standards for the collection of HPCs from umbilical cord blood, primarily for the purpose of banking, are found in the NetCord-FACT Standards, which are specific to facilities providing this service.

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.

Evidence:

Processing Facilities must be inspected to ascertain that they meet the Standards in regards to their interactions with the Marrow Collection Facility. If a Processing Facility is already FACT or JACIE accredited to provide services to multiple facilities, this may satisfy the inspection requirement.

Example(s):

Documentation of evidence may include the Processing Facility's FACT or JACIE certificate of accreditation, agreements, vendor qualifications, etc.

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 of 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 these Standards does not guarantee compliance with all applicable laws and regulations. Governmental regulations must also be followed. It is the responsibility of the individual Marrow Collection Facility to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the Marrow Collection Facility may apply; for example, when a facility is sending or receiving cellular therapy products from outside of its immediate jurisdiction.

Although many of the existing standards may be applicable to cellular therapy products not obtained from living humans, a facility cannot be cited for not following standards in cases

where a deviation is recognized as limited to products not covered by the scope of these Standards.

Compliance with any of the numerous national and international regulations should indicate that the Marrow Collection Facility is safely run and that the personnel are familiar with the principles of Good Tissue Practice (GTPs). However, compliance with other organizations' standards or governmental regulations does not imply that FACT-JACIE Standards have been met. In all cases, governmental regulations supersede any organization's standards if the standards are inconsistent with a specific regulation. However, a FACT-JACIE standard that is more rigorous than a governmental regulation must be followed.

Marrow Collection Facilities that are not in compliance with applicable laws and regulations cannot be accredited by FACT or JACIE.

Evidence:

Current certifications will demonstrate what areas of facility function have been certified by other organizations and/or competent authorities.

While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with applicable laws and regulations.

Example(s):

Documentation of evidence may include facility registration or licensure. In the U.S., minimally manipulated HPC, Marrow is currently not regulated under either of these federal regulations. Both minimally manipulated HPC, Apheresis and TC 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). If these products are extensively manipulated, from an unrelated donor, 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 are regulated under the Public Health Service Act 351 and therefore are referred to as 351 products.

In the Member States of the Europe Union (EU), both HPC and TC fall under the European Directive (EUD) 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 EUD 2006/17/EC and EUD 2006/86/EC. The EUD 2001/83/EC regulates products that are classified as medicinal products (MP). This includes somatic cell therapy MPs and gene therapy MPs. The TMP-Regulation 1394/2007 entered in force on December 30, 2008 to include tissue engineered products as well. The consequence of classification as an MP is that a GMP environment is required for the production of these cells. Furthermore, each Member State in the EU may add on additional regulations to the EUDs, which have to be followed, but Member State-specific regulations will not be specified in the guidance to these Standards.

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, acceptable Occupational Safety and Health Administration (OSHA) inspections, or accreditation by the AABB, American Society for Histocompatibility and Immunogenetics/European Foundation for Immunogenetics (ASHI/EFI), the College of American Pathologists (CAP), or any other applicable accreditation body.

STANDARD:

CM1.3.1 The Marrow Collection Facility shall be licensed, registered, and/or accredited as required by the appropriate governmental authority for the activities performed.

Explanation:

Marrow Collection Facilities must be appropriately licensed, registered, and/or accredited as required by applicable laws and regulations. National 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 Marrow Collection Facility; however, the Marrow Collection Facility 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 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.

STANDARD:

CM1.4 For initial accreditation, the Marrow Collection Facility, including a Marrow Collection Facility Medical Director and at least one staff member, shall have been in place and performing cellular therapy product collections for at least twelve (12) months preceding accreditation.

Explanation:

The Marrow Collection Facility must have a Marrow Collection Facility Medical Director and at least one staff member who meet the personnel standards (see CM3) for at least twelve (12) months prior to initial accreditation.

Evidence:

Current employee files should document evidence as to length of employment and experience with marrow collections.

Example(s):

Documentation of evidence may include the Marrow Collection Facility Medical Director's CV and employee files.

STANDARD:

CM1.4.1 A minimum of one (1) marrow collection procedure shall have been performed in the twelve (12) months preceding accreditation.

CM1.5 The Marrow Collection Facility shall perform a minimum average of one (1) marrow collection procedure per year within the accreditation cycle.

Explanation:

These standards refer specifically to the number of marrow collection procedures, not the number of donors from whom HPC and/or TC were collected, and may include allogeneic and/or autologous donors. Bone marrow aspiration procedures do not count towards the number of bone marrow collection procedures.

This standard allows Marrow 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 data to demonstrate compliance to the Standards, and the facility's team must be experienced and mature (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 Marrow Collection Facility statistical reports can be used to ascertain whether the facility has complied with the required minimum number of marrow collection procedures.

Example(s):

Quality and/or statistical reports of the number of procedures performed within the accreditation cycle may serve as documentation of compliance.

FACT and JACIE will use the average number of collections per year over the accreditation cycle to determine if a Marrow Collection Facility meets the minimum collection volume. For example, if a program performs two marrow collection procedures in the first year, zero in the second, and then four 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.

STANDARD:

CM2 MARROW COLLECTION FACILITY

CM2.1 There shall be appropriate designated areas for collection of cellular therapy products, for the product collected, and for storage of supplies, reagents, and equipment.

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 Marrow 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 Marrow 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 Marrow 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 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 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 Marrow Collection Facility is to be relocated, qualification and validation must be performed to ensure the new space meets the Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT Policy 6.1.001 Inspection Process. This includes a description and floor plan of the new facility, QM documents, and relocation date. The policy can be found on the FACT website. 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 products prior to release or distribution.

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:

A demonstration by Marrow Collection Facility 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. To assess the adequacy of space and design, an investigation of what other activities are performed on the equipment and in the space assigned to the Marrow Collection Facility can be performed. This may help determine if such activities might interfere with the collection process.

Example:

If the space seems to be inadequate, this should be discussed by the inspectors and appropriate citations and/or suggestions should be included in the report to the FACT or JACIE Accreditation Committee as appropriate.

STANDARD:

CM2.1.3 There shall be a process for confidential donor examination and evaluation.

Explanation:

Marrow Collection Facilities perform an interim donor assessment prior to the marrow collection procedure. A separate space may not always be required; however, the Marrow Collection Facility must have a process for ensuring confidentiality.

Evidence:

A demonstration of how the interim assessment is performed should provide verification that there is an appropriate process for confidential donor examination and evaluation. The inspector can request a mock interview if there is a question of space size and/or location.

Example(s):

A Marrow Collection Facility may conduct interim donor assessments in the pre-operating room prior to the collection procedure. If there is only one patient in the room, it would be suitable for confidential examination and evaluation. If there are multiple patients in the room; however, this may not be suitable and the facility must take necessary actions to ensure the assessment is not heard nor seen by others in the room.

STANDARD:

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:

Marrow 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 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 When using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled where appropriate for temperature, humidity, ventilation, air quality, and surface contaminants.

CM2.4 Marrow Collection Facility parameters and environmental conditions shall be controlled to ensure the safety and comfort of patients, donors, and personnel.

Explanation:

The Marrow Collection Facility must identify the facility parameters that need to 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.

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 Marrow Collection Facility must assess if temperature, humidity, ventilation, air quality, and surface contaminants should be controlled. If any of these conditions could result in contamination or cross-contamination, the facility must control them. 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 Marrow Collection Facility should provide documentation of its reasoning. 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):

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 Marrow 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 be maintained in a clean, sanitary, and orderly manner.

CM2.6 There shall be adequate equipment and materials for the procedures performed.

Explanation:

The amount of relevant equipment in the Marrow Collection Facility should be appropriate for the type of collection performed, proportionate to the volume of work done, and should be conveniently located.

The Marrow Collection Facility should have policies and procedures 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 procedures that prevent subsequent delay in collections, such as an additional machine for back up or arrangements with other collection agencies or centers.

The Marrow Collection Facility should follow local policies regarding cleaning and sanitation. These will be usually hospital policies covering the operating room.

Evidence:

The inspector will evaluate whether there is adequate equipment available in the Marrow 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 autologous and/or CMV-appropriate and irradiated blood products.

CM2.8 There shall be access to an intensive care unit and/or emergency services.

Explanation:

These standards aim to protect donor and patient safety in the rare emergency situation. The Marrow Collection Facility 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.

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.

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 as to the minimal expectations of the Marrow Collection Facility should 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 Marrow Collection Facilities). If the only emergency response available to the Marrow Collection Facility is a community-based emergency service (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:

CM2.9 SAFETY REQUIREMENTS

CM2.9.1 The Marrow Collection Facility shall be operated in a manner designed to minimize the risks to the health and safety of employees, patients, donors, visitors, and volunteers.

CM2.9.2 The Marrow Collection Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease or to chemical, biological, or radiological hazards, where applicable.

Explanation:

This standard applies 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 Marrow Collection Facility's policies and procedures, 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 program must be covered in the program'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 reviewed this information.

Facilities should post warning signs wherever radioactive materials are in use. All persons who may be exposed to blood or body fluids must have appropriate personal protective equipment available to them. This includes those exposed to HPC 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 provided. Gloves must be provided whenever potential infectious exposure exists and when sterile procedures are required to protect the product and/or patient.

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 being handled and discarded (e.g., incinerator, waste field, etc.) and compare his/her observations with the written protocols. The inspector should examine selected employee files for compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures. Compliance with state and federal regulations should be addressed by the facility and verified by the inspector. The presence of unused equipment, excessive traffic from unauthorized personnel, and inappropriate storage of reagents and supplies may also contribute to an unsafe environment and should be noted by the inspector.

The inspector can also review training documentation for infection control and applicable laws and regulations and safety procedures.

The inspector should examine how cellular therapy products are being handled and discarded (e.g., incinerator, waste field, etc.) and compare his/her observations with the written protocols. The inspector should examine selected employee files for compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures. Compliance with state and federal regulations should be addressed by the Marrow Collection Facility and verified by the inspector. The presence of unused equipment, excessive traffic from unauthorized personnel, and inappropriate storage of reagents and supplies may also contribute to an unsafe environment and should be noted by the inspector.

The inspector can also review training documentation for infection control and OSHA regulations and safety procedures.

Example(s):

Safety training, including standard 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 via computer. 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. A Standard Operating Procedure (SOP) that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice.

The Marrow 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 safety manual is kept updated with institutional revisions. Such a document should focus on those hazards that are most likely to occur in the facility, such as needle sticks or handling patients with a known communicable disease.

STANDARD:

CM3 PERSONNEL

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 training in cell collection and/or 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 Marrow 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 should have been submitted with the Marrow Collection Facility's application, and should be available to the inspector prior to the on-site inspection. A copy of the current license may be requested if the inspector notes the one provided has expired.

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 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 Marrow 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 these Standards and applicable laws and regulations.

The Marrow Collection Facility Medical Director is directly responsible for the medical care of donors and patients during the collection procedure, including the pre-collection evaluation of the prospective donor at the time of donation, performance of the collection procedure, supervision of assistants for the procedure, care of any complications resulting from the collection procedure, and compliance with FACT-JACIE 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 Marrow 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) (for example, residents) and what their responsibilities are.

Example(s):

Documentation of evidence may include the Marrow Collection Facility Medical Director's signature for reviewing SOPs and the QM Plan. 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 one year experience in cellular therapy product collection procedures.

CM3.1.3.1 The Marrow Collection Facility Medical Director shall have performed or supervised at least ten (10) marrow collection procedures within his/her career.

Explanation:

The Marrow Collection Facility Medical Director must have at least one year of experience in the collection procedure for which accreditation is required. The Medical Director shall have performed or supervised at least 10 marrow collection procedures within his/her career.

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 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:

CM3.1.4 The Marrow Collection Facility Medical Director shall participate regularly in educational activities related to cellular therapy product collection and/or transplantation.

Explanation:

The Marrow Collection Facility Medical Director is expected to participate regularly (at least annually) in educational activities related to the field of cellular collection and/or transplantation. The purpose of this requirement is for key personnel to keep up with current advancements in the field. The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation should be in an activity that includes substantive information related to the field of cellular collection or transplantation.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not a Marrow Collection Facility Medical Director meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material. Recognized educational activities include those for which certified continuing education credits are offered, examples included in this Accreditation Manual, and internal training programs that are specific to HPC transplantation 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 accreditation cycle:

- Title of activity.
- Type of activity (for example, webinar, meeting, grand round, etc.).
- Topic of activity (for example, hematology, cell transplantation, etc.).
- 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 CME or CPD certificates and either formal or informal study, such as those that meet the requirements of applicable national or international continuing education programs. Presentation of CME or CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies (such as those representing apheresis, transfusion medicine, cell therapy and scientific research) includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. A Marrow Collection Facility Medical Director may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and publication of a manuscript related to HPC transplantation).

Grand Rounds may meet the standard as long as they are related to the field of cellular collection or transplantation and the individual is in attendance. If Grand Rounds are to be considered for meeting this standard, it is incumbent on the Marrow Collection Facility to clearly outline the subject, location, and date of these activities.

STANDARD:

CM3.2 QUALITY MANAGEMENT SUPERVISOR

CM3.2.1 There shall be a Marrow Collection Facility Quality Management Supervisor approved by the Marrow Collection Facility Medical Director to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Marrow Collection Facility.

CM3.2.2 The Marrow Collection Facility Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular therapy, cell collection, and/or quality management.

Explanation:

The Marrow Collection Facility must identify at least one person with responsibility for quality management (QM) supervision. This individual can be the Marrow Collection Facility Medical Director or a qualified designee. Delegation of a qualified designee should be documented, either in the QA plan or in a procedure related to it. The QM Supervisor may be shared with other portions of the cellular therapy program and/or the institution.

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 QM Supervisor should be an individual with at least 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 Collection Facility, or it could be a member of the Marrow Collection Facility who has additional responsibilities within the facility.

The QM Supervisor must have an active role in preparing, reviewing, approving, or implementing QM policy procedures and must ensure that the procedures are in compliance with these Standards and all applicable state and government laws and regulations before implementation. A key role of the QM supervisor is to develop systems for auditing Marrow Collection Facility activities to ensure compliance with the written SOPs and policies.

The Marrow Collection Facility QM Supervisor is required to participate regularly in educational activities related to cellular therapy and/or QM.

Evidence:

The inspector should look for documentation that a QM Supervisor is in place and performs or oversees the functions covered in the QM section of the Standards.

To assess the appropriateness of the amount and type of continuing education in which the Marrow Collection Facility Quality Management Supervisor participated, the following

information must be submitted for each of the completed continuing education activities within the accreditation cycle:

- Title of activity.
- Type of activity (for example, webinar, meeting, grand round, etc.).
- Topic of activity (for example, hematology, cell transplantation, etc.).
- 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 QM Supervisor’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 QM Supervisor may have an operational role in the Marrow Collection Facility 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 supervisory responsibilities as long as there is documentation of who is assigned the supervisor 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.

CM3.3.2 There shall be adequate numbers of trained collection personnel available in the Marrow Collection Facility.

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 FACT-JACIE Standards. There should be sufficient staff present to manage in the event of any donor emergency without neglecting ongoing collections.

The Marrow Collection Facility Medical Director should indicate personnel responsible for specific activities in the Marrow Collection Facility and confirm that they are appropriately trained to perform those activities, including confirmation that they have been trained in appropriate age-specific issues for the patient population they serve. Personnel should be retrained as necessary to remain up to date on current collection methods. Additional information related to training and competency is addressed in the QM section of the Standards and this Manual.

Mid-level practitioners may be trained and competent in bone marrow harvesting. In these cases, physicians still have ultimate responsibility for the procedure and well being of the patient.

Evidence:

The inspector, as well as the applicant, will make a judgment of the adequacy of the staff support. 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 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, including long-term employees.

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 in performing these procedures.

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 competency in dealing with pediatric patients as well as experience. The inspector may look for specific training applying to pediatrics.

Example(s):

Examples of training and experience documentation include experience such as the number of pediatric collections performed by staff.

STANDARD:

CM4 QUALITY MANAGEMENT

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 ensure 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.

STANDARD:**CM5 POLICIES AND PROCEDURES**

CM5.1 The Marrow Collection Facility shall establish and maintain policies and/or 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:

The policies and/or procedures required in CM4 pertain to the QM Program, whereas those required in this section are operational in nature. The standard requires that each Marrow Collection Facility have written policies and procedures 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 in CM5.1 include the minimum requirements; a facility may exceed these requirements, but not omit any of these.

Evidence:

When multiple topics are covered by a single SOP, it will aid the inspection process if the Marrow Collection Facility prepares a crosswalk between the list of required procedures in CM5.1 and the facility's own SOP Manual.

This should be verified by the inspector. The inspector should verify the procedure for development and review for all policies and procedures is being followed and that the policies and procedures are comprehensive and define all aspects of the Marrow Collection Facility function.

There will not be time for the inspector to read all policies and procedures during the on-site inspection. The inspector will have received a copy of the Table of Contents for the Procedure 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 procedures and other activities that can only be verified in person at the inspection site.

Example(s):

The policies and procedures can be generated within the Marrow 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 procedures are inadequate to meet standards or where there are issues that are specific to the Marrow Collection Facility, the Marrow Collection Facility must develop its own policies and procedures to supplement those of the institution. In situations where institutional policies and procedures are utilized, there must be a defined mechanism for initial approval and review and approval of revisions every two years by the Marrow Collection Facility.

STANDARD:

CM5.1.1 Donor and recipient confidentiality.

CM5.1.2 Donor consent.

CM5.1.3 Donor treatment.

CM5.1.4 Donor screening.

CM5.1.5 Management of donors, including pediatric donors if applicable.

CM5.1.6 Cellular therapy product collection.

CM5.1.7 Labeling (including associated forms and samples).

CM5.1.8 Cellular therapy product expiration dates.

CM5.1.9 Cellular therapy product storage.

CM5.1.10 Release and exceptional release.

CM5.1.11 Transportation and shipping to include methods and conditions to be used for distribution to external facilities.

CM5.1.12 Critical equipment, reagent, and supply management.

CM5.2 The Marrow Collection Facility shall comply with B5.2 if it operates independently of a Clinical Program.

Explanation:

The SOP Manual is a compilation of policies and procedures containing written detailed instructions required to perform procedures. The purpose of the SOP Manual is to maintain the policies and procedures in an organized fashion so that all current documents can be found. Many Marrow Collection Facilities have adopted an electronic method of compiling its policies and procedures, 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 B4.5.

Evidence:

Marrow 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 procedures are comprehensive and define all aspects of the facility. The inspector should verify the procedure for development and review for all policies and procedures is being followed.

The inspector must verify that all elements of an SOP are present as defined in the “SOP for SOPs,” and that there is consistency in format from one SOP to another. The inspector should also ensure that the SOPs adhere to the requirements for all controlled documents as specified in B4.5.

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):

A Marrow Collection Facility may choose to have one SOP Manual or divide policies and procedures 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 procedure 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 Marrow Collection Facility desires.

STANDARD:

CM5.3 Standard Operating Procedures required in CM5.1 shall be sufficiently detailed and unambiguous to allow qualified technical 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, where applicable.

CM5.3.4 A stepwise description of the procedure.

CM5.3.5 Reference to other Standard Operating Procedures or policies required to perform the procedure.

CM5.3.6 A reference section listing appropriate literature, if applicable.

CM5.3.7 Documented approval of each procedure by the Marrow Collection Facility Medical Director, as appropriate, prior to implementation and every two years thereafter.

CM5.3.8 Documented approval of each procedural modification by the Marrow Collection Facility Medical Director or designated physician prior to implementation.

CM5.3.9 A current version of orders, worksheets, reports, labels, and forms, where applicable.

Explanation:

This standard defines the minimum elements required in each SOP. Current versions of worksheets, reports, labels, and forms, where applicable, must become a part of 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.

The policies and procedures must be detailed, unambiguous, and adequately define all operational aspects of the Collection Facility. The minimum elements that must be included in a policy or procedure are listed in CM5.3. Specific requirements for how these procedures must be conducted are elsewhere in the Standards.

It is recognized that the practice of medicine requires some flexibility and the Marrow Collection Facility may choose to designate policies for some clinical care of collection practices as practice guidelines rather than critical document SOPs to allow this.

The Marrow 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. Determination of the mean \pm 1 or 2 standard deviations defines an acceptable range.

It is recognized that the reference to relevant policies within an SOP requires some flexibility. Some Marrow Collection Facilities like to include it in the body of the SOP at the end of the relevant step, whereas others may include 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. It is expected to see in the SOP describing how to write an SOP (the "SOP for SOPs") how this is to be done.

The Standards require documented review of each SOP by the Marrow Collection Facility Medical Director every two years. It is important that the documentation of review every two years 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 procedures may be revised throughout the year. Review of SOPs should include review of the applicable worksheets, forms, and attachments.

Evidence:

The inspector should review the SOP manual and documentation of Marrow Collection Facility Medical Director review.

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 prudent to attach one or more completed forms to illustrate possible real life scenarios. Although not required by these Standards, 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.

For example, procedures or policies for reporting adverse reactions to product infusion or procedures 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 Copies of Standard Operating Procedures 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 Marrow 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 procedure 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 ensure access to the manual at all times, even if the network is not available. For bone marrow harvests, the collection SOP must be readily available in the OR.

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 and the process to get access to them if needed.

Example(s):

The Marrow Collection Facility's SOP Manual is usually physically located in the management team member's office (for example, the Clinical Program QM supervisor for the marrow collection SOP). 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 get access to them in case they are needed and the staff should be familiar with that process of ready availability (such as how to access the electronic version).

STANDARD:

CM5.5 All personnel in the Marrow Collection Facility shall follow the Standard Operating Procedures related to their positions.

CM5.6 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.

Explanation:

Personnel are required to adhere to the approved SOPs in their SOP Manual. Although only review every two years is required, when conditions require that a procedure or practice be modified, SOP review and revision must occur in a timely fashion.

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 procedure until they have undergone a documented review and training.

Before a staff member is allowed to perform new and revised policies and procedures, 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 procedure, but must document an individual's review and/or training before that person uses the revised policy or procedure.

Evidence:

Inspectors should observe procedures or question personnel regarding how they would perform a procedure compared to the written SOP or policy.

Documentation that approved and implemented procedures or policies 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 procedure and associated revisions to document that each staff member required to review a policy or procedural revision has done so prior to performing a procedure. This could be done via an electronic system that identifies users and records their activity on the system. An effective date will be determined by the appropriate management (e.g. director, QM supervisor) after the necessary amount of staff has been trained. However, each staff member who performs the procedure must complete documentation of training and review of the policy and/or procedure. 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 procedure 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:

CM5.7 There shall be a process to address age-specific issues in the Standard Operating Procedures as appropriate.

Explanation:

Depending on the age range of patients treated in the cellular therapy program, Marrow Collection Facilities should be able to demonstrate the processes by which age specific issues are addressed. 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. Elderly patients (greater than 65 years of age) should have appropriate access to rehabilitation and social support.

Collection of HPC and/or TC from pediatric donors requires specific policies and procedures 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.

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 parent or legal guardian. Specific consent is required for the use of growth factor, if utilized, 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 parents or legal guardians in accordance with local regulations, assent should also be obtained in an age-appropriate manner.

Small donors undergoing marrow harvest 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 marrow 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 harvest require attention because of the size of the iliac crests. Surgical considerations of temperature control and pain management also require pediatric expertise.

Evidence:

Review of the relevant policies and procedures and their listing in the Table of Contents of the Marrow Collection Facility SOP Manual should provide evidence that age-specific procedures are in place. There should be evidence of training on age-specific issues.

Example(s):

It may be helpful to include a child life specialist, a social worker, or another qualified individual in the consent process to ensure that the minor donor has age appropriate understanding.

STANDARD:

CM6 ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

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. Marrow 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 Marrow 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.

Facilities should endeavor to ensure 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.

These standards cover the requirements for donor (autologous and allogeneic) identification, evaluation, and management. The Marrow 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 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 xenograft in the donor or in someone with whom the donor has had close contact, and 3) 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.

In addition, this standard requires that the Marrow 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.

These standards also require that if allogeneic donors selected for transplant 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 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.

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):

It is recommended that a separate medical record be maintained for allogeneic donors. For donors with abnormal test results, it is recommended that appropriate follow-up evaluations be completed by either the transplant physician or referral be made to an appropriate alternative physician.

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>.

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:

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 and parent of the donor who is a minor 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 The donor shall have an opportunity to ask questions.

CM6.2.3 The donor shall have the right to refuse to donate.

CM6.2.3.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.

CM6.2.4 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.

CM6.2.4.1 Informed consent from the allogeneic donor should be obtained by a licensed health care professional other than the intended recipient's primary transplant physician.

CM6.2.5 In the case of a minor donor, informed consent shall be obtained from the donor's parent or legal guardian in accordance with applicable laws and regulations and shall be documented.

Explanation:

These standards apply to informed consent for the specific collection procedure. Clinical Programs typically obtain informed consent to donate; Marrow 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 marrow 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 Marrow 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.

Informed consent from the donor and recipient regarding variances to these standards must be clearly documented. The procedure for obtaining consent from donors must comply with applicable laws and regulations. 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.

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 should be consented by a member of the team other than the primary physician of the intended recipient or a clinician who is not a member of the BMT team but is knowledgeable with the collection procedures.

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:

CM6.2.6 The allogeneic donor shall give informed consent and authorization in advance to release the donor's health information to the transplant physician and/or the recipient as appropriate.

CM6.2.7 Documentation of consent shall be available to the Marrow Collection Facility staff prior to the collection procedure.

Explanation:

The purpose of this standard is to protect donor confidentiality regarding his or her health information. The Marrow 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 include authorization to release relevant donor health information should be available.

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:

CM6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION

CM6.3.1 There shall be criteria and evaluation procedures in place to protect the safety of donors during the process of cellular therapy product collection.

Explanation:

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

STANDARD:

CM6.3.1.1 The Marrow Collection Facility shall ensure that any abnormal findings are reported to the donor with documentation in the donor record of recommendations made for follow-up care.

CM6.3.1.2 Allogeneic donor suitability should be evaluated by a licensed health care professional who is not the primary transplant physician or health care professional overseeing care of the recipient.

Explanation:

It is highly recommended that an independent physician or health care professional be utilized for evaluating donor suitability to reduce potential bias of the recipient's physician(s) or health care professional(s). This individual should not be the primary transplant physician of the patient 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 transplant 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.

Donor suitability refers to issues related to the general health of the donor and in general design to protect donor safety.

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 abnormalities be communicated and that recommendations be made to that donor for follow-up care. The Marrow Collection Facility must confirm these actions are documented in the donor's medical record.

Evidence:

Documentation in the medical record that prospective donors were informed of the abnormal findings including recommendations for work-up, treatment, and follow-up. 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 in many Marrow Collection Facilities. The inspector should request to review a chart of an ineligible donor to verify documentation of abnormal results.

Example(s):

The activities may be performed by the Clinical Program conducting tests in relation to donor selection; however, the Marrow Collection Facility is still responsible for ensuring the actions occurred.

A potential donor could be evaluated by another member of the BMT program or by a clinician who is not a member of the team, 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 Clinical Program.

STANDARD:

CM6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

CM6.3.2 The risks of donation shall be evaluated and documented, including:

CM6.3.2.1 Anesthesia for marrow collection.

Explanation:

Communicable disease testing or screening of autologous donors in connection with cellular therapy product collection is no longer required by these Standards. However, in agreement with C1.3, testing required by applicable laws and regulations is required.

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 Marrow Collection Facility is responsible for verifying that appropriate testing and evaluation has been performed.

STANDARD:

CM6.3.3 A pregnancy assessment shall be performed for all female donors with childbearing potential within seven (7) days preceding donor mobilization, cellular therapy product collection, or initiation of the recipient's preparative regimen, whichever occurs earliest.

Explanation:

Pregnancy assessment is required since the donation of HPC may pose a risk to the fetus. There should be documentation in the medical record of these results prior to initiating donor mobilization, collection, or the recipient's preparative regimen, whichever occurs earlier. 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., hysterectomy). The purpose of this standard is to prevent donor mobilization (although atypical prior to marrow collection), collection, and recipient conditioning occurring before finding out that the donor is pregnant.

Evidence:

The inspector may look for the process or documentation of pregnancy assessment of the donor.

Example(s):

Pregnancy assessment may include a test, but a test is not required. If a pregnancy test is performed, testing should be performed utilizing serologic assays.

If an HPC product is collected from the donor and subsequently cryopreserved for infusion weeks later, the donor does not have to be reassessed for pregnancy. Also, in a rare event in which the recipient is on a 21-day conditioning regimen, a pregnancy assessment must be performed within seven days prior to beginning that regimen.

STANDARD:

CM6.3.4 Laboratory testing of all donors shall be performed by a laboratory accredited, registered, or licensed in accordance with applicable laws and regulations using one or more donor screening tests approved or cleared by the governmental authority.

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 for HPCs and within seven days for leukocyte-rich products prior to or after the collection 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 laws and regulations.

Example(s):

Agreements with the supplier for IDM testing and qualification of this supplier are examples.

Examples of relevant accreditation organizations include CLIA, CAP, ASHI, AABB, and JCAHO.

STANDARD:

CM6.3.5 A donor advocate should 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 should 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](#)," (Walraven et al, 2010) provides recommendations for donor advocacy in the related transplant setting.

STANDARD:

CM6.3.6 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the transplant 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 transplant physician. However, a designee may actually document that decision. The Marrow 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 its documentation as well documentation of communication.

STANDARD:

CM6.3.7 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Collection Facility staff. Collection staff shall document review of these issues prior to collection.

CM6.3.8 There shall be a policy for follow-up of donors that includes routine management and the management of donation-associated adverse events.

Explanation:

There should be a policy that provides guidelines for the post-collection care of donors. All donors should be monitored closely following the collection procedure.

Example(s):

The guidelines for post-collection care of donors may include the following short- and long-term measures:

1. A defined minimum duration of admission for observation and clear guidelines for discharge.
2. 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.
3. Discharge instructions that include a phone number to call when they experience symptoms and signs of adverse event such as prolonged fatigue, high fever, wound infection, etc.
4. Follow-up appointments usually within 1 – 3 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 - 3 weeks after collection.

5. Long-term follow-up guidelines beyond a few weeks after collection may be defined by the Marrow 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:

CM6.3.9 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.

CM6.3.10 A red cell antibody screen shall be performed on allogeneic recipients.

Explanation:

The donor's and recipient's ABO group and Rh type must be determined and documented prior to collection. There needs to be documentation in the medical record of these results prior to initiating the collection process.

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 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 personnel. 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.

Discrepancies between the two samples must be resolved before proceeding with the processing or administration of the product. Additionally, it is inappropriate to label a product with historical results of testing. If there is to be a label on the cellular therapy product with this information, the data must be derived from a current sample.

SOPs to manage ABO and Rh mismatches between the donor and recipient should be established.

Evidence:

Records of ABO and Rh typing results and antibody screening in the collection chart records document compliance.

Example:

Allogeneic donors may be tested at the time they are initially evaluated for donor suitability and

eligibility and a second test performed at the time of cellular therapy product collection. Alternatively, both tests may be performed prior to collection. Tests can also 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:

CM7 CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

CM7.1 ISBT 128 CODING AND LABELING

CM7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate modifiers and attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

Explanation:

Another requirement for product identification is the use of a product's proper name, attributes, and modifiers according to the standard terminology for cellular therapy products. The terminology that is required is *ISBT 128*, 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 the 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, 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 work of CTCLAG can be found in the following publications:

- Ashford, P. et al: *Standards for the Terminology and Labeling of Cellular Therapy Products*. *Transfusion* 2007; 47:1319-27
- Ashford, P. et al: *ISBT 128 Implementation Plan for Cellular Therapy Products*. *Transfusion* 2007; 47:1312-8

The three main pieces of the standard terminology to unambiguously describe a product are class, modifiers, and attributes. Classes are broad descriptions of products (such as HPC, Apheresis), modifiers describe the next step in categorization (such as Cryopreserved), 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 optional characteristics 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 designed using common, well defined terms that are printed in eye-readable format on the label. 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 modifiers or attributes were included because of the 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.iccbbba.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.iccbbba.org, or contact ICCBBA directly for additional information and assistance.

To utilize *ISBT 128* to its full advantage in the unique identification of products worldwide and in the use of common language, facilities should register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each product's unique alphanumeric identifier. Facilities in or affiliated with hospitals may find that their Blood Bank has already registered and a unique facility code already exists. Stand-alone facilities can individually register and pay a nominal annual membership fee.

Evidence:

Inspectors will inspect the Marrow 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.iccbbba.org before conducting an inspection. It would be helpful to have the document available for reference during the inspection.

Example(s):

Labels that meet the appropriate information as defined by *ISBT 128* will also comply with these Standards.

STANDARD:

CM7.1.2 If the Marrow Collection Facility has not fully implemented ISBT 128 technology, an implementation plan for the usage of ISBT 128 coding and labeling shall be in place.

Explanation:

The use of *ISBT 128* for all cellular therapy products provides a uniform coding and labeling system worldwide. *ISBT 128* is an international standard for the transfer of information associated with human tissue transplantation, cellular therapy, and blood transfusion. It provides for a globally unique donation numbering system, internationally standardized product definitions, and standard data structures for bar coding and electronic data interchange.

In the previous version of the standards, *ISBT 128* terminology became mandatory. In a survey among cellular therapy facilities worldwide, it has been shown that although *ISBT 128* is being supported by FACT and JACIE accredited facilities, the transition towards full implementation of

ISBT 128 is not yet completed by most of them. In this version of the standards, an implementation plan of *ISBT 128* coding and labeling is mandatory, which has been supported by FACT and JACIE and numerous other organizations in the field for cellular therapy. On the ICCBBA website (<http://www.iccbba.org/subject-area/cellular-therapy>), the most recent versions of the terminology are published. Moreover, the advisory group published a paper to help centers to implement *ISBT 128*.

Evidence:

The cellular therapy coding and labeling advisory group of ICCBBA has published the detailed terminology and the use of these product codes need to be verified. An *ISBT 128* implementation plan describes the steps necessary to reach *ISBT 128* implementation within three years must be present.

Example(s):

ISBT 128 is the subject of a pending decision by the EU on a European Coding System. JACIE inspectors visiting facilities in EU member states should take into account the uncertainty this pending decision causes Marrow Collection Facilities in terms of regulations in this area.

STANDARD:

CM7.2 LABELING OPERATIONS

Explanation:

The labeling SOPs should indicate that there are procedures in place for each of the following:

- Ordering: initial orders and reorders
- Receipt and quarantine
- Verification of accuracy
- Proper storage
- Version control
- 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) and example labels will be available to the inspector prior to the inspection visit. 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. The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors.

The inspector should review all relevant labeling SOPs (see CM5.1.7). The inspector should review documentation of verification of accuracy.

Example(s):

A checklist where changes to a label's content are described is an example of how to document labeling changes. This could also include documentation of label content accuracy and destruction of obsolete labels. A master list of labels in use with version numbers helps with document control.

STANDARD:

CM7.2.1 Labeling operations shall be conducted in a manner adequate to prevent mislabeling or misidentification of cellular therapy products and product samples.

CM7.2.2 The labeling operation for pre-printed labels shall include, at a minimum, the following controls:

CM7.2.2.1 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 ensure 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 Marrow Collection Facility Medical Director or designee.

Inspection must include comparison with a label approved by the Marrow 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:

The inspector should review all relevant labeling SOPs (see CM5.1.7). 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 Marrow Collection Facility Medical Director or designee can be documented on this form. The same form can be used to document acceptability of the new label and inspection of content by two staff.

STANDARD:

CM7.2.2.2 Stocks of unused labels for 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 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 different types of products stored together with no separation.

Evidence:

The inspector should observe that the Marrow Collection Facility has 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:

CM7.2.2.3 Stocks of obsolete labels shall be destroyed.

CM7.2.3 Print-on-demand label systems shall be validated to ensure accuracy regarding identity, content, and conformity of labels to templates approved by the Marrow Collection Facility Medical Director or designee.

Explanation:

These requirements also apply to labels that are printed “on demand.” “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 ensure accuracy regarding identity, content, and conformity to the templates. Personnel do, however, need to confirm that the correct label was printed.

The Marrow Collection Facility should first develop a validation protocol for implementation of an “on-demand” computer software. Upon implementation of the process, the facility must ensure 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 Marrow Collection Facility or cellular therapy program. Any change in the label or label element that would change the interpretation of the label information 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):

For example, 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.

STANDARD:

CM7.2.4.1 Representative obsolete labels shall be archived for ten (10) years with inclusive dates of use or as defined by applicable laws and regulations.

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.

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:

CM7.2.5 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 Appendix I and II 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:

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.

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 or bacterial contamination that could affect the safety of the product, and clots that could reduce the efficacy of the product.

For Marrow 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 C11.6.

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.

For systems using computer-assisted label verification to ensure label accuracy (such as bar-code scanning), procedures and records should show how the automatic verification works.

Example(s):

Marrow Collection Facilities may use the manufacturer's label on the product container to affix the final product label. If additional information is needed, the information can be recorded on a tag and attach to the product with a tie if acceptable in accordance with Appendix I.

STANDARD:

CM7.2.7 The information entered on a container label shall be verified by at least two (2) staff members.

Explanation:

No fewer than two people must ensure 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 ensure 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.

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, and
- Indelible ink (blue or black is recommended).

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 and any additional label requirements required by local governmental laws or regulations must be present. The Marrow Collection Facility should review applicable governmental requirements for labeling and format labels accordingly.

Evidence:

The inspector should verify that the appropriate label is present.

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 as indicated in CM7.3.

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 also need to be demonstrated to be resistant to alcohol wipes and sprays if they are likely to be subjected to them at collection, in the processing lab 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. Marrow 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):

Marrow 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:

The inspector should verify that such labels have been validated. Labels must have been validated to ensure they remain legible under the conditions in which they are used. This is of particular importance for labels used on cryopreserved products.

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, such as during cryopreservation.

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 and to all records describing the handling and final disposition of the product.

CM7.3.1.1 The cellular therapy product and donor and product 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 Marrow Collection Facility must have a procedure 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 cell 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 procedure for labeling the product with 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:

CM7.3.2 Marrow Collection Facilities may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular therapy product.

CM7.3.2.1 Supplementary identifiers shall not obscure the original identifier.

CM7.3.2.2 The facility associated with each identifier shall be noted on the label.

Explanation:

The Marrow 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 labeling if this function is being performed by the Marrow Collection Facility; if not, the inspector will verify that the supplemental labeling procedure 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 Marrow Collection Facility may record the supplemental identifier to a tag and attach the product.

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 I.

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 I represents minimum requirements, and must be present as indicated at the various stages of product collection, processing, and distribution. Labeling requirements for the partial label and label at completion of collection are listed in Appendix I.

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 I, II, and IV.

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 Marrow 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 Marrow 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.

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.

Warning labels with or without a biohazard label 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 I). The exact statements that are required differ for autologous and allogeneic products.

With this edition of the Standards, communicable disease testing is not required for autologous donors 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 donor screening is not performed, these products must be labeled with the statement “Not Evaluated for Infectious Substances.” This statement must be also be 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 TC-T 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 these Standards may serve as the prescription. As of this writing, no cellular therapy product 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. Cryopreservation labels, 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 Marrow 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 I. The inspector should further verify that labels are available for every type of cellular therapy product collected, with suitable modifications. Examples of completed labels must not contain blank spaces. “N/A” or “none” or equivalent should be used as indicated.

Autologous product labels should be examined to ensure that “Not Evaluated for Infectious Substances” is present when the donor screening and testing does not contain all of the elements listed in B6.4 and B6.6. If the Marrow Collection Facility utilizes a partial label, the inspector must ensure 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.

Example(s):

Testing and screening within 30 days for TC-T cell products as well as HPC products 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 1.

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."

ISBT 128 provides an example of a label that may be used by facilities. This label is in Chapter Five, Product Labeling, in the document titled *ISBT 128 for Cellular Therapy: An Introduction*, available at www.iccbba.org/CTintrobooklet.pdf.

The inspector will review the labeling of products from NMDP-facilitated transplants to ensure this statement is used on the product or in the accompanying record (the infusion form or distribution record) issued with the product.

The recommended storage temperature may include ranges, e.g., 2-8° C, 20-26° C, etc.

STANDARD:

CM7.5 LABELING AT COMPLETION OF COLLECTION

CM7.5.1 Labeling at the end of collection shall occur before the cellular therapy product bag is removed from the proximity of the donor.

Explanation:

It is important for the collection staff to label the products before removing them from the proximity of the donor to prevent mix-up. Collection product labels, tie tags, sample tubes and associated forms are labeled completely and legibly before removing them from the proximity of the donor.

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 I.

Example(s):

Proximity of the donor may be described as at bedside where the product collection occurs. Labeling of product beside the donor will prevent mix-up when in a collection area there is more than one donor being collected from.

STANDARD:

CM7.6 ACCOMPANYING DOCUMENTATION AT THE END OF COLLECTION

CM7.6.1 Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix III at the time of distribution.

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 C7.6 and C7.7. 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 infusion, the product infusion form (see D8.2 and B7.3.2) can be used for this purpose. For products that are distributed to another facility, this information must be included. If the Marrow 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 Marrow 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).

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>.

Evidence:

The inspector should review the systems in place that ensure the Marrow Collection Facility has access to source data for the information that must be provided at distribution.

Example(s):

It is permissible to have hard copies of each item physically accompany the product, and in some cases, that may be appropriate, as when a product leaves the Marrow Collection Facility and is transported to another institution for processing, storage, and/or infusion.

STANDARD:

CM7.7 ADDITIONAL DOCUMENTATION AT OR IMMEDIATELY AFTER DISTRIBUTION

CM7.7.1 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 Marrow 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 Marrow Collection Facility's procedures.

Example(s):

Related documentation that allogeneic donor eligibility was completed during or after the use of the product is in the patient's collection records. Urgent medical needs documentation to release product should also be present.

STANDARD:

CM8 PROCESS CONTROLS

CM8.1 Collection of cellular therapy products shall be performed according to written collection 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.
- Storage times and conditions (including temperature).
- Procedures for distribution of the cells.
- Methods for detection of clerical errors.
- Procedures for quality testing.

Evidence:

The inspector should observe a portion of a collection procedure if possible to determine whether or not the personnel follow the SOP and measure that performance against the written procedure. If there is no collection procedure scheduled for the day of the on-site inspection, the inspector should ask the Marrow 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, the inspector 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 procedures.

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 Marrow 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 procedure.

STANDARD:

CM8.2 There shall be a process for inventory control that encompasses equipment, reagents, supplies, and labels.

CM8.2.1 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.

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 or 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 CM5.1.12). 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.

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 cellular therapy 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 ensure 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.

The inspector should review the inventory control process and documentation of supply and reagent examinations at receipt to verify that the Marrow Collection Facility takes steps to ensure there is no obvious evidence of damage (for example, leakage, damaged box, etc.).

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, for example, the use of various tissue culture media. However, Marrow Collection Facilities are expected to keep up to date on current collection techniques.

Evidence:

The inspector should request certificate of analysis (COA) of the reagents that are approved for human use or of pharmaceutical grade. Package inserts of the reagents and supplies have the information regarding their intended use.

Example(s):

A COA may be obtained from the manufacturer of the reagents and supplies used in the collection procedure. Upon receipt of reagents and supplies, personnel may review package inserts to ensure that there are no changes of the intended use and retain the most current package insert for reference.

STANDARD:

CM8.3 Equipment for the marrow collection procedure shall conform to applicable laws and regulations, where applicable.

Example(s):

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

CM8.4.1 There shall be peripheral blood count criteria to proceed with collection.

Explanation:

Day-to-day management of the donor is the responsibility of the Marrow Collection Facility. It is incumbent on the collection team to ensure 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 procedures 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.

The collection team must document this evaluation as part of the permanent record of the donor. The evaluation must be performed by a member of the collection team competent in assessing the health status of the donor. Competency should be defined in the facility procedure manual. The Marrow Collection Facility should have a system in place to confirm donor identity so that all samples, labels, and records are appropriately and consistently completed.

A unique donor file should be generated in which all pertinent documentation related to the collection may be assembled, including such items as physician orders, consents, worksheets, logs, pre-collection laboratory data, and cellular therapy product distribution records. This file may also contain the product processing and disposition records.

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:

CM8.5 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 initially evaluates the donor and makes the decision to proceed is not always the same one who actually collects the cell. The written order is required as a mechanism to ensure 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),
- Date and time of collection,
- Date and time the cells are needed by the recipient,
- Cell type (HPC or TC),
- Source of cells (marrow or peripheral blood),
- Cell dose required,
- Appropriate authorized signatures,
- Blood group determination,
- Recipient weight,
- Donor weight, and
- Pre- and post-collection laboratory result guidelines.

Pre- and post-collection laboratory result guidelines may include relevant hematologic and biochemical analyses. SOPs should outline how the Marrow Collection Facility will handle patients whose hematology lab values and/or electrolytes are outside of acceptable ranges.

Evidence:

The inspector should confirm that the written order meets the criteria and, if there are any deviations, that they are approved.

Example(s):

Written orders will clarify the desired end result of a collection procedure. The information on the written order will help achieve the HPC or TC product cell dose needed for the recipient.

STANDARD:

CM8.6 General or regional anesthesia, if required, shall be performed or supervised by a licensed, specialist-certified anesthesiologist.

CM8.7 Administration of mobilization agents shall be under the supervision of a licensed health care professional experienced in their administration and management of complications in persons receiving these agents.

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 Marrow Collection Facility should have a mechanism in place to ensure 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:

CM8.8 The Marrow Collection Facility shall utilize a process for assessing the quality of cellular therapy products to ensure their 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 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 CM5.1.6).

The Marrow Collection Facility Medical Director is responsible for defining release criteria for cellular therapy products distributed by the Marrow 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 infusion. This information must be clearly outlined in an SOP (see CM5.1.10). 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:

CM8.8.1 Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to ensure products meet predetermined release specifications.

CM8.8.2 Methods for collection shall employ procedures validated to result in acceptable cell viability 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 Marrow Collection Facility may request this information and use it for a retrospective validation of the method of collection.

STANDARD:

CM8.9 Collection methods shall employ aseptic technique to ensure that cellular therapy products do not become contaminated during collection.

Explanation:

This standard requires the use of aseptic technique as defined in A3 of these 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.

The transfer bags should be closed or sealed securely at the collection site, labeled appropriately, and placed in a secondary container such as a zip-type resealable bag prior to transfer to a processing facility, regardless of the distance of transfer. This is to prevent the loss of a portion of the collection, to minimize the potential of post-collection contamination of the cellular therapy product, and to prevent potential spillage of biohazard material in areas where it may pose a risk to employees, visitors, volunteers, or patients.

Evidence:

Aseptic technique during peripheral blood access and venous catheter access can be verified by reviewing the sterility of the cellular therapy products collected.

STANDARD:

CM8.10 Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures.

Explanation:

See guidance for CM5.7.

Evidence:

The inspector should verify that the donor collection record reflects the appropriate parameters for pediatric donors as described in the Marrow Collection Facility's SOP.

Example(s):

Collection SOPs may reference the method applicable for pediatric donors, such as the use of blood prime.

STANDARD:

CM8.11 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 HPC or TC 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 saved 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:

CM8.12 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 in-line 500 and 200 micron filters are certified by the manufacturer and this certification should be retained for qualification of the supply.

STANDARD:

CM8.13 Records shall be made concurrently with each step of collection of each cellular therapy product in such a way that all steps may be accurately traced.

Explanation:

Records must be used during cellular therapy product collection and must be completed in real time as the procedure is performed. For marrow 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.

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):

Marrow Collection Facilities 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 collection record. Use of electronic records should have the concurrent documentation elements.

Concurrent record keeping is required in 21 CFR 1271.270(a).

STANDARD:**CM9 CELLULAR THERAPY PRODUCT STORAGE**

CM9.1 Marrow Collection Facilities shall establish policies for the duration and conditions of storage prior to distribution to a Processing Facility or Clinical Program.

Explanation:

The Marrow Collection Facility shall establish a process to ensure that cellular therapy products are stored in a manner that maintains their integrity and potency and that ensures that products are not released prematurely before all release criteria have been met.

The Marrow 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 infusion constitutes storage. Particular attention shall be paid to the security of the facility and control of temperature and humidity when cellular therapy products are stored in the facility for extended periods, such as overnight. 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 Marrow 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 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 ensure adequate 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.

Labeling requirements for storage temperature are defined in Appendix I.

Evidence:

The inspector should review the Marrow Collection Facility's established storage criteria for all relevant products, and inspect the storage conditions and space to ensure adequacy of separation to prevent contamination and mix-ups.

Example(s):

EU Directive 2006/86/EC requires that the expiry date shall be part of the product information for all tissues and cells.

STANDARD:**CM10 CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING**

CM10.1 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 facility personnel.

CM10.1.1 The primary cellular therapy product container shall be placed in a secondary container that is sealed to prevent leakage.

CM10.1.2 The cellular therapy product shall be transported and/or shipped to the Processing Facility at a temperature defined in the transportation and shipping procedure.

CM10.1.3 Cellular therapy products that are transported and/or shipped from the collection site to any non-contiguous 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.

CM10.1.4 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported by a qualified courier.

CM10.2 The cellular therapy product shall be transported and/or shipped with required accompanying records as defined in the transportation and shipping procedure and in compliance with CM7.6.

CM10.3 There shall be a record of the date and time of cellular therapy product distribution.

Explanation:

Cellular therapy products may be transported and/or shipped from the Marrow 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 Marrow Collection Facility, Processing Facility, and Clinical Program regarding transport and/or shipping conditions and the responsibilities of each facility. 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 transport.

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. Human tissue, regardless of infectious disease testing, shall be considered potentially infectious. Procedures will vary depending on the distance, whether or not the courier and product leave a building, and the nature of the outside container.

These procedures shall ensure 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 that are not adjacent to each other shall always use 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 Marrow Collection Facility and the Processing Facility varies widely. For situations where transport from the Marrow 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 and/or shipping of cellular therapy products that are shipped from the Marrow 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 ensure 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.

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. Outer containers containing cellular therapy products should not be exposed for prolonged periods to extreme heat or cold and should not be exposed to gamma irradiation or X-Ray devices designed to detect metal objects.

Accompanying documentation shall include all documentation of allogeneic donor eligibility as defined in CM7.6. It is not necessary that the records in their entirety accompany a cellular therapy product from the Marrow 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 I and II.

Evidence:

The inspector shall determine if the transport and shipping procedures in use within the Marrow Collection Facility are adequate for the conditions.

Example(s):

Cellular therapy products transported from a Marrow Collection Facility to a Processing Facility located in an adjacent building must be doubled bagged at a minimum.

STANDARD:*CM11 RECORDS*

CM11.1 The Marrow Collection Facility shall comply with B10 if it operates independently of a Clinical Program.

CM12 DIRECT DISTRIBUTION TO CLINICAL PROGRAM

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, D8, D10, D12, and the Appendices apply.

Explanation:

If the Marrow 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, D8, D10 and D12. Rarely, products cannot be distributed as intended or cannot be administered after distribution to the Clinical Program and might be returned to the facility. The facility must have a plan regarding where to store these products in a controlled environment for intermediate and long-term storage in order to conserve the cells for later use.

See the guidance in the referenced sections for additional details.

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PART C: APHERESIS COLLECTION FACILITY STANDARDS

- C1 General
- C2 Apheresis Collection Facility
- C3 Personnel
- C4 Quality Management
- C5 Policies and 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

C1.1 These Standards apply to the Apheresis Collection Facility for collection activities of all cellular therapy products collected from living donors.

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:

Part C describes the collection of HPCs and TCs from living autologous, syngeneic, and allogeneic donors for transplantation and for research. Part C applies to peripheral blood as the source for those cells. Part CM applies to the collection of cells from marrow. Standards for the collection of HPCs from umbilical cord blood, primarily for the purpose of banking, are found in the NetCord-FACT Standards, which are specific to facilities providing this service.

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.

Evidence:

Processing Facilities must be inspected to ascertain that they meet the Standards in regards to their interactions with the Apheresis Collection Facility. If a Processing Facility is already FACT or JACIE accredited to provide services to multiple facilities, this may satisfy the inspection requirement.

Example(s):

Documentation of evidence may include the Processing Facility's FACT or JACIE certificate of accreditation, agreements, vendor qualifications, etc.

STANDARD:

C1.3 The Apheresis Collection Facility shall abide by all applicable laws and regulations.

Explanation:

FACT and JACIE are inspection and accreditation programs sponsored by the American and European Societies of 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 these Standards does not guarantee compliance with all applicable laws and regulations. Governmental regulations must also be followed. It is the responsibility of the individual Apheresis Collection Facility to determine which laws and regulations are applicable. In some cases, regulations of governmental authorities outside of the jurisdiction of the Apheresis Collection Facility may apply; for example, when a facility is sending or receiving cellular therapy products from outside of its immediate jurisdiction.

Although many of the existing standards may be applicable to cellular therapy products not obtained from living humans, a facility cannot be cited for not following standards in cases

where a deviation is recognized as limited to products not covered by the scope of these Standards.

Compliance with any of the numerous national and international regulations should indicate that the Apheresis Collection Facility is safely run and that the personnel are familiar with the principles of Good Tissue Practice (GTPs). However, compliance with other organizations' standards or governmental regulations does not imply that FACT-JACIE Standards have been met. In all cases, governmental regulations supersede any organization's standards if the standards are inconsistent with a specific regulation. However, a FACT-JACIE standard that is more rigorous than a governmental regulation must be followed.

Apheresis Collection Facilities that are not in compliance with applicable laws and regulations cannot be accredited by FACT or JACIE.

Evidence:

Current certifications will demonstrate what areas of facility function have been certified by other organizations and/or competent authorities.

While observing facilities and processes, inspectors will note if there are apparent practices that are not in compliance with applicable laws and regulations.

Example(s):

Documentation of evidence may include facility registration or licensure.

In the U.S., both minimally manipulated HPC, Apheresis and TC, Apheresis) 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). If these products are extensively manipulated, from an unrelated donor, 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 are regulated under the Public Health Service Act 351 and therefore are referred to as 351 products.

In the Member States of the Europe Union (EU), both HPC and TC fall under the European Directive (EUD) 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 EUD 2006/17/EC and EUD 2006/86/EC. The EUD 2001/83/EC regulates products that are classified as medicinal products (MP). This includes somatic cell therapy MPs and gene therapy MPs. The TMP-Regulation 1394/2007 entered in force on December 30, 2008 to include tissue-engineered products as well. The consequence of classification as an MP is that a GMP environment is required for the production of these cells. Furthermore, each Member State in the EU may add on additional regulations to the EUDs, which have to be followed, but Member State-specific regulations will not be specified in the guidance to these Standards.

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 Foundation for Immunogenetics (ASHI/EFI), the College of American Pathologists (CAP), or any other applicable accreditation body.

STANDARD:

C1.3.1 The Apheresis Collection Facility shall be licensed, registered, and/or accredited as required by the appropriate governmental authority for the activities performed.

Explanation:

Apheresis Collection Facilities must be appropriately licensed, registered, and/or accredited as required by applicable laws and regulations. National 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 Apheresis 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):

Documentation of evidence may include facility registration or licensure.

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 Apheresis 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). Products that fall under this requirement include the following: HPC, Apheresis; HPC, Cord Blood; and TC. 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. An Apheresis 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 an Apheresis 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.

STANDARD:

C1.4 For initial accreditation, the Apheresis Collection Facility, including an Apheresis Collection Facility Director, an Apheresis Collection Facility Medical Director, and at least one staff member, shall have been in place and performing cellular therapy product collections for at least twelve (12) months preceding accreditation.

Explanation:

The Apheresis Collection Facility must have an Apheresis Collection Facility Director, an Apheresis Collection Facility Medical Director, and at least one staff member who meet the personnel standards (see C3) for at least twelve (12) months prior to initial accreditation. 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 should document evidence as to length of employment and experience with cellular therapy product collections.

Example(s):

Documentation of evidence may include the Apheresis Collection Facility Director and Apheresis Collection Facility Medical Director CVs and employee files.

STANDARD:

C1.4.1 A minimum of ten (10) cellular therapy products shall have been collected by apheresis in the twelve (12) months preceding accreditation.

C1.5 The Apheresis Collection Facility shall collect a minimum average of ten (10) cellular therapy products by apheresis per year within the 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 HPC and/or TC 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 Apheresis 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 data to demonstrate compliance to the Standards, and the facility's team must be experienced and mature (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 Apheresis 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):

Quality and/or statistical reports of the number of procedures performed within the accreditation cycle may serve as documentation of compliance.

FACT and JACIE will use the average number of collections per year over the accreditation cycle to determine if an Apheresis Collection Facility meets the minimum collection volume. For example, if a 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 be considered to have met the standard.

STANDARD:

C2 APHERESIS COLLECTION FACILITY

C2.1 There shall be appropriate designated areas for collection of cellular therapy products, for the product collected, and for storage of supplies, reagents, and equipment.

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 Apheresis Collection Facility overnight and transported the following day with a second collection from that donor.

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 Apheresis 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 Apheresis Collection Facility during the on-site inspection, including all locations where products are collected, stored, and distributed. The inspector should observe the organization, design, location, and amount of space available in the Apheresis Collection Facility to 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 transplant patients and/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 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 Apheresis Collection Facility is to be relocated, qualification and validation must be performed to ensure the new space meets the Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT Policy 6.1.001 Inspection Process. This includes a description and floor plan of the new facility, QM documents, and relocation date. The policy can be found on the FACT website. 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 process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all products prior to release or distribution.

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:

A demonstration by Apheresis Collection Facility 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 patients and donors. The inspector should investigate what other activities are performed on the equipment and in the space assigned to the Apheresis Collection Facility.

Example(s):

If the space seems to be inadequate, this should be discussed by the inspectors and appropriate citations and/or suggestions should be included in the report to the FACT or JACIE Accreditation Committee as appropriate.

STANDARD:

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

Explanation:

At a minimum, such space should provide for auditory privacy at the time of donor interview and full privacy for examination. This applies for both the initial donor evaluation and interim assessment evaluations on the day of collection. It is critical that patients' and donors' confidentiality and privacy is protected by all reasonable means. It is usually not acceptable to perform a complete donor interview at the bedside unless privacy is preserved and/or limited interim assessment is performed.

Evidence:

A demonstration of how the interim assessment is performed should provide verification that there is an appropriate process for confidential donor examination and evaluation. The inspector can request a mock interview if there is a question of space size and/or location. The Apheresis Collection Facility should also detail donor privacy in an SOP.

Example(s):

An example of an adequate method to ensure confidentiality is the use of separate donor exam rooms.

STANDARD:

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:

Apheresis 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 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 Critical Apheresis Collection Facility parameters that may affect cellular therapy product viability, integrity, contamination, sterility, or cross-contamination during

collection shall be identified, controlled, monitored, and recorded to demonstrate ongoing compliance.

C2.3.1 When using collection methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled where appropriate for temperature, humidity, ventilation, air quality, and surface contaminants.

C2.3.2 Apheresis Collection Facility parameters and environmental conditions shall be controlled to ensure the safety and comfort of patients, donors, and personnel.

Explanation:

The Apheresis Collection Facility must identify the facility parameters that should be controlled and monitored based on their potential effect on product quality. The facility must perform an assessment of facility conditions to determine if any parameters need to be controlled, monitored, and recorded.

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 Apheresis Collection Facility uses collection methods that may result in contamination or cross-contamination, it must assess if temperature, humidity, ventilation, air quality, and surface contaminants should be controlled. If any of these conditions could result in contamination or cross-contamination, the facility must control them.

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 as in apheresis.

There must be ongoing monitoring of any parameters that have been determined to be critical and these should be defined by an SOP (see C4.14.1) and compliance documented through quality records.

Evidence:

If no parameters are controlled, the Apheresis Collection Facility should provide documentation of its reasoning. 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 Apheresis Collection Facility operates with unclassified air, but may require control of temperature and humidity at a minimum to ensure 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.

For example, contamination in the Apheresis 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).

In the U.S., no specific air quality classification is required where collections are performed using closed systems as in apheresis.

STANDARD:

C2.4 The Apheresis Collection Facility shall be maintained in a clean, sanitary, and orderly manner.

C2.4.1 There shall be documentation of facility cleaning and sanitation to ensure adequate conditions for proper operations.

Explanation:

Apheresis 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 C5.1.14). 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 Apheresis Collection Facility must verify that the cleaning and sterilization methods used remove infectious agents.

Evidence:

Apheresis Collection Facility cleaning must be documented and the records maintained for the period of time specified in institutional policies or applicable laws and regulations.

The inspector should review the Apheresis Collection Facility cleaning and sanitation SOP and records of this process, such as cleaning logs.

Example(s):

A checklist to document that facility cleaning and sanitation was performed according to SOPs can be left for the cleaning staff to complete when cleaning is performed after hours.

STANDARD:

C2.5 There shall be adequate equipment and materials for the procedures performed.

Explanation:

The amount of relevant equipment in the Apheresis Collection Facility should be appropriate for the type of collection performed, proportionate to the volume of work done, and should be conveniently located.

The Apheresis Collection Facility should have policies and procedures 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 procedures 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:

C2.6 There shall be access to autologous and/or CMV-appropriate and irradiated blood products.

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

Explanation:

These standards aim to protect donor and patient safety in the rare emergency situation. The Apheresis Collection Facility 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.

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.

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 as to the minimal expectations of the Apheresis Collection Facility should 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:

C2.8 SAFETY REQUIREMENTS

C2.8.1 The Apheresis Collection Facility shall be operated in a manner designed to minimize the risks to the health and safety of employees, patients, donors, visitors, and volunteers.

C2.8.2 The Apheresis Collection Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease or to chemical, biological, or radiological hazards, where applicable.

Explanation:

This standard applies to all facilities involved in cellular therapy (Clinical Programs and Collection and Processing Facilities). Safety training, including standard precautions, for handling blood may be a requirement of national OSHA bodies.

The Apheresis Collection Facility policies and procedures, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to standard precautions and to applicable laws and regulations regarding safety to protect personnel, patients, donors, visitors, and volunteers. Safety, infection control, or biohazard waste disposal procedures that are unique to the facility should 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 been appropriately trained for the relevant activities and has reviewed this information on a regular basis.

Apheresis Collection Facilities should post warning signs wherever radioactive materials are in use. Facility personnel responsible for these activities should be identified. All persons who may come into contact with blood or body fluids must have appropriate personal protective equipment available to them. 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 provided. Gloves must be worn whenever potential infectious exposure exists and when sterile procedures are required to protect the product and/or patient.

In case of exposure either to communicable disease or other hazards such as chemical, biological, or radiological hazards, the response and action taken might be time sensitive and thus could affect the outcome of the exposure. Therefore, it is critical that the Apheresis Collection Facility has a safety manual and the staff members have access to instructions regarding the best method to respond to a specific incident as outlined in the safety manual.

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 being handled and discarded (e.g., incinerator, waste field, etc.) and compare his/her observations with the written protocols. The inspector should examine selected employee files for compliance and training in biological, chemical, and radiation safety (when appropriate) in addition to reviewing safety procedures. Compliance with state and federal regulations should be addressed by the Apheresis Collection Facility and verified by the inspector. The presence of unused equipment, excessive traffic from unauthorized personnel, and inappropriate storage of reagents and supplies may also contribute to an unsafe environment and should be noted by the inspector.

The inspector can also review training documentation for infection control and OSHA regulations and safety procedures.

Example(s):

Safety training, including standard 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 via computer. 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. A Standard Operating Procedure (SOP) that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice.

The Apheresis 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 safety manual is kept updated with institutional revisions. Such a document should focus on those hazards that are most likely to occur in the facility, such as needle sticks or handling patients with a known communicable disease.

STANDARD:

C3 PERSONNEL

C3.1 APHERESIS COLLECTION FACILITY DIRECTOR

C3.1.1 There shall be an Apheresis Collection Facility Director who is an individual 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. 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 in nursing) can be an Apheresis Collection Facility Director if he/she has considerable experience in directing a facility.

Evidence:

The inspector should review 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.

STANDARD:

C3.1.2 The Apheresis Collection Facility Director shall be responsible for all technical procedures, performance of the collection procedure, supervision of staff, administrative operations, and the Quality Management Program, including compliance with these Standards and other 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 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 Apheresis Collection Facility with these 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 Apheresis Collection Facility could be operational. The Apheresis Collection Facility Director's responsibilities should be specifically documented.

Evidence:

The inspector should review the Apheresis 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 at least one year experience in cellular therapy product collection procedures.

C3.1.3.1 The Apheresis Collection Facility Director shall have performed or supervised a minimum of four (4) cellular therapy product apheresis collection procedures in the twelve (12) months preceding accreditation and a minimum average of four (4) cellular therapy product apheresis collection procedures per year within the accreditation cycle.

Explanation:

The Apheresis Collection Facility Director must have at least one year of experience in the collection procedure for which accreditation is requested. For HPC, Apheresis, the director shall have performed or supervised a minimum of four (4) collection procedures in the year immediately preceding accreditation and shall have performed or supervised a minimum average of four (4) collection procedures per year within the accreditation cycle.

Evidence:

The Apheresis Collection Facility 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 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:

C3.1.4 The Apheresis Collection Facility Director shall participate regularly in educational activities related to cellular therapy product collection and/or transplantation.

Explanation:

The Apheresis Collection Facility Director is expected to participate regularly (at least annually) in educational activities related to the field of cellular collection and/or transplantation. The purpose of this requirement is for key personnel to keep up with current advancements in the field. The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation should be in an activity that includes substantive information related to the field of cellular collection or transplantation.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not an Apheresis Collection Facility Director meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material. Recognized educational activities include those for which certified continuing education credits are offered, examples included in this Accreditation Manual, and internal training programs that are specific to HPC transplantation 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 Apheresis Collection Facility Director participated, the following information must be submitted for each of the completed continuing education activities within the accreditation cycle:

- Title of activity.
- Type of activity (for example, webinar, meeting, grand round, etc.).
- Topic of activity (for example, hematology, cell transplantation, etc.).
- 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 CME or CPD certificates and either formal or informal study, such as those meeting the requirements of applicable national or international continuing education programs. Presentation of CME or CPD lectures, papers at scientific meetings, or publication of manuscripts related to collection and/or transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies (such as those representing apheresis, transfusion medicine, cellular therapy, and scientific research) includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. An Apheresis Collection Facility Director may be

considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and/or publication of a manuscript related to HPC transplantation).

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 training in cell collection and/or transplantation. The Apheresis Collection Facility Medical Director may also serve as the Apheresis Collection Facility Director, if appropriately credentialed.

Explanation:

The Medical Director must be a physician licensed to practice medicine in the state, province, or country in which the Apheresis 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 should have been submitted with the Apheresis Collection Facility's application, and should be available to the inspector prior to the on-site inspection. A copy of the current license may be requested if the one provided has expired.

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:

C3.2.2 The Apheresis Collection Facility Medical Director or designee shall be responsible for the medical care of patients 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 patients during the collection procedure, including the pre-collection evaluation of the prospective donor at the time of donation, performance of the collection procedure, supervision of assistants for the procedure, care of any complications resulting from the collection procedure, and compliance with these 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 Apheresis Collection Facility is operational. The Apheresis Collection Facility Medical 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) (for example, 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 one year experience in cellular therapy product collection procedures.

C3.2.3.1 The Apheresis Collection Facility Medical Director shall have performed or supervised a minimum of four (4) cellular therapy product apheresis collection procedures in the twelve (12) months preceding accreditation and a minimum average of four (4) cellular therapy product apheresis collection procedures per year within the 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 Medical Director shall have performed or supervised a minimum of four (4) collection procedures in the year preceding accreditation and shall have performed or supervised a minimum average of four (4) collection procedures per year within the 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 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:

C3.2.4 The Apheresis Collection Facility Medical Director shall participate regularly in educational activities related to cellular therapy product collection and/or transplantation.

Explanation:

The Apheresis Collection Facility Medical Director is expected to participate regularly (at least annually) in educational activities related to the field of cellular collection and/or transplantation. The purpose of this requirement is for key personnel to keep up with current advancements in the field. The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is

annually; however, this annual participation should be in an activity that includes substantive information related to the field of cellular collection or transplantation.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not an Apheresis Collection Facility Medical Director meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material. Recognized educational activities include those for which certified continuing education credits are offered, examples included in this Accreditation Manual, and internal training programs that are specific to HPC transplantation 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 Apheresis Collection Facility Medical Director participated, the following information must be submitted for each of the completed continuing education activities within the accreditation cycle:

- Title of activity.
- Type of activity (for example, webinar, meeting, grand round, etc.).
- Topic of activity (for example, hematology, cell transplantation, etc.).
- 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 CME or CPD certificates and either formal or informal study, such as those that meet the requirements of applicable national or international continuing education programs. Presentation of CME or CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies (such as those representing apheresis, transfusion medicine, cellular therapy, and scientific research) includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. An Apheresis Collection Facility Medical Director may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and/or publication of a manuscript related to HPC transplantation).

Grand Rounds may meet the standard as long as they are related to the field of cellular collection or transplantation and the individual is in attendance. If Grand Rounds are to be considered for meeting this standard, it is incumbent on the Apheresis Collection Facility to clearly outline the subject, location, and date of these activities.

STANDARD:**C3.3 QUALITY MANAGEMENT SUPERVISOR**

C3.3.1 There shall be an Apheresis Collection Facility Quality Management Supervisor approved by the Apheresis Collection Facility Director to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Apheresis Collection Facility.

Explanation:

The Apheresis Collection Facility must identify at least one person with responsibility for QM supervision. 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 Apheresis Collection Facility QM Supervisor 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 QM Supervisor may be shared with other portions of the cellular therapy program and/or the institution.

The QM Supervisor must have an active role in preparing, reviewing, approving or implementing QM policies and procedures and must ensure that the procedures are in compliance with these Standards and all applicable laws and regulations before implementation. A key role of the QM Supervisor is to develop systems for auditing Apheresis Collection Facility activities to ensure compliance with the written policies and procedures.

The Apheresis 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 QM Supervisor. The Apheresis Collection Facility Director as specified throughout these Standards may play an active role in reviewing the work of personnel, including quality management procedures. The Apheresis Collection Facility Director is ultimately responsible for the QM Plan and proper implementation of the plan for the Apheresis Collection Facility. SOPs should clearly define the role(s) of the Apheresis Collection Facility Director, Apheresis Collection Facility Medical Director, the QM Supervisor, and other QM personnel in the QM Program.

Evidence:

The inspector should look for documentation (audit reports, proficiency test reports, etc.) that a QM Supervisor is in place and performs or oversees the functions covered in the Quality Management section of the Standards. During inspection the inspector may want to inquire about procedures in place to avoid bias when QM supervisors must review their own work.

Example(s):

Formal training may include practical work experience in a facility, fellowship, or a certification program.

These Standards do not prohibit the QM Supervisor from participating in Apheresis Collection Facility activities, as many facilities or institutions may not be large enough to support a free standing QM staff. However, the QM Supervisor 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 Apheresis Collection Facility Director or Apheresis Collection Facility Medical Director. The QM supervisor can review procedures 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 may be defined by the facility's policies and procedures.

The Apheresis Collection Facility Director or Medical Director can also assume the QM Supervisor role as long as the role does not pose a conflict on proper implementation of QM Plan for the Apheresis Collection Facility. Such a situation may occur more often in a small Apheresis Collection Facility where technical responsibilities do not allow time for the activities of QM supervision.

A QM Supervisor may have an operational role in the Apheresis Collection Facility 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 quality management supervisory responsibilities as long as there is documentation of who is assigned the supervisor role. If the QM Supervisor serves an operational role within the Apheresis Collection Facility, it is acceptable for the individual's job description to state "other duties as assigned," rather than specifically list quality management supervisory responsibilities as long as there is documentation of who is assigned the supervisor role.

STANDARD:

C3.3.2 The Apheresis Collection Facility Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular therapy, cell collection, and/or quality management.

Explanation:

The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation should be in an activity that includes substantive information related to the field of quality management and/or cellular processing or transplantation.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not a QM Supervisor meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material.

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 accreditation cycle:

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

Example(s):

Evidence of compliance may include either formal or informal study, such as meets the requirements of applicable national or international continuing education programs. Presentation

of CME or CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. A Quality Management Supervisor may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and/or publication of a manuscript related to quality management).

Grand Rounds may meet the standard as long as they are related to the field of cellular processing or transplantation and the Quality Management Supervisor is in attendance. If Grand Rounds are to be considered for meeting this standard, it is incumbent on the Apheresis Collection Facility to clearly outline the subject, location, and date of these activities.

STANDARD:

C3.4 STAFF

C3.4.1 There shall be adequate numbers of trained collection personnel available in the Apheresis Collection Facility.

Explanation:

This standard requires that there be an adequate number of trained personnel available for the collection of cells relative to the workload. The number of staff available and other responsibilities of the staff will vary from institution to institution based on the size and scope of the facility, and no specific numbers of staff members are required by these Standards. There should be sufficient staff present to manage in the event of any donor emergency without neglecting ongoing collections.

The Apheresis Collection Facility Director should indicate personnel responsible for specific activities in the Apheresis Collection Facility and confirm that they are appropriately trained to perform those activities, including confirmation that they have been trained in appropriate age-specific issues for the patient population they serve. Personnel should be retrained as necessary to remain up to date on current collection methods. Additional information related to training and competency is addressed in the QM section of the Standards and this Manual.

Evidence:

The inspector, as well as the applicant, will make a judgment of the adequacy of the staff support. 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 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, including long-term employees.

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 in performing these procedures.

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 Apheresis 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 dealing with pediatric patients as well as experience. The inspector might look for specific training applying to pediatrics.

Example(s):

Examples of training and experience documentation include experience such as the number of pediatric collections performed by staff.

STANDARD:

C4 QUALITY MANAGEMENT

C4.1 The Apheresis Collection Facility shall establish and maintain a written Quality Management Plan.

Explanation:

Development of a written, comprehensive QM Program is often the most challenging and time-consuming exercise that the Apheresis Collection Facility will encounter when preparing for a FACT or JACIE inspection. These Standards have a broad scope of requirements of the QM Plan for the facility to comply with cGMP, cGTP, and other applicable international regulatory requirements.

QM involves ongoing assessment of the stability, reproducibility, and effectiveness of critical processes in order to continually improve program integrity, efficiency, and patient outcomes.

Quality assessment findings are compared to pre-established specifications. When pre-established specifications are not met, implementation of corrective or improvement strategies is undertaken and monitored with follow-up assessment to determine the effectiveness of the change.

The QM Plan is the written document that outlines how a Clinical Program will implement its QM Program (quality assurance, control, assessment, and improvement activities). There must be a written QM Plan that includes all of the elements listed in D4. The specific procedure 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 QM Plan does not necessarily need to be a stand-alone document, serving only the Apheresis Collection Facility.

Many of the requirements for the QM Program are identical in all parts of these Standards (Clinical, Collection, and Processing), although the activities required for compliance with a given standard may be performed by individuals within only one of the facilities or a dedicated Quality Assurance unit. However, it remains the responsibility of the Apheresis Collection Facility to ensure that all elements of the QM Program required in D4 are in place and functioning and that documentation of compliance to these Standards that are not performed by facility staff is available.

The thoroughness and attention to detail of the written QM Plan is an indication of how QM is perceived and executed within the Apheresis Collection Facility.

Evidence:

The written QM Plan for the Apheresis Collection Facility will be provided to the inspector prior to the on-site inspection. If policies and procedures are referenced in the QM Plan, they must also be submitted 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 and Processing Facility.

Example(s):

For some elements required of the QM Plan, the Apheresis Collection Facility may choose to participate in an existing quality program in its affiliated hospital(s). In such a case, the written QM Plan should include all elements listed in the standard and clarify the extent of participation by not only the facility, but other departments and/or institutions. An integrated cellular therapy program may have one QM Plan that addresses all aspects of the Clinical Program and Collection and Processing Facilities.

STANDARD:

C4.2 The Quality Management Plan shall include an organizational chart of key positions, personnel, and functions within the Apheresis Collection Facility.

C4.2.1 The Quality Management Plan shall include a description of how these key personnel interact to implement the quality management activities.

Explanation:

The organizational chart should include titles of key positions, the names of key personnel, and the reporting structure for the Apheresis Collection Facility QM Program.

The description of the operation of the QM Program should include the processes in place to accomplish its goals, e.g., meetings, participants, schedule, 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 entire cellular therapy program, as well as for the Apheresis Collection Facility, will be provided to the inspector prior to the on-site inspection. The inspector will verify that the organization and daily function is as described.

The inspector should review any documents that support the described organizational structure and support the interactions among key personnel with regards to QM activities. The documentation should include the names, titles, and responsibilities of all critical staff.

Example(s):

One way to satisfy both requirements for the organizational chart and the description of interactions is to utilize an organizational chart showing the reporting structure and a short description of responsibilities from as high as the administrative level positions down to the collection staff.

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.

If an Apheresis Collection Facility contracts its processing service to an outside entity, the organizational chart must include the contracted service.

STANDARD:

C4.2.2 There shall be an Apheresis Collection Facility Director or designee who is responsible for the Quality Management Plan as it pertains to the Apheresis Collection Facility.

C4.2.2.1 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.

C4.2.2.2 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.

C4.2.2.3 The Apheresis Collection Facility Director or designee shall report on quality management activities, at a minimum, quarterly.

C4.2.2.4 The Apheresis Collection Facility Director or designee shall report on the performance of the Quality Management Plan, at a minimum, annually. This report shall also be provided to the Clinical Program Director, as applicable.

Explanation:

The intent of this standard is that there shall be an individual (i.e., the Apheresis Collection Facility Director or a qualified designee) at the Apheresis Collection Facility in charge of the elements of the QM Plan that are directly related to the facility. The Apheresis Collection Facility Director, or a qualified designee, is responsible for the QM Plan as it pertains to the facility. A designated person must have sufficient knowledge and training to facilitate the identification of improvement opportunities by the staff. Delegation of a qualified designee should be documented, either in the QM Plan or in procedures related to it.

Any person responsible for overseeing the QM activities should not be directly responsible for review of work solely performed by that person. 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. 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 Apheresis Collection Facilities where there may be only one person responsible for most of the collection activity, the Apheresis Collection Facility Director, Apheresis Collection Facility Medical Director, or a person from the Processing Facility may be designated for review of these activities.

QM activities shall be reported, at a minimum, quarterly to review the performance of the QM Plan. This is to ensure that 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 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 to effect 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.

In addition, an annual report on the overall performance of the QM Plan will be provided to the directorship. 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 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. Review by the Apheresis Collection Facility Director is to be documented.

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.

The inspector should ask to see evidence of appropriate designee training and a description of the QM elements delegated to the designee. The inspector should also ask to review the quarterly reports of the activities and progress of the quality activities as well as the annual report on the effectiveness of the QM Program. Regularly scheduled QM meeting minutes are good resources for evidence of QM activities for the Apheresis Collection Facility and the cellular therapy program.

Example(s):

In some larger programs, a Transplant Program Director is ultimately responsible for performance of the QM Plan and monitoring of all cellular therapy program elements, internal or contracted. Also, many QM elements, such as a disaster plan and personnel policies, are controlled at the institutional level.

The designee for managing QM activities 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 Apheresis Collection Facility, or he/she could be a member of the cellular therapy program who has additional responsibilities within the program.

The same person may be responsible for QM of all components of the cellular therapy program or each facility may have a distinct individual responsible for QM, as long as there is a process for appropriate disbursement of information to all participating entities. 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.

Apheresis Collection 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.

STANDARD:

C4.3 The Quality Management Plan shall include, or summarize and reference, personnel education, experience, and training requirements for each key position in the Apheresis Collection Facility. Personnel requirements shall include at a minimum:

C4.3.1 Current job description for all staff.

C4.3.2 A system to document the following for each staff member:

C4.3.2.1 Initial qualifications.

C4.3.2.2 Orientation.

C4.3.2.3 Initial training.

C4.3.2.4 Competency for each critical function performed.

C4.3.2.5 Continued competency at least annually.

C4.3.2.6 Training and retraining.

C4.3.2.7 Provisions for continuing education.

C4.3.3 A description of minimal trainer qualifications and a uniform plan for staff training.

Explanation:

Procedures for personnel training (initial and retraining) and ongoing competency assessment (at least annually) must be defined in SOPs. The training plan SOP should also define the minimal qualifications and training of designated trainers.

Personnel requirements are to be included in the Apheresis Collection Facility QM Plan and should ensure that each position or job category has specified qualifications, training, job duties and responsibilities, and processes for regular performance and competency assessment.

Initial qualifications generally include minimal educational requirements, for example, Registered Nurse (RN) or formal training or education that is preferred but not required. Initial training documentation must include all specific procedures that a specific 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.

Evidence:

The inspector should review procedures or policies describing the elements of staff training and continued competency as described in C4.3. The inspector should review the records of one or more employees to determine if all of the required elements have been documented, and verify that documentation of trainer qualification is in compliance with the Apheresis Collection Facility's minimal qualifications for trainers. Documentation of annual competency assessment and continuing education should also be verified.

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

Example(s):

Initial competency and continued annual 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 Apheresis Collection Facility.

EU regulations contain some specific requirements for personnel training that are not specifically stated in these 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 these Standards.

STANDARD:

C4.4 The Quality Management Plan shall include, or summarize and reference, policies and procedures for development, approval, validation, implementation, review, revision, and archival for all critical processes, policies, and procedures.

Explanation:

Documents serve multiple purposes for the QM Program. Documents provide the structure needed for quality assurance through policies and procedures, ensure quality control using such forms as preprinted orders and worksheets, and substantiate QM activities with audit reports, outcome analyses, training records, etc. The QM Program needs to identify the documents critical to the Apheresis Collection Facility and describe how they are conceived, generated, implemented, distributed, reviewed, and stored. The QM Program must further describe how individual parts (including documents) fit together to constitute a process.

These Standards define a process as “A goal-directed, interrelated series of actions, events, or steps.” Although a process could be described in a single SOP, for example, product distribution to the Processing Facility, other processes may require multiple documents for its performance.

Standard C4.4 requires that the QM Plan have methods or make a reference to procedures describing methods for all aspects of process development and requires that in addition to the individual steps, the overall process itself must be controlled.

In previous versions of these Standards, this was referred to as protocol development. In these current Standards, it is emphasized that protocols should be translated into written procedures that are readily available to staff in order to consistently manufacture reproducible quality products and to correctly put together the multiple pieces that constitute critical processes.

Archival is specifically mentioned in this standard and is an important element of the QM Program. 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 policies, procedures, and forms to determine if an operational change is the cause.

The specific parameters to be reviewed prospectively in a regular fashion should be identified in the QM Plan. These should address all key elements of the Apheresis Collection Facility, whether internal or contracted.

Evidence:

The inspector should review documented evidence that policies, processes, and procedures have been written and verified to be accurate and effective and have been approved by the Apheresis Collection Facility Director prior to implementation. The inspector will look to see how the Apheresis Collection Facility controls modifications of documents and whether retrospective review is possible. The inspector should expect to find a written plan, results, and discussion of prospective indicators, actions taken, and follow-up assessments.

Example(s):

The process by which HPC, Apheresis product collections are handled requires multiple procedures, forms, and worksheets to be in place. This process might include a description of product collection procedure, receipt, sampling, and labeling, among others. It would also

describe the steps for communication between the Apheresis Collection Facility and the physician regarding target cell doses. The process document would describe how these pieces are put together to ensure that the desired number of HPCs are available for the recipient.

Performance measures may include, for example, measurement of collection efficiency, product sterility testing, treatment-related morbidity, specific complication rates, and other clinical outcomes, as well as adherence to selected policies or procedures. Additional activities influencing positive outcomes include policy and procedure review, staff training and education, competency evaluations, proficiency testing, data and records management, and the review of all errors, accident reports, adverse reactions, and complaints.

STANDARD:

C4.5 The Quality Management Plan shall include, or summarize and reference, a system for document control. The document control system shall include at a minimum the following elements:

C4.5.1 Listing of all active critical documents that shall adhere to the document control system requirements. Controlled documents shall include at a minimum:

C4.5.1.1 Policies

C4.5.1.2 Standard Operating Procedures.

C4.5.1.3 Worksheets.

C4.5.1.4 Forms.

C4.5.1.5 Labels.

C4.5.2 A procedure for preparation, approval, implementation, review, revision, and archival of all policies and procedures.

C4.5.2.1 Archived policies and procedures, 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.

C4.5.3 A standardized format for policies, procedures, worksheets, forms, and labels.

C4.5.4 Assignment of numeric or alphanumeric identifier and title to each document and document version regulated within the system.

C4.5.5 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.

C4.5.6 A system to ensure that controlled documents cannot undergo accidental or unauthorized modification.

C4.5.7 A system for document change control that includes a description of the change, the signature of the approving individual(s), approval date, and effective date.

C4.5.8 A system for the retraction of obsolete documents to prevent unintended use.

C4.5.9 A system for record creation, assembly, review, storage, archival, and retrieval.

Explanation:

This standard primarily addresses the need for a comprehensive document control system that covers all of the critical documents used by the Apheresis Collection Facility. The types of documents listed in the standard are what minimally have to be included in the document control system; however, Apheresis Collection Facilities should review their document management system to identify if other documents should also be included, such as

- Protocols.
- Directives.
- Checklists.

There must be a listing of active critical documents. This list must include all critical documents that are currently in effect. Documents in electronic format should follow the described document control process of the Apheresis Collection Facility's SOPs.

The document control system must include the assignment of a unique identifier for each individual document, a mechanism to identify the document version and its effective dates of use; a process for the creation, approval, and implementation of each document; a method to control document changes that will prevent unintended modification and/or the use of obsolete documents; a system for the use, assembly, storage, archival, and retrieval of documents; and a mechanism for training. The Apheresis Collection Facility Director should determine which documents fall under this system.

The change control policy and/or procedure(s) 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 on existing processes, procedures and policies; approval of change; communication and/or training on the change as applicable; and implementation of the change.

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. Archiving is specifically mentioned in this standard and is an important element of the QM Program. If outcomes change over time, one needs to be able to go back to previous versions of policies, procedures, and forms to determine if an operational change is the cause.

Evidence:

The inspector should confirm that the change control policy and/or procedure meets these minimal criteria and that the policy and/or procedure is followed. He/she should confirm that a written change control policy and/or procedure exists and is effective to prevent unintended changes to processes, policies, or procedures.

The inspector should confirm the effectiveness of the document control by tracking at least one controlled document (e.g., a form or SOP) from initial creation, through the proposal, approval, and implementation of revisions and/or new versions, and archival.

The inspector will look to see how the Apheresis Collection Facility controls modifications of documents, whether retrospective review is possible, and whether previous policies and procedures can be identified.

Example(s):

The inspector should review SOPs for consistency in format as described in the Apheresis Collection Facility's SOP for development of documents and look for evidence on how the document has met the established criteria and if documents in paper copy have the current version number in use as listed in the master document list.

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, the whole document, or to prevent printing or have printed copies indicated as copies. Control over the location and number of SOP manuals and the photocopying of documents is another method. The intention is to make sure that only the currently approved document is available for use.

Apheresis Collection Facilities accredited by JACIE can utilize the JACIE Quality Management Guide (see www.jacie.org/document-centre) for further document control examples.

STANDARD:

C4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the cellular therapy product.

C4.6.1 Agreements shall include the responsibility of the facility performing any step in collection, processing, or testing to comply with applicable laws and regulations and these Standards.

C4.6.2 Agreements shall be dated, reviewed, and renewed on a regular basis.

Explanation:

These agreements should clearly define roles and responsibilities for critical tasks. All such agreements must be dated, reviewed, and renewed on a regular basis, and should include provision for the maintenance of records following termination of the agreement. If there are any changes in the substance of a written agreement by either party, the agreements must be renewed and only need to be sent to legal departments if there are changes requiring legal review as determined by the Apheresis Collection Facility.

How such agreements are executed is a function of the type of Apheresis Collection Facility. In all cases, a process must exist for the development and implementation of such agreements. The Apheresis Collection Facility Director and Medical Director should be aware of the terms of these agreements, whether or not they have actual signatory authority.

In the event the Apheresis Collection Facility (or an entity with which the facility has agreements) terminates its activities, it is essential that traceability data and records concerning the quality and safety of the cellular therapy products be preserved and provided to the relevant parties.

It is expected that Apheresis Collection Facilities will only use Processing Facilities that meet these Standards. An accredited Apheresis Collection Facility may, however, collect products for one or more programs that are not FACT or JACIE accredited and do not meet these Standards.

Evidence:

The inspector should review the process for establishing agreements or contracts with entities outside of the Apheresis Collection Facility that participate in cellular therapy product collection, testing, storage, transport, or other critical services that might affect the quality of the product. If agreements exist, examples should be reviewed by the inspector for adherence to the established process.

Example(s):

Written agreements should be reviewed every two years, similar to SOPs, although greater or lesser time intervals may be appropriate under some conditions. The effective dates of an agreement could be specified within the agreement itself. It would be helpful to have a list of written agreements to inventory whether each one is reviewed and renewed appropriately.

An example of a written agreement is a service agreement or contract between the Apheresis Collection Facility and the customer.

Such agreements may include, but are not limited to, donor qualification, determination of donor suitability and eligibility (allogeneic donor only), procurement (collection) of the cellular therapy product, donor or product testing, and long-term storage. 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 should include provision for the maintenance of records following termination of the agreement.

Stand-alone facilities may execute agreements directly with the service providers (or institutions for which they provide services), whereas agreements involving facilities in academic institutions may be between the institution and the service provider.

STANDARD:

C4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of outcome analysis and product efficacy, as appropriate, including at least:

C4.7.1 For HPC products intended for hematopoietic reconstitution, a process for documentation and review of time to engraftment following product administration.

C4.7.2 For other cellular therapy products, the criteria for product efficacy and/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, including engraftment in the case of HPC products. Acceptable criteria for each cellular therapy product should be developed by the Apheresis Collection Facility in conjunction with the clinical team, and this process defined in SOPs. Evaluation of patient outcome is required to ensure that the product that was manufactured and distributed met expected specifications. Any unexpected outcomes should 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. This evaluation must be documented, and, if indicated, the facility should initiate the appropriate corrective action.

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 Apheresis Collection Facility personnel must be aware of the time to neutrophil and platelet engraftment for all recipients for whom they have supplied products. 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 procedures what party will assume responsibility.

The analysis should include the average (or median) and observed ranges of engraftment for the various cellular therapy products and transplant procedures performed by the cellular therapy program. Product characteristics, especially CD34 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 Apheresis Collection Facility. It is acceptable to share the same data between clinical, collection, and processing; however, the Apheresis 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.

If an Apheresis Collection Facility provides cellular therapy products to one or more Clinical Programs, it is the responsibility of the facility to solicit engraftment data from each program.

Product efficacy based on outcome may be more difficult to document for other TC products 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.

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 engraftment data in addition to its mere collection. The inspector should ask to see the engraftment data and/or minutes of meetings, including the personnel in attendance and where engraftment data are presented.

Example(s):

This information can be obtained and analyzed directly by the Apheresis 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 Apheresis Collection Facility may also consider the number of collections per patient, cell yield per collection, or duration of each collection in its analysis.

Graphs of patient outcome data points with mean and standard deviation limits and reports showing patient data selected for outcome analysis and recognition of outliers are examples of how outcome data can be presented.

STANDARD:

C4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a timetable 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 procedures.

C4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

C4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, and implement corrective actions when necessary.

C4.8.3 Audits shall include, at a minimum:

C4.8.3.1 Documentation of proper donor eligibility determination prior to start of collection procedure.

C4.8.3.2 Documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

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 procedure. Compliance is verified by examination of objective evidence. Audits are conducted to ensure 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 Apheresis Collection Facility QM Program should identify areas to be audited and audit frequency. Standard C4.8.1 indicates that audits should be performed regularly. This means the audit process should be performed throughout the year in accordance with the Apheresis Collection Facility's QM Plan, including reporting of the results of this activity.

To be effective, audits must be conducted by individuals with sufficient knowledge to identify problems and their probable causes, but should not be performed by the individual directly responsible for the activity being audited. While it is desirable that someone from outside of the Apheresis Collection Facility conducts the audit, such individuals may not have the needed expertise. The process by which the facility performs audits must be defined by an SOP.

Audits should be performed of activities where failure may result in a compromised cellular therapy product or potentially compromised care. Where specific problems are identified by audits, these issues should be re-audited on a regular basis until such problems have been

resolved. Audits that routinely demonstrate compliance with applicable standards, regulations, and expected performance should be documented and a new area identified for audit.

There should be evidence that audit reports are shared with the Apheresis Collection Facility Director, Medical Director, and staff, and, as appropriate, others with potential interest. 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.

Audit results should be used to identify trends. 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 expected 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, etc.).

One of the required audits is documentation of proper allogeneic donor eligibility determination prior to the start of the collection procedure. 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.

Evidence:

The Apheresis Collection Facility must provide the inspector with its audit procedure, audit timetable (i.e., the schedule of audits), and example audits (including documentation of the required audits). The inspector will review this documentation to determine that the audit process is ongoing and that the QM records demonstrate corrective actions or process improvement activities that are based on audit findings when necessary.

The inspector may review audit schedules and results, but it is not the intent to use a facility's audits to identify deficiencies during an inspection.

Example(s):

Examples of audits in the Apheresis Collection Facility include:

- Adherence to policies and procedures (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

Audits of external facilities may be accomplished by reviewing the facilities' internal and external audit reports, performing onsite inspections for compliance, or receiving periodic performance reports from the facility. There may be other alternatives, but the contracting facility must ensure that their contracted services are meeting requirements.

STANDARD:

C4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on 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.

C4.9.2 Investigation of cause.

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

Explanation:

The Apheresis Collection Facility (or cellular therapy program, as applicable) 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 infused. Policies and procedures are required in all three areas of a cellular therapy program – clinical, collection, and processing – to deal with elements for which that area of the program is responsible. This standard lists the topics that must be addressed in policies and/ or procedures, but does not dictate a single policy or procedure that must be followed.

Policies and procedures 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. Apheresis Collection Facility personnel are responsible for investigation of the relevant collection events.

Policies and procedures must also be in place for the timely notification of clinical staff of the positive culture result, so that appropriate patient care can be delivered to the donor, and, if the product has already been infused, to the recipient. For cellular therapy products found to have positive microbial cultures prior to infusion, procedures should describe notification of the responsible transplant physician, determination of who is authorized to decide whether or not a specific product with a positive culture result will be used, how that decision will be documented, how recipient notification will be handled, labeling, and reporting of positive culture results to appropriate governmental agencies in accordance with applicable law. Labeling requirements may be defined by the Apheresis Collection Facility and should include requirements for the use of a biohazard label and warning statements.

In other cases, a positive result may only become known after the product has been infused. The Processing Facility is usually the first facility to be notified of a positive culture result. There should be timely notification of the Apheresis 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 be contaminated and review how the Apheresis Collection Facility managed the process.

Example(s):

Examples of evidence of compliance to this requirement may include:

- Policy on management of products with positive microbial culture results.
- Procedure 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. If there is such a policy, the procedure(s) that is followed must be referenced.

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.

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.

In the U.S., regulations for 351 and 361 products must be followed and the program should have policies that cover responsibility for reporting.

STANDARD:

C4.10 The Quality Management Plan shall include, or summarize and reference, policies and procedures for errors, accidents, adverse events, biological product deviations, and complaints.

C4.10.1 Policies and procedures shall include methods for:

C4.10.1.1 Detection.

C4.10.1.2 Investigation.

C4.10.1.3 Evaluation.

C4.10.1.4 Documentation.

C4.10.1.5 Reporting.

C4.10.1.6 Corrective action.

C4.10.1.7 Follow-up for effectiveness of corrective action.

C4.10.2 Documentation of each adverse event that occurs in the Apheresis Collection Facility shall be reviewed in a timely manner by the Apheresis Collection Facility Director and/or Apheresis Collection Facility Medical Director, as appropriate.

C4.10.3 A written description of adverse events shall be made available to the donor's physician, the recipient's physician, and the Processing Facility, if appropriate.

C4.10.4 When applicable, adverse events shall be reported to appropriate regulatory agencies within the required timeframes.

C4.10.5 Deviations from Standard Operating Procedures shall be documented.

C4.10.5.1 Planned deviations shall be pre-approved by the Apheresis Collection Facility Director or designee.

C4.10.5.2 Unplanned deviations and associated corrective actions shall be reviewed by the Apheresis Collection Facility Director or designee.

C4.10.6 There shall be a defined process improvement plan that includes policies or procedures for the recognition and investigation of the cause of all issues that require corrective action.

C4.10.6.1 The implementation of corrective actions shall include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence.

C4.10.6.2 Follow-up activities shall be conducted to determine if the corrective actions were effective.

Explanation:

There must be a mechanism to detect, evaluate, document, and report errors, accidents, adverse events, and complaints in a timely fashion to key individuals, including the Apheresis Collection Facility Director, Medical Director and appropriate governmental agencies (as appropriate). The Apheresis Collection Facility should define errors, accidents, deviations, adverse reactions, and complaints in an SOP along with when and how each is reported. See the definitions of each of these types of incidents in Part A Definitions.

If an adverse reaction occurs to any cellular therapy product for which there is a reasonable possibility that the response may have been caused by that product, reporting of the adverse reaction must be done to all facilities associated with collecting, processing, and/or infusing that product. This includes graft failure. Usually the Clinical Program is responsible for making the initial report; however, all involved facilities must participate in the investigation and evaluation of what caused the reaction.

A goal of a QM Program is to continuously improve processes. An important aspect of continuous improvement is the recognition of opportunities for improvement. It is recommended that Apheresis Collection Facilities also define, document, investigate, take corrective action, report, and track and trend less severe adverse events, such as fever during infusion, fluid overload, etc. This practice may lead to significant process improvements within the program.

The Apheresis Collection Facility must have procedures in place for personnel to follow when a need for improvement is identified. There should be a policy that all personnel participate in continuous improvement activities, as well as a procedure that outlines how an identified area for improvement should be submitted and through what chain of command.

A biological product deviation is defined in A3. Such products are released by the Apheresis Collection Facility for use by Clinical Programs 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 infusion has occurred. How the Apheresis Collection Facility manages biological product deviations in general should be addressed by the QM Plan or by other policies or procedures and must be defined in an SOP. 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.

If there is a complaint related to cellular therapy product performance, delivery of service, or transmission of disease, it must be investigated and resolved. Corrective action or process improvement must be implemented to prevent reoccurrence as defined by an SOP.

Evidence:

The inspector should ask to see SOPs that describe how adverse events are detected, investigated, and reported, files of adverse events, and evidence that adverse reactions are reviewed by the Apheresis Collection Facility Director and reported as appropriate to the Clinical Program Director, the Processing Facility, and appropriate governmental agencies.

The inspector should review the complaint file and determine if corrective, preventive, or process improvement actions have been defined, implemented, and are adequate to prevent future occurrences.

Example(s):

For example, an Apheresis Collection Facility may choose to have a form that includes the process involved, the area needing improvement, suggested improvements, and date the improvement was evaluated. The procedure should also outline who has the authority to review these suggestions, such as the QM Supervisor.

Communication of adverse reaction 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.

The FDA defines an adverse reaction, which is an adverse event, as one involving the transmission of a communicable disease, 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. They may also include unexpected reactions to the graft that are designated as possibly, probably, or definitely related. For suspected adverse reactions to infusion 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, TC-T) or GMP (products produced under IND or IDE) must be reported to FDA within their specified guidelines.

EUD 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.

STANDARD:

C4.11 The Quality Management Plan shall include, or summarize and reference, policies and 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:

One of the most important paper trails in the Apheresis Collection Facility allows for tracking and tracing of information about the cellular therapy product at all steps between the donor and the recipient. Documentation in the product collection record should include the identity and content of the cellular therapy product, the unique identification of the donor, the donor eligibility status (for allogeneic donors), and the unique identity of the intended recipient. There should also be a means, direct or indirect, that will allow outcome information to be related back to a specific product and communicated to any other facilities involved in collection, processing, and/or distribution of the product. The final disposition of the product must also be documented, whether the product was infused, destroyed, released for research, remains in storage, or other outcome. The process for product tracking must be defined by an SOP.

Evidence:

The inspector should review examples of specific products at the Apheresis Collection Facility and determine if tracing and tracking from the donor selection through final product and its disposition is unequivocally possible. Each critical step should identify the individual who performed the step or action and the date and time it was completed.

Example(s):

Collection and comparison 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, recipient identity and Apheresis Collection Facility unique product identifier.
- Product collection records showing donor identity and Apheresis Collection Facility's unique product identifier.

STANDARD:

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

Explanation:

Apheresis Collection 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 procedure is required for addressing emergencies and disasters (see C5), the facility must have a plan for how to handle interruptions that do not rise to the disaster level. It is appreciated that 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.

The Apheresis Collection Facility should ensure 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 ensure quality collections when the electronic records are unavailable.

Specifically in the Apheresis Collection Facility, this should include a mechanism to ensure 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.

Example(s):

Previous editions of these Standards specifically required a plan for when electronic record systems cease to function, and this is one example of a situation that would interrupt Apheresis Collection Facilities. Other examples include drug shortages, power outages, equipment failures, etc.

STANDARD:

C4.13 The Quality Management Plan shall include, or summarize and reference, policies and procedures for qualification of critical reagents, supplies, equipment, and facilities.

Explanation:

Quality can be maintained only if there is control over critical supplies, reagents, equipment, and the facility itself. Qualification is defined in these Standards as, "The establishment of confidence that equipment, supplies, and reagents function consistently within established limits."

The QM Plan must include a process to qualify reagents and supplies to ensure 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. Other, more specific, standards require practices to minimize this likelihood.

Evidence:

The inspector should observe the Apheresis Collection Facility in operation, if possible, or should question personnel regarding the procedures in place when multiple products are undergoing collection and the procedures used for sequential collection.

The inspector should find evidence of equipment qualification and facility change control and/or qualification procedures. Procedures should include instructions of requalification and under which circumstances qualification is required.

Example(s):

Qualification of a readily used reagent in the field (i.e. 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.

STANDARD:

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

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

C4.14.2 Changes to a process shall be verified or validated to ensure that they do not create an adverse impact anywhere in the operation.

Explanation:

Validation is confirmation by examination and provision of objective evidence that particular requirements can be consistently fulfilled. A process (or procedure) is validated by establishing, by objective evidence, that the process consistently produces a cellular therapy product meeting its predetermined specifications. 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. Qualification is another term commonly used in this setting and is most similar to verification in that it is the part of the process that confirms functional performance.

Validations can be performed prospectively, concurrently or retrospectively. Validations should be performed on processes and the use of equipment, reagent, and supplies. In the Apheresis 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 procedures to be performed using it, including collection of HPC, TC, and/or concurrent plasma. Subsequent machines of the same type may be qualified to document performance according to expected parameters, and a more limited verification of processes.
- The collection process. This validation should include all the variables used in the collection of each 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.
- Labels and labeling. The validation of the label would demonstrate that the labels in use were checked against an approved template, were approved for use, maintain integrity during use, remain affixed or attached as required, are readable, do not contain any blank data points, and do include all of the required elements as listed on the label table (FACT-JACIE Standards, Appendix I). 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.
- Reagents, supplies, and disposables for intended use. Most Apheresis 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.

Validation studies should be performed according to a validation procedure, utilizing a consistent format for conducting the studies, analyzing the data, drawing conclusions, and documenting the implementation of changes resulting from the investigation. The design of the study should be adequate to determine if the process achieves the purpose for which it is intended. The validation or verification plan should state specifically the tests to be performed, the number of samples to be tested, and the range of acceptable results. There should be an explanation, follow-up, and/or repeat of any test that fails to meet the expected outcome. Reports of these activities should be complete, legible, and organized for review.

The validation studies must include documented review by the QM Supervisor and/or other appropriate individuals from Quality Management.

Plans of validation studies shall be reviewed and approved by the Apheresis Collection Facility Director and Medical Director or designee prior to execution of the plan.

All reagents and supplies must be validated for their intended use to meet specifications designed to prevent transmission of infectious disease and/or impairment of product function or integrity. Validation may be performed by the Apheresis Collection Facility or the manufacturer. In the case of manufacturer validation, the certificate of analysis should be available in the Apheresis Collection Facility.

Evidence:

The inspector should review a sampling of validation studies of the facility, processes, reagents, and equipment. The inspector should ensure that the validation study is being executed according to the SOP. The inspector should note poorly designed or inadequately performed validation studies during the review process.

Example(s):

It is acceptable, but not required, for the Apheresis Collection Facility to utilize validation plans, formats, and personnel from the Processing Facility to perform validation studies, or to contract these validation services to a contract vendor. In either case, the validations must be performed on the processes in place in the Apheresis Collection Facility for the specific cellular therapy procedures performed at that facility.

STANDARD:

C5 POLICIES AND PROCEDURES

C5.1 The Apheresis Collection Facility shall establish and maintain policies and/or 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:

The policies and/or procedures required in C4 pertain to the QM Program, whereas those required in this section are operational in nature. The standard requires that each Apheresis Collection Facility have written policies and procedures that comprehensively address all important aspects of the Apheresis Collection 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 in C5.1 include the minimum requirements; an Apheresis Collection Facility may exceed these requirements, but not omit any of these.

Evidence:

When multiple topics are covered by a single SOP, it will aid the inspection process if the Apheresis Collection Facility prepares a crosswalk between the list of required procedures in C5.1 and the facility's own SOP Manual.

This should be verified by the inspector. The inspector should verify the procedure for development and review for all policies and procedures is being followed and that the policies and procedures are comprehensive and define all aspects of the Apheresis Collection Facility function.

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 procedures and other activities that can only be verified in person at the inspection site.

Example(s):

The policies and procedures can be generated within the Apheresis 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 procedures are inadequate to meet standards or where there are issues that are specific to the Apheresis Collection Facility, the Apheresis Collection Facility must develop its own policies and procedures to supplement those of the institution (see C5.1.14, C5.1.15, C5.1.16, and C5.1.17). In situations where institutional policies and procedures 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 treatment.*
- C5.1.4 Donor screening, testing, and eligibility determination.*
- C5.1.5 Management of donors, including pediatric donors if applicable.*
- C5.1.6 Product collection.*
- C5.1.7 Labeling (including associated forms and samples).*
- C5.1.8 Product expiration dates.*
- C5.1.9 Product storage.*
- C5.1.10 Release and exceptional release.*

Explanation:

Release is defined as the removal of a cellular therapy product from in-process status when it meets specified criteria. Apheresis 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 (commonly to a Processing Facility for processing and storage).

Each 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 released for urgent medical need, an SOP must define the process for exceptional release, outlining the steps to take for documentation and approval when a product does not meet release criteria.

The Apheresis Collection Facility must define the expiration dates and storage conditions (e.g. container, temperature, etc.) of all of its collected products, including those not only applicable to directly releasing a cellular therapy product for administration, but also to releasing a cellular therapy product to another facility (commonly to a Processing Facility for processing and storage).

Evidence:

The inspector will review the SOP(s) describing what the release criteria are and the process for release of cellular therapy products that meet those criteria. The inspector will also verify that an SOP describes the process for exceptional release, including documentation and approval, when a product does not meet release criteria.

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 for Apheresis Collection Facilities include, but are not limited to:

- Correct labeling including storage temperature and expiration date.
- Sealed secondary container.
- Completed allogeneic donor eligibility documentation.

STANDARD:

C5.1.11 Transportation and shipping to include methods and conditions to be used for distribution to external facilities.

C5.1.12 Reagent and supply management.

C5.1.13 Equipment operation, maintenance, and monitoring to include corrective actions in the event of failure.

C5.1.14 Cleaning and sanitation procedures to include identification of the individuals responsible for the activities.

C5.1.15 Disposal of medical and biohazard waste.

C5.1.16 Facility management and monitoring.

C5.1.17 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 procedures are utilized, there must be a defined mechanism for review and approval. Standard C5.1.17 requires that the Apheresis 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 product is undergoing cryopreservation at the moment of the disaster or what to do if you need to move products. Examples of disasters include fires, hurricanes, floods, earthquakes, nuclear accidents, etc. In cases where institutional policies and procedures are inadequate to meet these Standards or where there are issues that are specific to the Apheresis Collection Facility, the facility must develop its own policies and procedures.

Evidence:

If a Collection Facility is operated out of a transfusion service and shares certain procedures or policies with the transfusion service, then an index of the shared procedures and policies should also be submitted.

The inspector will review the emergency and disaster plan, verifying that appropriate details are provided for Apheresis Collection Facility 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 individual Clinical Programs:

<http://asbmt.affiniscape.com/associations/11741/files/EmergencyPreparednessGuidelines.pdf>.

STANDARD:

C5.2 The Apheresis Collection Facility shall maintain a Standard Operating Procedures Manual.

C5.2.1 The Standard Operating Procedures Manual shall include a listing of all current Standard Operating Procedures.

Explanation:

The SOP Manual is a compilation of policies and procedures containing written detailed instructions required to perform procedures. The purpose of the SOP Manual is to maintain the policies and procedures in an organized fashion so that all current documents can be found. Many Apheresis Collection Facilities have adopted an electronic method of compiling its policies and procedures, 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 C4.5.

Evidence:

Apheresis 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 procedures are comprehensive and

define all aspects of the facility. The inspector should verify the procedure for development and review for all policies and procedures is being followed.

The inspector must verify that all elements of an SOP are present as defined in the “SOP for SOPs,” and that there is consistency in format from one SOP to another. The inspector should also ensure that the SOPs adhere to the requirements for all controlled documents as specified in C4.5.

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 Apheresis Collection Facility may choose to have one SOP Manual or divide policies and procedures 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 procedure 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 technical staff to follow and complete the procedures successfully. Each individual procedure shall include:

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, where applicable.

C5.3.4 A stepwise description of the procedure.

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

C5.3.6 A reference section listing appropriate literature, if applicable.

C5.3.7 Documented approval of each procedure by the Apheresis Collection Facility Director or Medical Director, as appropriate, prior to implementation and every two years thereafter.

C5.3.8 Documented approval of each procedural modification by the Apheresis Collection Facility Director or designated physician prior to implementation.

C5.3.9 A current version of orders, worksheets, reports, labels, and forms, where applicable.

Explanation:

This Standard defines the minimum elements required in each SOP. Current versions of worksheets, reports, labels, and forms, where applicable, must become a part of 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 C4.5.

The policies and procedures must be detailed, unambiguous, and adequately define all operational aspects of the Apheresis Collection Facility. The minimum elements that must be included in a policy or procedure are listed in C5.3. Specific requirements for how these procedures must be conducted are elsewhere in the Standards; for example, requirements for donor treatment, screening, and management (see C5.1.3, C5.1.4, and C5.1.5) are within the Donor Evaluation and Management section.

It is recognized that the practice of medicine requires some flexibility and the Apheresis Collection Facility may choose to designate policies for some clinical care of collection practices as practice guidelines rather than critical document SOPs to allow this.

The Apheresis 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. Determination of the mean \pm 1 or 2 standard deviations defines an acceptable range.

It is recognized that the reference to relevant policies within an SOP requires some flexibility. Some Apheresis 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. It is expected to see in the SOP describing how to write an SOP (the "SOP for SOPs") how this is to be done.

These Standards require documented review of each SOP by the Apheresis Collection Facility Director or by the Apheresis Collection Facility Medical Director every two years. It is important that the documentation of review every two years 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 procedures may be revised throughout the year. Review of SOPs should include review of the applicable worksheets, forms, and attachments.

Evidence:

The inspector should review the SOP manual and documentation of Apheresis Facility Collection Director and/or Medical Director review.

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 prudent to attach one or more completed forms to illustrate possible real life scenarios. Although not required by these Standards, 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.

For example, procedures or policies for reporting adverse reactions to product infusion or procedures for reporting the results of microbial testing should be approved and reviewed by the Apheresis 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 Copies of Standard Operating Procedures 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 Apheresis 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 procedure 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 ensure access to 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 Apheresis Collection Facility and the process to get access to them if needed.

Example(s):

The Apheresis Collection Facility's SOP Manual is usually physically located in the facility (apheresis unit) 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 of ready availability (such as how to access the electronic version).

STANDARD:

C5.5 All personnel in the Apheresis Collection Facility shall follow the Standard Operating Procedures related to their positions.

C5.6 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.

Explanation:

Personnel are required to adhere to the approved SOPs in their SOP Manual. Although only review every two years is required, when conditions require that a procedure or practice be modified, SOP review and revision must occur in a timely fashion.

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 procedure until they have undergone documented review and training. Clinical Programs 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 procedure.

Evidence:

Inspectors should observe procedures or question personnel regarding how they would perform a procedure compared to the written SOP or policy.

Documentation that approved and implemented procedures or policies 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 procedure and associated revisions to document that each staff member required to review a policy or procedural revision has done so prior to performing a procedure. This could be done via an electronic system that identifies users and records their activity on the system. An effective date will be determined by the appropriate management (e.g. director, QA supervisor) after the necessary amount of staff has been trained. However, each staff member who performs the procedure must complete documentation of training and review of the policy and/or procedure. 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 procedure 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:

C5.7 There shall be a process to address age-specific issues in the Standard Operating Procedures as appropriate.

Explanation:

Depending on the age range of patients treated in the cellular therapy program, Apheresis Collection Facilities should be able to demonstrate the processes by which age-specific issues are addressed. 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. Elderly patients (greater than 65 years of age) should have appropriate access to rehabilitation and social support.

Collection of HPC and/or TC from pediatric donors requires specific policies and procedures 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.

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 parent or legal guardian. Specific consent is required for the use of growth factor, if utilized, 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 parents or legal guardians in accordance with local regulations, assent should also be obtained in an age-appropriate manner.

Collection of HPC or TC 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 frequently have inadequate peripheral vein size to accommodate apheresis needles. In these cases, there must be policies and procedures for central venous access 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.

Evidence:

These policies and procedures should be reviewed by the inspector; an indication of the presence of such procedures should be apparent from review of the Table of Contents of the Apheresis Collection Facility SOP Manual. There should be evidence of training on age-specific issues.

Example(s):

It may be helpful to include a child life specialist, a social worker, or another qualified individual in the consent process to ensure that the minor donor has age appropriate understanding.

STANDARD:

C6 ALLOGENEIC AND AUTOLOGOUS DONOR EVALUATION AND MANAGEMENT

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

Explanation:

Standards in C6 mirror those in B6, reflecting the fact that these responsibilities are usually the primary responsibility of the Clinical Program staff. Apheresis 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 Apheresis 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 ensure the safety of the donor and recipient as well as the safety and efficacy of the stem cell product. For allogeneic donors, additional requirements are detailed in C6.4 to ensure appropriate histocompatibility matching and to protect the recipient from the risks of transmissible disease.

Facilities should endeavor to ensure 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.

These standards cover the requirements for donor (autologous and allogeneic) identification, evaluation and management. The Apheresis 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 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.

In addition, this standard requires that the Apheresis 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.

These standards also require that if allogeneic donors selected for transplant 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. 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.

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):

It is recommended that a separate medical record be maintained for allogeneic donors. For donors with abnormal test results, it is recommended that appropriate follow-up evaluations be completed by either the transplant physician or a referral be made to an appropriate alternative physician.

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>.

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:

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 and parent of the donor who is a minor 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 The donor shall have an opportunity to ask questions.

C6.2.3 The donor shall have the right to refuse to donate.

C6.2.3.1 The allogeneic donor shall be informed of the potential consequences to recipient of such refusal.

C6.2.4 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.

C6.2.4.1 Informed consent from the allogeneic donor should be obtained by a licensed health care professional other than the intended recipient’s primary transplant physician.

C6.2.5 In the case of a minor donor, informed consent shall be obtained from the donor’s parent or legal guardian in accordance with applicable laws and regulations and shall be documented.

Explanation:

This standard applies to informed consent for the specific collection procedure. Clinical Programs typically obtain informed consent to donate; Apheresis 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.

Informed consent from the donor and recipient regarding variances to these standards must be clearly documented. The procedure for obtaining consent from donors must comply with applicable laws and regulations. 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 ensure 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.

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 should be consented by a member of the team other than the primary physician of the intended recipient or a clinician who is not a member of the BMT team but is knowledgeable with the collection procedures.

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:

C6.2.6 The allogeneic donors shall give informed consent and authorization in advance to release the donor's health information to the transplant physician and/or the recipient as appropriate.

C6.2.7 Documentation of consent shall be available to the Apheresis Collection Facility staff prior to the collection procedure.

Explanation:

The purpose of this standard is to protect donor confidentiality regarding his or her health information. The Apheresis 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 authorization to release relevant donor health information may verify compliance.

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:**C6.3 ALLOGENEIC AND AUTOLOGOUS DONOR SUITABILITY FOR CELLULAR THERAPY PRODUCT COLLECTION**

C6.3.1 There shall be criteria and evaluation procedures in place to protect the safety of donors during the process of cellular therapy product collection.

Explanation:

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

STANDARD:

C6.3.1.1 The Apheresis Collection Facility shall ensure that any abnormal findings are reported to the prospective donor with documentation in the donor record of recommendations made for follow-up care.

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

Explanation:

It is highly recommended that an independent physician or health care professional be utilized for evaluating donor suitability to reduce potential bias of the recipient's physician(s) or health care professional(s). This individual should not be the primary transplant physician of the patient 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 transplant 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.

Donor suitability refers to issues that relate to the general health of the donor and protection of donor safety.

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 abnormalities be communicated to the donor and that recommendations be made to that donor for follow-up care. The Apheresis Collection Facility must confirm these actions are documented in the donor's medical record.

Evidence:

Documentation in the medical record that prospective donors were informed of the abnormal findings including recommendations for work-up, treatment, and follow-up. 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 Apheresis Collection Facilities. The inspector should request to review a chart of an ineligible donor to verify documentation of abnormal results.

Example(s):

The activities may be performed by the Clinical Program conducting tests in relation to donor selection; however, the Apheresis Collection Facility is still responsible for ensuring the actions occurred.

A potential donor could be evaluated by another member of the BMT program or by a clinician who is not a member of the team, 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 Clinical Program.

STANDARD:

C6.3.1.3 Autologous donors shall be tested as required by applicable laws and regulations.

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

C6.3.2.1 Possible need for central venous access.

C6.3.2.2 Mobilization therapy for collection of HPC, Apheresis.

C6.3.3 The donor should be evaluated for the risk of hemoglobinopathy prior to administration of the mobilization regimen.

C6.3.4 A pregnancy assessment shall be performed for all female donors with childbearing potential within seven (7) days preceding donor mobilization, cellular therapy product collection, or initiation of the recipient's preparative regimen, whichever occurs earliest.

Explanation:

Communicable disease testing or screening of autologous donors in connection with cellular therapy product collection is no longer required by these Standards. However, in agreement with C1.3, testing required by applicable laws and regulations is required.

The purpose of this standard is to evaluate the donor for potential risks associated with the collection such as central venous catheters and the use of mobilization agents. Donors need to be assessed for the risks of central venous catheters, including significant complications such as hematomas, pneumothorax, hemothorax, and bacterial infections.

Hemoglobinopathy assessment is recommended since administration of mobilization agents such as G-CSF may pose a risk to the donor as it was associated with morbidity and mortality in donors with Sickle cell disease (HbSS), HbSC, and with compound hemoglobinopathies such as sickle-beta-thalassemia.

Pregnancy assessment is required since the donation of HPC from peripheral blood may pose a risk to the fetus. There should be documentation in the medical record of these results prior to donor mobilization, collection, or the recipient's preparative regimen, whichever occurs earlier.

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., hysterectomy). The purpose of this standard is to prevent donor mobilization and recipient conditioning occurring before finding out that the donor is pregnant.

Donor selection and evaluation is in general the responsibility of the Clinical Program, but the Apheresis Collection Facility is responsible for verifying that appropriate testing and evaluation has been performed.

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.

Pregnancy assessment may include a test, but a test is not required. If a pregnancy test is performed, testing should be performed utilizing serologic assays.

If a cellular therapy product is collected from the donor and subsequently cryopreserved for infusion weeks later, the donor does not have to be reassessed for pregnancy. Also, in a rare event in which the recipient is on a 21-day conditioning regimen, a pregnancy assessment must be performed within seven days prior to beginning that regimen.

STANDARD:

C6.3.5 Laboratory testing of all donors shall be performed by a laboratory accredited, registered, or licensed in accordance with applicable laws and regulations using one or more donor screening tests approved or cleared by the governmental authority.

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 for HPCs and within seven days for leukocyte-rich products prior to or after the collection 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):

Agreements with supplier for IDM testing, and qualification of this supplier, are examples.

Examples of relevant accreditation organizations include CLIA, CAP, ASHI, AABB, and JCAHO.

STANDARD:

C6.3.6 A donor advocate should 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 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 should 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](#)," (Walraven et al, 2010) provides recommendations for donor advocacy in the related transplant setting.

STANDARD:

C6.3.7 Collection from a donor who does not meet Clinical Program collection safety criteria shall require documentation of the rationale for his/her selection by the transplant 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 transplant physician. However, a designee may actually document that decision. The Apheresis 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 its documentation as well as the communication's documentation.

STANDARD:

C6.3.8 Issues of donor health that pertain to the safety of the collection procedure shall be communicated in writing to the Apheresis Collection Facility staff. Collection staff shall document review of these issues prior to collection.

C6.3.9 There shall be a policy for follow-up of donors that includes routine management and the management of donation-associated adverse events.

Explanation:

There should be a policy that provides guidelines for the post-collection care of donors. All donors should be monitored closely following the collection procedure.

Example(s):

The guidelines for post-collection care of donors may include the following short and long-term measures:

1. 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.
2. 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.
3. Discharge instructions should be given.
4. The donor should be given a follow-up appointment in the BMT clinic post donation, if feasible. If the donor leaves the immediate location and cannot return to the clinic, a follow-up evaluation phone call should be made.
5. The donor should be contacted in 1 - 3 weeks for follow-up post donation.
6. Long-term follow up may be defined as recommended by the WHO.

STANDARD:

C6.4 ADDITIONAL REQUIREMENTS FOR ALLOGENEIC DONORS

C6.4.1 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.

C6.4.2 A red cell antibody screen shall be performed on allogeneic recipients.

Explanation:

The donor's and recipient's ABO group and Rh type must be determined and documented prior to the collection. There needs to be documentation in the medical record of these results prior to initiating the collection process.

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 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 personnel. 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.

Discrepancies between the two samples must be resolved before proceeding with the processing or administration of the cellular therapy product. Additionally, it is inappropriate to label a product with historical results of testing. If there is to be a label on the product with this information, the data must be derived from a current sample.

SOPs to manage ABO and Rh mismatches between the donor and recipient should be established and verified by the inspector.

Evidence:

Records of ABO and Rh typing results and antibody screening in the clinical chart records document compliance.

Example:

Allogeneic donors may be tested at the time they are initially evaluated for donor suitability and eligibility and a second test performed at the time of cellular therapy product collection. Alternatively, both tests may be performed prior to collection. Tests can also 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:

C6.4.3 The Apheresis Collection Facility shall comply with B6.4.3 through B6.4.4.8 when primarily responsible for donor screening for transmissible disease.

Explanation:

These Standards and the FDA require that all donors be screened by medical history and risk factors for human transmissible spongiform encephalopathy, 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 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.

STANDARD:

C6.4.4 The Apheresis Collection Facility shall comply with B6.4.5 through B6.4.9 when primarily responsible for infectious disease testing of HPC donors.

Explanation:

Standard C6.4.3 and C6.4.4 only applies to Apheresis Collection Facilities that are primarily responsible for evaluating and testing donors for transmissible and infectious diseases. 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.

Evidence:

If these standards apply, the Apheresis Collection Facility inspector will be responsible for completing the inspector portion of the checklist accordingly.

STANDARD:

C6.4.5 The Apheresis Collection Facility shall comply with B6.4.10 through B6.4.11 when primarily responsible for testing for the selection of allogeneic donors.

C6.4.6 The Apheresis Collection Facility shall ensure 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.

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

C6.4.8 Allogeneic donor eligibility shall be communicated in writing to the Processing Facility.

Explanation:

For allogeneic donors, a physician other than the recipient's physician (e.g., a different BMT physician or a clinician who is not a member of the BMT team 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.

While donor suitability usually refers to issues relate 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.

These standards also require that if allogeneic donors selected for transplant 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.

C6.4.5 only applies to Apheresis Collection Facilities that are primarily responsible for testing allogeneic donors during the donor selection process. This testing is usually conducted by the Clinical Program during the donor selection process. 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.

This standard is meant to require the Apheresis Collection Facility Medical Director or designee to review all donor data prior to collection of HPC or therapeutic cells from peripheral blood, and to document in the record that the donor is appropriate for the intended recipient and is suitable to undergo the collection procedure (“in writing” includes electronic documentation). The health care professional responsible for obtaining the health history must ensure that the donor has confirmed that all the information provided is true to the best of his/her knowledge.

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.

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 Apheresis Collection Facility (or transplant program, if applicable) should have a clearly defined policy or procedure 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 B6.4. However, there must be a procedure for communicating test results of donors who are positive or reactive for CMV antibody.

Evidence:

If the referenced standards apply, the Apheresis Collection Facility inspector will be responsible for completing the inspector portion of the same section accordingly.

Example(s):

It is recommended that the Apheresis Collection Facility utilize a screening tool such as the National Marrow Donor Program’s “Donor Health History Screening Questionnaire.”

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>.

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 (www.factwebsite.org).

STANDARD:

C6.5 DONOR RECORDS

C6.5.1 There shall be a policy covering the creation, regular review, and retention of donor records.

C6.5.2 Apheresis Collection Facility donor records shall include at a minimum the following:

C6.5.2.1 Donor identification including at least name and date of birth.

C6.5.2.2 Age, gender, and medical history, and, if applicable, behavioral history.

C6.5.2.3 Consent to donate.

C6.5.2.4 Results of laboratory testing.

C6.5.2.5 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). 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 for the chosen recipient must be documented. For unrelated donations, when the organization responsible for procurement has limited access to recipient data, the transplanting organization must be provided with donor data relevant for confirming suitability.

- 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.

STANDARD:

C7 CODING AND LABELING OF CELLULAR THERAPY PRODUCTS

C7.1 ISBT 128 CODING AND LABELING

C7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate modifiers and attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

Explanation:

A requirement for product identification is the use of a product’s proper name, attributes, and modifiers according to the standard terminology for cellular therapy products. The terminology that is required is *ISBT 128*, 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 the 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, 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 work of CTCLAG can be found in the following publications:

- Ashford, P. et al: *Standards for the Terminology and Labeling of Cellular Therapy Products*. *Transfusion* 2007; 47:1319-27
- Ashford, P. et al: *ISBT 128 Implementation Plan for Cellular Therapy Products*. *Transfusion* 2007; 47:1312-8

The three main pieces of the standard terminology to unambiguously describe a product are class, modifiers, and attributes. Classes are broad descriptions of products (such as HPC, Apheresis), modifiers describe the next step in categorization (such as Cryopreserved), 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 optional characteristics 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 designed using common, well defined terms that are printed in eye-readable format on the label. 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 modifiers or attributes were included because of the 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 Apheresis 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.

To utilize *ISBT 128* to its full advantage in the unique identification of products worldwide and in the use of common language, facilities should register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each product's unique alphanumeric identifier. Facilities in or affiliated with hospitals may find that their blood bank has already registered and a unique facility code already exists. Stand-alone facilities can individually register and pay a nominal annual membership fee.

Evidence:

Inspectors will inspect the Apheresis 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):

Labels that meet the appropriate information as defined by *ISBT 128* will also comply with these Standards.

STANDARD:

C7.1.2 If the Apheresis Collection Facility has not fully implemented ISBT 128 technology, an implementation plan for the usage of ISBT 128 coding and labeling shall be in place.

Explanation:

The use of *ISBT 128* for all cellular therapy products provides a uniform coding and labeling system worldwide. *ISBT 128* is an international standard for the transfer of information associated with human tissue transplantation, cellular therapy, and blood transfusion. It provides for a globally unique donation numbering system, internationally standardized product definitions, and standard data structures for bar coding and electronic data interchange.

In the previous version of the standards, *ISBT 128* terminology became mandatory. In a survey among cellular therapy facilities worldwide, it has been shown that although *ISBT 128* is being supported by FACT and JACIE accredited facilities, the transition towards full implementation of *ISBT 128* is not yet completed by most of them. In this version of the standards, an implementation plan of *ISBT 128* coding and labeling is mandatory, which has been supported by FACT and JACIE and numerous other organizations in the field for cellular therapy. On the ICCBBA website (<http://www.iccbba.org/subject-area/cellular-therapy>), the most recent versions of the terminology are published. Moreover, the advisory group published a paper to help centers to implement *ISBT 128*.

Evidence:

The cellular therapy coding and labeling advisory group of ICCBBA has published the detailed terminology and the use of these product codes need to be verified. An *ISBT 128* implementation plan describes the steps necessary to reach *ISBT 128* implementation within three years must be present.

Example(s):

ISBT 128 is the subject of a pending decision by the EU on a European Coding System. JACIE inspectors visiting facilities in EU member states should take into account the uncertainty this pending decision causes Apheresis Collection Facilities in terms or regulations in this area.

STANDARD:

C7.2 LABELING OPERATIONS

Explanation:

The labeling SOPs should indicate that there are procedures in place for each of the following:

- Ordering: initial orders and reorders,
- Receipt and quarantine,
- Verification of accuracy,
- Proper storage,
- Version control, and
- Destruction of obsolete or unusable labels.

STANDARD:

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

C7.2.2 The labeling operation for pre-printed labels shall include, at a minimum, the following controls:

C7.2.2.1 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 ensure 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 Apheresis 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 C5.1.7). 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 Apheresis Collection Facility Director, Apheresis Collection Facility Medical Director, or designee can be documented on this form. The same form can be used to document acceptability of the new label and inspection of content by two staff.

STANDARD:

C7.2.2.2 Stocks of unused labels for 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 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 different types of products stored together with no separation.

Evidence:

The inspector should observe that the Apheresis Collection Facility has 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:

C7.2.2.3 Stocks of obsolete labels shall be destroyed.

C7.2.3 Print-on-demand label systems shall be validated to ensure accuracy regarding identity, content, and conformity of labels to templates approved by the Apheresis Collection Facility Director or designee.

Explanation:

These requirements also apply to labels that are printed “on demand.” “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 ensure accuracy regarding identity, content, and conformity to the templates. Personnel do, however, need to confirm that the correct label was printed.

The Apheresis Collection Facility should first develop a validation protocol for implementation of an “on-demand” computer software. Upon implementation of the process, the facility must ensure 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 or cellular therapy program. Any change in the label or label element that would change the interpretation of the label information 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):

For example, changes in the requirement for a uniform product proper name (i.e. from Hematopoietic Progenitor Cells-Apheresis, to HPC, Apheresis) 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 for ten (10) years with inclusive dates of use or as defined by applicable laws and regulations.

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.

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:

C7.2.5 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 Appendix I and II 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.

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 or bacterial contamination that could affect the safety of the product, and clots that could reduce the efficacy of the product.

For Apheresis 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 C11.6

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.

For systems using computer-assisted label verification to ensure label accuracy (such as bar-code scanning), procedures and records should show how the automatic verification works.

Example(s):

Apheresis Collection Facilities may use the manufacturer's label on the product container to affix the final product label. If additional information is needed, the information can be recorded on a tag and attach to the product with a tie if acceptable in accordance with Appendix I.

STANDARD:

C7.2.7 The information entered on a container label shall be verified by at least two (2) staff members.

Explanation:

No fewer than two people must ensure 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 ensure 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.

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, and
- Indelible ink is used (black or blue ink is recommended).

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 and any additional label requirements required by local governmental laws or regulations must be present. The Apheresis Collection Facility should review FDA, EU, and/or other applicable governmental requirements for labeling and format labels accordingly.

Evidence:

The inspector should verify that the appropriate label is present.

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 as indicated in C7.4.

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 also need to be demonstrated to be resistant to alcohol wipes and sprays if they are likely to be subjected to them at collection, in the processing lab 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:

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. Apheresis 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):

Apheresis 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:

The inspector should verify that such labels have been validated. Labels must have been validated to ensure they remain legible under the conditions in which they are used. This is of particular importance for labels used on cryopreserved products.

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, such as during cryopreservation.

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 and to all records describing the handling and final disposition of the product.

C7.3.1.1 The cellular therapy product, concurrent plasma, and donor and product 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.

Each Apheresis Collection Facility must have a procedure 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 cell 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 procedure for labeling the product with 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:

C7.3.2 Apheresis Collection Facilities may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular therapy product.

C7.3.2.1 Supplementary identifiers shall not obscure the original identifier.

C7.3.2.2 The facility associated with each identifier shall be noted on the label.

Explanation:

The Apheresis 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 labeling if this function is being performed by the Apheresis 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 Apheresis Collection Facility may record the supplemental identifier to a tag and attach it to the product.

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 I.

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 I represents minimum requirements, and must be present as indicated at the various stages of product collection, processing, and distribution. Labeling requirements for the partial label and label at completion of collection are listed in Appendix I.

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 Apheresis 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 B6.4 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.

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.

Warning labels with or without a biohazard label 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 I). The exact statements that are required differ for autologous and allogeneic products.

With this edition of the Standards, communicable disease testing is not required for autologous donors 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 donor screening is not performed, these products must be labeled with the statement “Not Evaluated for Infectious Substances.” This statement must be also be 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 TC-T products (allogeneic and autologous products). Testing and screening within 30 days for TC-T cell products as well as HPC products are required under EU guidelines. 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 these Standards may serve as the prescription. As of this writing, no cellular therapy product has reached the level of licensure.

Autologous product labels should be examined to ensure that “Not Evaluated for Infectious Substances” is present when the donor screening and/or testing does not contain all of the elements listed in B6.4.3 through B6.4.7.

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. Cryopreservation labels, 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 Apheresis 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 I. The inspector should further verify that labels are available for every type of cellular therapy product collected, with suitable modifications. Examples of completed labels must not contain blank spaces. "N/A" or "none" should be used as indicated.

Autologous product labels should be examined to ensure that "Not Evaluated for Infectious Substances" is present when the donor screening and testing does not contain all of the elements listed in B6.4 and B6.6. If the Apheresis Collection Facility utilizes a partial label, the inspector must ensure 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 ensure 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 I.

ISBT 128 provides an example of a label that may be used by facilities. This label is in Chapter Five, Product Labeling, in the document titled *ISBT 128 for Cellular Therapy: An Introduction*, available at www.iccbbba.org/CTintrobooklet.pdf.

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."

STANDARD:**C7.5 LABELING AT COMPLETION OF COLLECTION**

C7.5.1 Labeling at the end of collection shall occur before the cellular therapy product bag is disconnected from the donor.

Explanation:

It is important for the collection staff to label the products before disconnecting them from the donor to prevent mix-up. Collection product labels, tie tags, sample tubes and associated forms are labeled completely and legibly before removing them from the proximity of the donor. Labeling of the product before disconnecting it from the donor will prevent mix-up when in a collection area there is more than one donor being collected from.

Evidence:

The inspector should verify that labeling at the completion of the collection occurs before the product is disconnected from the donor and contains all the information listed in Appendix I.

STANDARD:**C7.6 ACCOMPANYING DOCUMENTATION AT THE END OF COLLECTION**

C7.6.1 Cellular therapy products collected in or designated for use in the U.S. shall be accompanied by the elements listed in the Accompanying Documents at Distribution table in Appendix III at the time of distribution.

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 D7.5 and D7.6. 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 infusion, the product infusion form can be used for this purpose. For products that are distributed to another facility, this information must be included (see C11.7 for records to be shared when responsibility for the product is divided). If the Apheresis 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 Apheresis 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).

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>.

Evidence:

The inspector should review the systems in place that ensure the Apheresis Collection Facility has access to source data for the information that must be provided at distribution.

Example(s):

It is permissible to have hard copies of each item physically accompany the product, and in some cases, that may be appropriate, as when a product leaves the Apheresis Collection Facility and is transported to another institution for processing, storage, and/or infusion.

STANDARD:

C7.7 ADDITIONAL DOCUMENTATION AT OR IMMEDIATELY AFTER DISTRIBUTION

C7.7.1 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 Apheresis 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 Apheresis Collection Facility's procedures.

Example(s):

Related documentation that allogeneic donor eligibility was completed during or after the use of the product is in the patient's collection records. Urgent medical needs documentation to release product should also be present.

STANDARD:

C8 PROCESS CONTROLS

C8.1 Collection of cellular therapy products shall be performed according to written procedures in the Apheresis Collection Facility's Standard Operating Procedures Manual.

Explanation:

This standard applies to marrow cells and peripheral blood cells used as HPC and/or as TC.

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.
- Storage times and conditions (including temperature).
- Procedures for transport and/or shipping of the cells.
- Methods for detection of clerical errors.
- Procedures for quality testing.

Evidence:

The inspector should observe a portion of a collection procedure if possible to determine whether or not the personnel follow the SOP and measure that performance against the written procedure. If there is no collection procedure scheduled for the day of the on-site inspection, the inspector should ask the Apheresis 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, the inspector 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 procedures.

Questions may be asked to determine: Are cellular therapy products from different patients stored in the Apheresis 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 Apheresis 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 procedure.

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, or 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 Apheresis 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.

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 ensure 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.

The inspector should review the inventory control process and documentation of supply and reagent examinations at receipt to verify that the Apheresis Collection Facility takes steps to ensure there is no obvious evidence of damage (for example, leakage, damaged box, etc.).

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, Apheresis Collection Facilities are expected to keep up to date on current collection techniques.

Evidence:

The inspector should request certificate of analysis (COA) of the reagents that are approved for human use or of pharmaceutical grade. Package inserts of the reagents and supplies have the information regarding their intended use.

Example(s):

A COA may be obtained from the manufacturer of the reagents and supplies used in the collection procedure. Upon receipt of reagents and supplies, personnel may review package inserts to ensure that there are no changes of the intended use and retain the most current package insert for reference.

STANDARD:

C8.3 Equipment shall be standardized and calibrated on a regularly scheduled basis as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

C8.4 Equipment shall conform to applicable laws and regulations, where applicable.

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 Apheresis 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 ensure 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.

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 procedures 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 Apheresis Collection Facility, such as sterilization equipment, it is the facility's responsibility to ensure that equipment is properly maintained and calibrated. Such records should be available to the inspector.

It is also important to maintain a schedule of equipment cleaning, sanitation, and disinfection that is described by an SOP (see C5.1.14). 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 C5.1.13). 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.

EUD 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 EUDs. Staff using such equipment must have appropriate training. For additional guidelines regarding this requirement, see: <http://ec.europa.eu/enterprise/newapproach/legislation/guide/>.

STANDARD:

C8.5 There shall be written documentation of an interim assessment of donor suitability for the collection procedure performed by a qualified person immediately prior to each collection procedure.

C8.5.1 A complete blood count, including platelet count, shall be performed within 24 hours prior to each HPC collection by apheresis.

C8.5.2 There shall be peripheral blood count criteria to proceed with collection.

Explanation:

Day-to-day management of the donor is the responsibility of the Apheresis Collection Facility. It is incumbent on the collection team to ensure 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 procedures 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.

The collection team must document this evaluation as part of the permanent record of the donor. The evaluation must be performed by a member of the collection team competent in assessing the health status of the donor. Competency should be defined in the Apheresis Collection Facility procedure manual. The Apheresis Collection Facility should have a system in place to confirm donor identity so that all samples, labels, and records are appropriately and consistently completed.

A unique donor/ file should be generated in which all pertinent documentation related to the collection may be assembled, including such items as physician orders, consents, worksheets, logs, pre-collection laboratory data, and cellular therapy product transport and/or shipping records. This file may also contain the product processing and disposition records.

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:

C8.6 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 initially 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 ensure 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),
- Date and time of collection,
- Date and time the cells are needed by the recipient,
- Cell type (HPC or TC),
- Source of cells (marrow or peripheral blood),
- 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
- Pre- and post-collection laboratory result guidelines.

Pre- and post-collection laboratory result guidelines may include relevant hematologic and biochemical analyses. SOPs should outline how the Apheresis Collection Facility will handle patients whose hematology lab values and/or electrolytes are outside of acceptable ranges.

Evidence:

The inspector should confirm that the written order meets the criteria and, if there are deviations, that they were approved.

Example(s):

Written orders will clarify the desired end result of a collection procedure. The information on the written order will help achieve the HPC or TC product cell dose needed for the recipient.

STANDARD:

C8.7 If required, central venous catheters shall be placed by a licensed health care professional qualified to perform the procedure.

C8.7.1 Adequacy of line placement shall be verified by the Apheresis Collection Facility.

Explanation:

Appropriate and safe placement 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 placement of a central venous line by an appropriate method. The method should be adequate to the site of placement (i.e. subclavian/jugular access – fluoroscopy, ultrasound) while femoral line placement could be confirmed by blood return and draw and ultrasonography (if used to aid the placement). The records describing the position of the catheter and the determination that the position is appropriate to proceed with the collection must be available to the collection team. The Apheresis Collection Facility staff must document satisfactory venous access in the donor record.

Prior to HPC or TC collection and use of a catheter, the Apheresis 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 ensure 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 Apheresis Collection Facility.

The inspector may look into the documentation of central line placement by the Apheresis Collection Facility.

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.

STANDARD:

C8.8 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 Apheresis Collection Facility should have a mechanism in place to ensure 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:

C8.9 The Apheresis Collection Facility shall utilize a process for assessing the quality of cellular therapy products to ensure their 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 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 C5.1.6).

The Apheresis Collection Facility Director is responsible for defining release criteria for cellular therapy products distributed by the Apheresis 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 infusion. This information must be clearly outlined in an SOP (see C5.1.10). 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:

- C8.9.1 Methods for collection shall include a process for controlling and monitoring the collection of cellular therapy products to ensure products meet predetermined release specifications.*
- C8.9.2 Methods for collection shall employ procedures validated to result in acceptable cell viability 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.

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 Apheresis Collection Facility should request this information and use it for a retrospective validation of the method of collection. New equipment is qualified for its functionality prior to use.

STANDARD:

- C8.10 Collection methods shall employ aseptic technique to ensure that cellular therapy products do not become contaminated during collection.*

Explanation:

This standard requires the use of aseptic technique as defined in A3 of these Standards. Peripheral blood progenitor cells must be collected by apheresis procedures utilizing commercially obtained disposable sets with sterile transfer bags approved for human use.

The transfer bags should be closed or sealed securely at the collection site, labeled appropriately, and placed in a secondary container such as a zip-type resealable bag prior to transfer to a processing facility, regardless of the distance of transfer. This is to prevent the loss of a portion of the collection, to minimize the potential of post-collection contamination of the cellular therapy product, and to prevent potential spillage of biohazard material in areas where it may pose a risk to employees, visitors, volunteers, or patients.

Evidence:

The inspector should verify the use of such items by the Apheresis Collection Facility. Peripheral blood access and venous catheter access aseptic technique can be verified by monitoring sterility of the cellular therapy products collected.

STANDARD:

C8.11 Collection methods for pediatric donors shall employ appropriate age and size adjustments to the procedures.

Explanation:

See guidance for C5.7.

Evidence:

The inspector should verify that the donor collection record reflects the appropriate parameters for pediatric donors as described in the Apheresis Collection Facility's SOP.

Example(s):

Collection SOPs may reference the method applicable for pediatric donors, such as the use of blood prime.

STANDARD:

C8.12 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 HPC or TC by apheresis or from bone marrow. Commercially available disposable sets are available and should be used for either type of 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 saved as part of the qualification of the vendor. Inspection of collected cellular therapy products for a proper seal may be used as a product release criterion.

STANDARD:

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

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.

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 Apheresis 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 collection record. Use of electronic record should have the concurrent documentation elements.

In the U.S., concurrent record keeping is required in 21 CFR 1271.270(a).

STANDARD:**C9 CELLULAR THERAPY PRODUCT STORAGE**

C9.1 Apheresis Collection Facilities shall control storage areas to prevent mix-ups, deterioration, contamination, cross-contamination, and improper release or distribution of products.

C9.2 Apheresis Collection Facilities shall establish policies for the duration and conditions of storage prior to distribution to a Processing Facility or Clinical Program.

Explanation:

The Apheresis Collection Facility shall establish a process to ensure that cellular therapy products are stored in a manner that maintains their integrity and potency and that ensures that products are not released prematurely 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 Apheresis 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 infusion 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 ensure adequate 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 Apheresis Collection Facility's established storage criteria for all relevant products, and inspect the storage conditions and space to ensure 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.

STANDARD:**C10 CELLULAR THERAPY PRODUCT TRANSPORTATION AND SHIPPING**

C10.1 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 facility personnel.

C10.1.1 The primary cellular therapy product container shall be placed in a secondary container that is sealed to prevent leakage.

C10.1.2 The cellular therapy product shall be transported and/or shipped to the Processing Facility at a temperature defined in the Apheresis Collection Facility Standard Operating Procedure Manual.

C10.1.3 Cellular therapy products that are transported and/or shipped from the collection site to any non-contiguous 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.

C10.1.4 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported by a qualified courier.

C10.2 The cellular therapy product shall be transported and/or shipped with required accompanying records as defined in the Apheresis Collection Facility's Standard Operating Procedure Manual and in compliance with C7.6.

C10.3 There shall be a record of the date and time of cellular therapy product distribution.

Explanation:

Cellular therapy products may be transported and/or shipped from the Apheresis 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 Apheresis Collection Facility, Processing Facility, and Clinical Program regarding transport and/or shipping conditions and the responsibilities of each facility. 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.

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.

These procedures shall ensure 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 that are not adjacent to each other shall always use 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 Apheresis Collection Facility and the Processing Facility varies widely. For situations where transport from the Apheresis 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 Apheresis 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 ensure 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.

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. Outer containers containing cellular therapy products should not be exposed for prolonged periods to extreme heat or cold and should not be exposed to gamma irradiation or X-Ray devices designed to detect metal objects.

Accompanying documentation shall include all documentation of allogeneic donor eligibility as defined in C7.6. It is not necessary that the records in their entirety accompany a cellular therapy product from the Apheresis Collection Facility to the Processing Facility. Donor eligibility documents can be summarized. However the entire document must be readily and easily accessible when needed.

Labeling requirements are defined in Appendices I and II.

Evidence:

The inspector shall determine if the transport procedures in use within the Apheresis Collection Facility are adequate for the conditions.

Example(s):

Cellular therapy products transported from an Apheresis Collection Facility to a Processing Facility located in an adjacent building must be doubled bagged at a minimum. Products transported to a facility by automobile must be placed in a validated outer container that is labeled as described in Appendix II.

STANDARD:

C11 RECORDS

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 receiving institution shall be informed of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

C11.1.2 Records shall be maintained in such a way as to ensure their integrity and preservation.

C11.1.2.1 If records are maintained in more than one location, there shall be a system to ensure prompt identification, location, and retrieval of all records.

C11.1.2.2 Records shall be accurate, legible, and indelible.

C11.1.3 All records and communications between the collection, processing, and transplant facilities, and their patients and donors, shall be regarded as privileged and confidential.

C11.1.3.1 Safeguards to assure this confidentiality shall be established and followed in compliance with applicable laws and regulations.

C11.1.4 Records shall be maintained in one or more forms that are retrievable.

Explanation:

Each Apheresis 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 ensure confidentiality of records, and/or
- 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 ensure prompt identification, location, and retrieval of all records.

The Apheresis 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 in accordance with applicable laws and regulations, or a defined program or institution policy, unless otherwise specified in these Standards.

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:

The inspector should review the Apheresis Collection Facility's records related to QM including documentation of periodic personnel training and cellular therapy product characteristics, and inspect the QM documents to ensure 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.

Explanation:

Since potency and efficacy of the cellular therapy product may be affected by the competency of the individual(s) performing the collection, it is critical that the responsible individual(s) be identified for each significant step. The Apheresis Collection Facility should maintain a comprehensive list of all relevant faculty and support staff with which it is associated.

Evidence:

The inspector should examine paperwork to determine if adequate records are maintained that identify the responsible individual(s) for all significant steps of collection.

Example(s):

This is most easily accomplished by including a place for initials or other identification on relevant worksheets and forms.

STANDARD:

C11.3 Patient 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 is latest.

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.

The Apheresis Collection Facility must have SOPs describing the maintenance of donor and recipient confidentiality (see C5.1.1).

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 US, NMDP requires that consent documents, screening and testing records, and records pertaining to allogeneic HPC(A) or TC-T 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:

C11.4 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 at a minimum: 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 collected in the Apheresis Collection Facility 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 identify and unique identifier to trace the records to the Apheresis 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 US, 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.

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 processed in the Apheresis Collection Facility 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 establish and 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:

C11.6.1.1 In lieu of paper.

C11.6.1.2 To make decisions.

C11.6.1.3 To perform calculations.

C11.6.1.4 To create and/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 Apheresis 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 they are used in lieu of paper, are used to make decisions based upon the data stored and/or created by the electronic record system (including outcome analysis), are used to make calculations via automated functions, and/or are 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 C4.14.1 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, Apheresis Collection Facilities may not have the authority to direct validation studies on these systems.

Evidence:

Inspectors should assess the Apheresis Collection Facility's list of critical electronic record systems to ensure 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.

STANDARD:

C11.6.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to ensure the accuracy, integrity, 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 ensure that all donor, cellular therapy product, and recipient identifiers are unique.

C11.6.5 For all critical electronic record systems, there shall be an alternative system for all electronic records that ensures 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.

C11.6.6 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.

C11.6.6.1 A method shall be established or the system shall provide for review of data before final acceptance.

C11.6.6.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

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 procedures are revised and issues with the use of critical electronic record systems are identified.

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 ensure all data is verified to be correct and to maintain documentation of who has entered pieces of information.

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:

C11.6.7 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.

C11.6.8 For all critical electronic record systems, there shall be validated procedures for and documentation of:

C11.6.8.1 Training and continuing competency of personnel in the use of the system.

C11.6.8.2 Monitoring of data integrity.

C11.6.8.3 Back-up of the electronic records system on a regular schedule.

Explanation:

These standards are not meant to require Apheresis Collection Facilities to assume responsibility for hospital-wide data systems. Any data system that does exist within the scope of control of the facility is required to meet these standards.

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 in lieu of 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 in lieu of paper records. If hard

copies are scanned, there shall be a program that creates searchable documents to facilitate inspection and review.

Each Apheresis 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.

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 in lieu of 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 ensure that problems are reported and resolved.
- 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.

Evidence:

The inspector should determine the scope of electronic records used by the Apheresis Collection Facility and any circumstances where the electronic record is used in lieu of 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):

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 in lieu of 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, etc.) 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 in lieu of 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/transparency/archival_policy/moreq/).

STANDARD:

C11.7 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

C11.7.1 If two (2) or more facilities participate in the collection, processing, or administration of the cellular therapy product, the records of each facility shall show plainly the extent of its responsibility.

C11.7.2 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.

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 Apheresis 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 Apheresis 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, and
- Distribution and storage of cells.

Donor and recipient confidentiality must be maintained through the use of identifiers whenever the identity of the 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. Facilities that participate in programs such as the NMDP will have well-defined procedures for divided responsibility. Applicable rules and regulations regarding the sharing of confidential information must be followed.

It is the responsibility of the Apheresis 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 Apheresis Collection Facility data and verify that the process is in place.

Example(s):

For example, the Apheresis Collection Facility may manufacture cellular therapy products for multiple clinical programs. The facility record should indicate where the product was collected, stored, and/or infused but does not need to contain a record of the supply and reagent lot numbers used for steps performed at the Processing or Clinical Facilities.

STANDARD:**C12 DIRECT DISTRIBUTION TO CLINICAL PROGRAM**

C12.1 Where cellular therapy products are distributed directly from the Apheresis Collection Facility to the Clinical Program for administration or subsequent processing, the Standards related to labeling, documentation, distribution, transportation, and recordkeeping in Sections D7, D8, D10, D12, and the Appendices apply.

Explanation:

If the Apheresis 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, D8, D10 and D12. Rarely, products cannot be distributed as intended or cannot be administered after distribution to the Clinical Program and might be returned to the facility. The facility must have a plan regarding where to store these products in a controlled environment.

See guidance in referenced sections for additional details.

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PART D: PROCESSING FACILITY STANDARDS

- D1 General
- D2 Processing Facility
- D3 Personnel
- D4 Quality Management
- D5 Policies and Procedures
- D6 Process Controls
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- D8 Distribution
- D9 Storage
- D10 Transportation, Shipping, and Receipt
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PART D: PROCESSING FACILITY STANDARDS

STANDARD:

D1 GENERAL

D1.1 These Standards apply to all processing, storage, and distribution activities performed in the Processing Facility on cellular therapy products obtained from living donors.

Explanation:

Part D standards apply to the processing of HPC products, regardless of tissue source (bone marrow, umbilical cord blood, peripheral blood, or other tissue source). These standards also apply to cells derived from any tissue source collected for therapeutic use (TCs) from a living donor. This includes but is not limited to cellular therapy products such TC-T Cells, TC-MS, TC-DC, TC-NK Cells, TC-CTL, and TC-T Reg Cells.

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 programs and facilities 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 these Standards to address processing of tissues or cells that are obtained from cadaveric donors. Nor do these 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 these Standards can only be cited for products specifically covered by these Standards.

Evidence:

Processing Facilities will provide information to FACT or JACIE, as appropriate, regarding the cell types and processing methods within their facilities. This ensures 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 TCs and some HPCs will often be under IND; however, unless otherwise stated, these Standards still apply to those cells and processing methods when within the Processing Facility requesting accreditation. 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 CT products in these facilities can be accredited by JACIE if applied for, 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, and/or accredited with the appropriate governmental authority for the activities performed.

Explanation:

FACT and JACIE are inspection and accreditation programs sponsored by the American and European Societies of 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 these 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 Processing Facility may apply; for example, when a facility is sending or receiving cellular therapy products from outside of its immediate jurisdiction.

Compliance with any of the numerous national or international regulations, or accreditation by any other accreditation body, should indicate that the Processing Facility is safely run and that the personnel are familiar with the principles of Good Laboratory Practice and Good Tissue Practice. However, compliance with other organizations' standards or governmental regulations does not imply that FACT-JACIE Standards have been met. In all cases, governmental regulations supersede any organization's standards if the standards are inconsistent with a specific regulation. However, a FACT-JACIE standard that is more rigorous than a governmental regulation must be followed.

Evidence:

The presence of current certifications, registrations, or licenses for the Processing Facility will demonstrate that the facility has been certified by other organizations and/or competent authorities as required by national or international laws and regulations.

A copy of validated 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, the inspector may ask to see it on site. The Processing Facility Director or Medical Director should know who in the institution is responsible for the registration, and where a copy may be obtained. It is not appropriate to request a faxed copy from the regulatory agency during the on-site inspection.

Example(s):

Products that are cultured prior to use, such as antigen-specific T cell lines (TC-CTL) or mesenchymal stromal cells (TC-MSC), 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) and where those requirements are more stringent than the FACT-JACIE Standards, the regulatory requirements must be followed.

In the U.S., HPC, Apheresis and minimally manipulated TC 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). However, if products are from an unrelated donor, or are extensively manipulated, combined with a device, or if their use is non-homologous (does not perform the same function in the recipient as in the donor), they fall under the 21 CFR 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 Europe Union (EU), both HPC products and TC products fall under the European Union Directive (EUD) 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 EUD 2006/17/EC and EUD 2006/86/EC. Under the EUD directives a tissue establishment license from the Competent Authority (CA) is required and the tissue establishments need to notify the CA on serious adverse events and reactions of tissues and cells.

The EU Directive 2001/83/EC regulates products that are classified as medicinal products (MP). These include somatic cell therapy MPs and gene therapy MPs. The new regulatory framework on Advanced Therapy Medicinal Products (ATMP) is being proposed to include 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. The definition of substantial manipulation is being done by defining 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 manufacturing license is required for the production of these cells. Furthermore, each Member State in the EU may add on additional regulations to the EUDs, which have to be followed, but MS specific regulations will not be specified in the guidance to these Standards.

In the Europe Union, 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. All required activities as described in the Directive 2004/23/EC must be performed, as this has been transposed into the national law.

STANDARD:

D1.3 The Processing Facility, including a Processing Facility Director, a Processing Facility Medical Director, and at least one staff member, shall have been in place and performing cellular therapy product processing for at least twelve (12) months preceding initial accreditation.

Explanation:

Processing Facilities are required to have been in place and operating with trained staff under the direction of a qualified 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 Processing 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.

Evidence:

The inspector should verify that both key staff and management have been in place and operating for one or more years at the time of the initial inspection and confirm that a sufficient amount of processing has been performed to demonstrate compliance with the Standards.

STANDARD:**D2 PROCESSING FACILITY**

D2.1 The Processing Facility shall be of adequate space, design, and location for the intended procedures.

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.

When an accredited Processing Facility is to be relocated, qualification and validation must be performed to ensure the new space meets the Standards. The requirements for maintaining FACT accreditation in the event of relocation are outlined in the FACT Policy 6.1.001 Inspection Process. This includes a description and floor plan of the new facility, QM documents, and relocation date. The policy can be found on the FACT website. 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.

Evidence:

The inspector will tour the Processing Facility during the on-site inspection, including all locations where cellular therapy products are received, processed, stored, and distributed. The inspector should observe the organization, design, location, and amount of space to determine if the facility is adequate for the number and types of procedures it performs.

Example(s):

A cluttered Processing Facility without a defined workflow is evidence that the Processing Facility does not have adequate space or is poorly designed. At a minimum, the inspector should be able to identify where receiving, labeling, processing, storage, and records keeping is taking place.

STANDARD:

D2.1.1 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.

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 Processing 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 and demonstrate segregation of product, supplies, and reagents. For shared equipment, the Processing Facility must have documentation that maintenance schedules are followed.

STANDARD:

D2.1.2 There shall be a process to control storage areas to prevent mix-ups, contamination, and cross-contamination of all cellular therapy products prior to release or distribution.

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 patients must be securely locked. Storage facilities must be provided 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. Physically separate areas, storage devices, or secured segregation within the device must be allocated in both quarantine and released storage locations for holding certain tissue and cells collected in compliance with special criteria. A process must be in place for secure quarantine for the storage of products with incomplete or unacceptable release testing results so as 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.

Evidence:

Processing Facility personnel can be asked to demonstrate the process for release of a cellular therapy product in quarantine so as to confirm that such products cannot be released without proper approvals.

STANDARD:

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

Explanation:

The Processing Facility must be secure. At all times, access to the facility shall be limited to authorized personnel.

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, personnel wear proper identification badges (where those are required), and that the management of the facility is clearly described within an SOP (see D5.1.20).

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). Video monitoring is an alternative and/or complementary method of limiting access to the Processing Facility. The facility should not be used by right of way by personnel who do not work in it.

STANDARD:

D2.1.4 The Processing Facility shall provide adequate lighting, ventilation, access to sinks, and air quality where applicable to prevent the introduction, transmission, or spread of communicable disease.

Explanation:

The physical plant should include ample lighting, a temperature-controlled environment, and access to sinks for hand-washing. The air quality shall be adequate to the type of processing, in accordance with applicable laws and regulations as described in the guidance to D2.3.

Evidence:

Processing 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 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 processing environment is adequate to minimize the risk of introduction, transmission, or spread of communicable disease.

Example(s):

When liquid nitrogen is used in the Processing Facility, proper ventilation is 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.

STANDARD:

D2.2 Critical facility parameters that may affect cellular therapy product processing, storage, or distribution shall be controlled, monitored, and recorded to demonstrate ongoing compliance.

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.

Methods to process cellular therapy products that expose the products to greater risks of contamination or cross-contamination, such as open systems, warrant more stringent environmental controls. If a Processing Facility uses processing methods that may result in contamination or cross-contamination, it must assess if temperature, humidity, ventilation, air quality, and surface contaminants should be controlled. If any of these conditions could result in contamination or cross-contamination, the facility must control them.

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.

There must be ongoing monitoring of any parameters that have been determined to be critical and these should be defined by an SOP and compliance documented through quality records.

Evidence:

If no parameters are controlled, the Processing Facility should provide documentation of its reasoning. 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 Processing Facility should assess the risk that parameters such as temperature and humidity could influence the product quality, spread of contaminants in the environment, or interfere with equipment performance.

STANDARD:

D2.3 When using processing methods that may result in contamination or cross-contamination of cellular therapy products, critical environmental conditions shall be controlled where appropriate for temperature, humidity, ventilation, air quality, and surface contaminants.

D2.3.1 Where appropriate, the Processing Facility shall provide environmental monitoring for microorganisms.

Explanation:

If a Processing Facility uses processing methods that may result in contamination or cross-contamination, it must assess if temperature, humidity, ventilation, air quality, and surface contaminants should be controlled. If any of these conditions are determined to be critical and could result in contamination or cross-contamination, the Processing Facility must control them. Also, staff comfort is also critical to the success of a processing procedure and should be considered when determining environmental conditions requiring control.

The typical Processing Facility may not require a classified environment for the facility provided that processing steps requiring exposure to the environment are performed in a biosafety cabinet (see D6.6.1). However, a facility that extensively manipulates 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 considerations for such processing steps should include temperature and humidity control, ventilation and air filtration, and disinfection of the room and equipment at appropriate times. Environmental monitors for

controlled space should include measures of air quality such as particle counts and microbial colony counts along with control of humidity and temperature to ensure that airborne contaminants are minimized.

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 should be defined by an SOP (see D5.1.17) 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.

STANDARD:

D2.4 The Processing Facility shall be maintained in a clean, sanitary, and orderly manner.

D2.5 There shall be documentation of facility cleaning and sanitation to ensure adequate conditions for proper 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 D5.1.16). 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 three (3) years.

Frequency of cleaning and sanitation should be based on the number and nature of products processed and on incidence of microbial contamination in the Processing Facility. The facility should verify that disinfectants and detergents used are adequate to prevent risk of contamination.

Evidence:

Records of cleaning and sanitation activities 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 the cleaning staff confirming that cleaning was performed according to the method and schedule defined by the appropriate SOP.

STANDARD:

D2.6 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 (for example, 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 D5.1.15). This plan should identify alternative equipment that can be used and should describe how that equipment is qualified for use to ensure 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 procedures for management of materials needed for product processing is acceptable so long as this practice can be confirmed by the inspector as having the desired result.

STANDARD:**D2.7 SAFETY REQUIREMENTS**

D2.7.1 The Processing Facility shall be operated in a manner designed to minimize risks to the health and safety of employees, patients, donors, visitors, and volunteers.

Explanation:

This standard applies to all facilities involved in the collection, processing, and administration of cellular therapy products derived from living donors (Clinical Programs and Collection and Processing Facilities).

Processing Facilities should post warning signs wherever radioactive materials are in use. The facility policies and procedures, including housekeeping and waste disposal, must document consistency with good biosafety procedures, including adherence to universal precautions and to governmental regulations regarding safety. 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 have appropriate personal protective equipment available to them. 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 provided. Gloves must be provided 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 D5.1.18).

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:

D2.7.2 The Processing Facility shall have a written safety manual that includes instructions for action in case of exposure to communicable disease or to chemical, biological, or radiological hazards, where applicable.

Explanation:

Each Processing Facility shall have a written safety manual readily available in the facility. There must be policies or procedures describing a general chemical safety plan (see D5.1.19). Policies and procedures describing institutional policies are also acceptable so long as facility-specific requirements are included and there is evidence of document review by relevant personnel.

Evidence:

The inspector will review the written safety manual and verify how personnel are prepared to handle accidents and emergencies and who is responsible for maintaining the emergency supplies and notifying and reporting events when applicable.

Example(s):

The manual may be an institution-wide document available by hard copy or via computer. 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. An SOP that defines the location of hard copies of the institutional safety manual, in the event of computer failure, will suffice.

The Processing 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 safety manual is kept updated with institutional revisions.

STANDARD:

D2.7.3 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.

D2.7.4 Gloves and protective clothing shall be worn while handling biological specimens. Such protective clothing shall not be worn outside the work area.

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 D5.1.21) 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 shredded or destroyed or stored in a secured container before disposal (see D5.1.1). When handling potentially hazardous substances, Processing Facility personnel must use appropriate protective attire. To prevent the spread of hazardous substances outside of the laboratory processing area, protective attire should be removed before leaving the workspace.

Evidence:

The inspector should examine how medical waste and chemicals are being handled and discarded (e.g., incinerator, waste field, etc.) and compare his/her observations with the written protocols. Review of laboratory procedures or policies should find a description for the use of protective attire.

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 disposed in accordance with applicable regulations. Written protocols should describe how the Processing Facility segregates, treats, and disposes of medical waste and identifies personnel responsible for these activities.

STANDARD:

D3 PERSONNEL

D3.1 PROCESSING FACILITY DIRECTOR

D3.1.1 There shall be a Processing Facility Director who is an individual with a medical degree or doctoral degree in a relevant science, qualified by training or experience for the scope of activities carried out in the Processing Facility. The Processing Facility Director may also serve as the Processing Facility Medical Director, if appropriately credentialed.

Explanation:

The Processing Facility Director must be an individual with a medical degree or a doctoral 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 for the scope of activities carried out by the Processing Facility. Experience requirements may exceed those required by these Standards based on applicable laws and regulations.

Evidence:

The Processing Facility Director is required to submit a Curriculum Vitae (CV) that demonstrates training and/or experience. The inspector can review this document for evidence of experience prior to the on-site inspection.

Example(s):

Experience can consist of time spent in training in another facility and/or on-the-job training. The Processing Facility Director's experience and/ or training may include Fellowship and/or Post-Doctoral training in performing or supervising cell processing procedures relevant to cellular therapy.

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 EUD 2004/23/EC).

STANDARD:

D3.1.2 The Processing Facility Director shall be responsible for all procedures, administrative operations, and the Quality Management Program of the Processing Facility, including compliance with these Standards and other applicable laws and regulations.

Explanation:

The Processing Facility Director is responsible for all procedures 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 Processing Facility Director, or designee approved by the Processing Facility Director, required by these Standards include:

- Development of and compliance with the Quality Management Program.
 - Approval of the Quality Management Supervisor.
 - 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.
- Authorize release of products with compromised containers or unverified donor information.
- Authorize 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 facility personnel at all times. The Processing Facility Director's responsibilities should be outlined in a job description or in the SOP Manual for the Processing Facility. If a designee fulfills some of the responsibilities of the Processing Facility Director, the designee should be adequately experienced with a higher degree of responsibility than a staff employee. Ideally, these designees should be supervisors or managers.

Evidence:

Evidence of the availability of the Processing Facility Director may be confirmed by examining documents, records, audits, and other records requiring Processing Facility Director review in order to ensure that he/she is available to the facility personnel when needed. Evidence should also be present to confirm that the responsibilities of the Processing Facility Director are actually performed by the designated individual and in a timely fashion.

STANDARD:

D3.1.3 The Processing Facility Director shall participate regularly in educational activities related to the field of cellular processing and/or transplantation.

Explanation:

The Processing Facility Director is required to 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. The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation

should be in an activity that includes substantive information related to the field of cellular processing or transplantation.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not a Processing Facility Director meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material.

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 the accreditation cycle:

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

Example(s):

Evidence of compliance may include either formal or informal study, such as meeting the requirements of applicable national or international continuing education programs. Presentation of CME or CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. A Processing Facility Director may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and/or publication of a manuscript related to HPC processing).

Grand Rounds may meet the standard as long as they are related to the field of cellular processing or transplantation and the Processing Facility Director is in attendance. If Grand Rounds are to be considered for meeting this standard, it is incumbent on the Processing Facility to clearly outline the subject, location, and date of these activities.

STANDARD:

D3.2 PROCESSING FACILITY MEDICAL DIRECTOR

D3.2.1 There shall be a Processing Facility Medical Director who is a licensed or certified physician with postgraduate training and at least one year practical and relevant experience in the preparation and clinical use of cellular therapy products. The Medical Director may also serve as the Processing Facility Director, if appropriately credentialed.

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 postdoctoral training and at least one year of experience in the preparation and clinical use of cellular therapy products.

The Processing Facility Medical Director must be qualified by training or experience for the scope of activities carried out by the Processing Facility. Experience requirements may exceed those required by these Standards based on applicable laws and regulations.

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 Processing Facility Medical Director is a physician. The inspector can review these documents for evidence of experience prior to the on-site inspection.

Example(s):

Experience can consist of time spent in training in another facility and/or on-the-job training. The Processing Facility Medical Director's experience and/or training may include Fellowship and/or Post-Doctoral training, but must include at least one year of experience in performing or supervising cell processing procedures relevant to cellular therapy for facilities operating in EU countries.

EU regulations require the responsible person to have minimally two years of practical experience in the relevant fields (according to the EUD 2004/23/EC).

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 Medical Director review include:

- Review of adverse events associated with cellular therapy product infusion.
- 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 facility personnel at all times. The Processing Facility Medical Director's responsibilities should be outlined in a job description or in the procedure manual for the Processing Facility.

Evidence:

The inspector must also confirm that the responsibilities of the Processing Facility Medical Director are actually performed by the designated individual in a timely fashion. Evidence of availability may be confirmed by examining documents, records, audits, and other records

requiring Processing Facility Medical Director review in order to ensure that Director is available to the facility personnel when needed.

STANDARD:

D3.2.3 The Processing Facility Medical Director shall participate regularly in educational activities related to the field of cellular processing and/or transplantation.

Explanation:

The Processing Facility Medical Director is required to 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. The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation should be in an activity that includes substantive information related to the field of cellular processing or transplantation.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not a Processing Facility Medical Director meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material.

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 the accreditation cycle:

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

Example(s):

Evidence of compliance may include either formal or informal study, such as meeting the requirements of applicable national or international continuing education programs. Presentation of CME or CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. A Processing Facility Medical Director may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and/or publication of a manuscript related to HPC processing).

Grand Rounds may meet the standard as long as they are related to the field of cellular processing or transplantation and the Processing Facility Medical Director is in attendance. If

Grand Rounds are to be considered for meeting this standard, it is incumbent on the Processing Facility to clearly outline the subject, location, and date of these activities.

STANDARD:

D3.3 QUALITY MANAGEMENT SUPERVISOR

D3.3.1 There shall be a Processing Facility Quality Management Supervisor approved by the Processing Facility Director to establish and maintain systems to review, modify, and approve all policies and procedures intended to monitor compliance with these Standards and/or the performance of the Processing Facility.

Explanation:

The Processing Facility must identify at least one person with responsibility for Quality Management (QM) Supervision. 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 Processing Facility QM Supervisor under ideal circumstances would be an individual with at least an undergraduate degree or equivalent in the field of health sciences or biological sciences who has training in the field of cellular therapy product processing. However, individuals with education or experience with either QM or cellular therapy product processing may still be regarded as fulfilling the minimal qualifications for the job as long as the Processing Facility Director can verify the proficiency of the individual to serve in this capacity.

The QM Supervisor must have an active role in preparing, reviewing, approving, and/or implementing QM policies and procedures and must ensure that they are in compliance with FACT-JACIE Standards and all applicable state and governmental laws and regulations before implementation. A key role of the QM Supervisor is to develop systems for auditing Processing Facility activities to ensure compliance with the written SOPs and policies.

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 QM Supervisor. The Processing Facility Director as specified throughout these Standards may play an active role in reviewing the work of the technologists, including quality management procedures. The Processing Facility Director is ultimately responsible for the QM Plan and proper implementation of the plan for the Processing Facility (see D4.2.2). SOPs should clearly define the role(s) of the Processing Facility Director, Processing Facility Medical Director, the QM Supervisor, and other QM personnel in the QM Program.

Evidence:

The inspector should look for documentation (audit reports, proficiency test reports, etc.) that a QM Supervisor is in place and performs or oversees the functions covered in the Quality Management section of the Standards. During inspection, the inspector may want to inquire about procedures in place to avoid bias when QM supervisors must review their own work.

Example(s):

Formal training may include practical work experience in a facility, fellowship, or a certification program.

FACT-JACIE Standards do not prohibit the QM Supervisor from participating in Processing Facility activities, as many facilities or institutions may not be large enough to support free-standing QM staff. However, the QM Supervisor 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 Processing Facility Director or Processing Facility Medical Director. The QM supervisor can review procedures where they have contributed to the activity following a reasonable time period to reduce the potential for bias. What constitutes a reasonable time lapse may vary based on the type of activity being reviewed. Calculations requiring a double check before proceeding to the next processing step may need to be reviewed within a few minutes or hours, whereas audits more often will be performed weeks or months after the activity that is being audited was performed. The reasonable time period for specific activities to be reviewed may be defined by the Processing Facility's policies and procedures ("facility-defined time period").

The Processing Facility Director or Medical Director can also assume the QM Supervisor role as long as the role does not pose a conflict on proper implementation of QM Plan for the Processing Facility. Such a situation may occur more often in a small Processing Facility (two to three full time employees) where technical responsibilities do not allow time for the activities of QM supervision.

If the QM Supervisor serves an operational role within the Processing Facility, it is acceptable for the individual's job description to state "other duties as assigned," rather than specifically list out quality management supervisory responsibilities as long as there is documentation of who is assigned the supervisor role.

STANDARD:

D3.3.2 The Processing Facility Quality Management Supervisor shall participate regularly in educational activities related to the field of cellular processing and/or quality management.

Explanation:

The amount of activity required to meet this standard depends on the type and frequency of the educational activities. The minimum amount of activity in most cases is annually; however, this annual participation should be in an activity that includes substantive information related to the field of quality management and/or cellular processing.

As evident above, there are many ways to meet this standard, and the standard is not meant to be prescriptive. The inspector should use his/her judgment on whether or not a QM Supervisor meets this standard by assessing not only the number of activities participated in, but also the type and volume of the educational material.

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 the accreditation cycle:

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

Example(s):

Evidence of compliance may include either formal or informal study, such as meeting the requirements of applicable national or international continuing education programs. Presentation

of CME or CPD lectures, papers at scientific meetings, or publication of manuscripts related to transplantation may also meet this standard. Educational activities do not necessarily have to require large time or financial resources; for example, participation in webinars or review of pertinent articles throughout the accreditation cycle may also meet this standard.

For example, the annual meeting of several professional societies includes information directly related to the field over the course of several days. Attendance of this annual meeting each year within the accreditation cycle would demonstrate compliance with this standard. Annual meetings, however, are not required. A Quality Management Supervisor may be considered to have participated in an adequate amount of activity if the type and volume of educational material received is similar to what would be received at an annual meeting (for example, three to five webinars and/or publication of a manuscript related to HPC processing).

Grand Rounds may meet the standard as long as they are related to the field of cellular processing or quality management and the Quality Management Supervisor is in attendance. If Grand Rounds are to be considered for meeting this standard, it is incumbent on the Processing Facility to clearly outline the subject, location, and date of these activities.

STANDARD:

D3.4 STAFF

D3.4.1 The Processing Facility shall have an adequate number of trained staff for the volume and complexity of all operations.

Explanation:

Parallel to Standards D2.1 and D2.6 requiring adequate facility space and equipment, there must also be sufficient technical and other support staff for the scope and number of services provided. The Processing Facility shall have an adequate number of trained processing personnel to perform all processing activities in compliance with the FACT-JACIE Standards and other applicable governmental laws and regulations. Trained technical personnel sufficient for the type of processing performed and in proportion to the volume of work are required. See D4.3 for specific requirements regarding documentation of personnel training.

Personnel responsible for cell processing must be adequately trained and supervised, and their continued competence must be documented. The Processing Facility Director should indicate personnel responsible for specific activities in the facility, and must confirm that they are approved for the execution of those activities.

Evidence:

The adequacy of staffing may be ascertained by the inspector by reviewing full-time and part-time staffing levels; looking at staff turnover; and reviewing of the frequency and types of errors, accidents, and deviations from SOPs. It may also be useful to talk directly with the technical personnel regarding workload requirements and the adequacy of staffing. The inspector should confirm the documentation of continued competency assessment.

Example(s):

A dated record of training with subsequent observation by the Processing Facility Director, supervisor, QM Supervisor, or trained co-worker will suffice. Proficiency testing done by individual technologists is also useful to document competency.

Media fill procedures can promote individual competency on aseptic working techniques. Participation in CAP proficiency programs for laboratory technologists is also a way to train staff.

STANDARD:**D4 QUALITY MANAGEMENT**

D4.1 The Processing Facility shall establish and maintain a written Quality Management Plan.

Explanation:

Development of a written comprehensive QM Program is often the most challenging and time-consuming exercise that the Processing Facility will encounter when preparing for a FACT or JACIE inspection. This edition of the Standards has a broad scope of requirements of the Quality Plan for the Processing Facility to be in line with cGMP, cGTP, and applicable laws and regulations.

QM involves ongoing assessment of the stability, reproducibility, and effectiveness of critical processes in order to continually improve program efficiency and patient outcomes. Quality assessment findings are compared to pre-established specifications. When pre-established specifications are not met, implementation of corrective or improvement strategies is undertaken and monitored with follow-up assessment to determine the effectiveness of the change.

The QM Plan is the written document that outlines how a Clinical Program will implement its QM Program (quality assurance, control, assessment, and improvement activities). There must be a written QM Plan that describes the Processing Facility's approach to compliance with the elements listed in D4. The specific procedure to be followed for each of these elements does not have to be fully described in the QM Plan, but should be referenced within the plan to the appropriate document where it is described. The QM Plan does not necessarily need to be stand-alone, serving only the facility. However, it remains the responsibility of the facility to ensure that all elements of the QM Program required in D4 are in place and functioning and that documentation of compliance to standards that are not performed by facility staff is available.

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

Evidence:

The written QM Plan for the Processing Facility will be provided to the inspector prior to the on-site inspection. If policies and procedures are referenced in the QM Plan, they must also be submitted in advance to enable the inspector to review the details of the QM program.

An incomplete or poorly written QM Plan is an indication that QM is not deemed an integral and important component of the Processing Facility. Under these circumstances, the inspector should pay particular attention to evaluating the QM efforts of the Processing 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.

Example(s):

For example, for some elements the Processing Facility may choose to participate in an existing quality program in its affiliated hospital. In such a case, the written QM Plan should include all elements listed in the standard and clarify the nature of participation by other areas and/or institutions. An integrated program may have one QM Plan that addresses all aspects of the Clinical Program and Collection and Processing Facilities. Many of the requirements for the QM Program are identical in all three parts, although the activities required for compliance with a given standard may be performed by individuals within only one of the facilities.

STANDARD:

D4.2 The Quality Management Plan shall include an organizational chart of key positions, personnel, and functions within the Processing Facility.

Explanation:

The organizational chart should include the reporting structure for the Processing Facility QM Program in addition to the key positions and the names of the key personnel. The description of the operation of the QM Program should include the mechanisms (meetings), participants, schedule, and documentation. Lines of responsibility and communications must be clearly defined in a way that is understood by all involved.

Evidence:

The inspector should review any documents that support the described organizational structure. The documentation should include the names and responsibilities of all critical staff. The organizational chart for the entire cellular therapy program and 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.

Example(s):

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

If a Processing Facility contracts its processing service to an outside entity, the organizational chart must include the contracted service.

STANDARD:

D4.2.1 The Quality Management Plan shall include a description of how these key personnel interact to implement the quality management activities.

D4.2.2 The Processing Facility Director or designee shall be responsible for the Quality Management Plan as it pertains to the Processing Facility.

D4.2.2.1 The Processing Facility Director or designee shall have authority over and responsibility for ensuring that the Quality Management Program is effectively established and maintained.

D4.2.2.2 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.

D4.2.2.3 The Processing Facility Director or designee shall report on quality management activities, at a minimum, quarterly.

D4.2.2.4 The Processing Facility Director or designee shall report on the performance of the Quality Management Plan, at a minimum, annually. This report shall be provided to the Clinical Program Director, as applicable.

Explanation:

The Processing Facility Director, or a properly qualified designee, is responsible for the QM Plan as it pertains to the Processing Facility. A Processing Facility QM Supervisor must be designated. Any person responsible for overseeing the QM activities should not be directly responsible for review of work solely performed by that person. 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. 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.

QM activities shall be reported, at a minimum, quarterly to review the performance of the QM Plan. This is to ensure that the elements in the QM Plan are relevant and effective, and necessary actions are taken in a timely manner. In addition, an annual report on the overall performance of the QM Plan will be provided to the directorship. 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.

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 to determine who was in attendance and what topics were covered. It is particularly important to ask for QM meeting minutes at a renewal accreditation inspection, representing the time since the previous accreditation, to determine that the QM Program is and has been on-going.

The inspector should ask to review the quarterly reports of the activities and progress of the quality activities as well as the annual report on the effectiveness of the QM Program.

Example(s):

The same person may be responsible for QM of all components of the cellular therapy program or each component may have a distinct individual responsible for QM, as long as there is a mechanism for appropriate disbursement of information to all participating entities.

It may be acceptable for the individual to review their own work product if there is assurance that the final review is non-biased, and there has been sufficient time away from the work for the review to be objective.

Communication is most effectively accomplished by regularly scheduled QM meetings. The minutes and attendance list of regularly scheduled QM meetings are an effective way to document communication of Quality Assessments to key individuals within participating facilities in the cellular therapy program.

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.

STANDARD:

D4.3 The Quality Management Plan shall include, or summarize and reference, personnel education, experience, and training requirements for each key position in the Processing Facility. Personnel requirements shall include at a minimum:

D4.3.1 Current job description for all staff.

D4.3.2 A system to document the following for each staff member:

D4.3.2.1 Initial qualifications.

D4.3.2.2 Orientation.

D4.3.2.3 Initial training.

Example(s):

Topics to be covered in initial training may include cGTPs or other regulatory requirements as applicable.

STANDARD:

D4.3.2.4 Competency for each critical function performed.

D4.3.2.5 Continued competency at least annually.

D4.3.2.6 Training and retraining.

D4.3.2.7 Provisions for continuing education.

D4.3.3 A description of minimal trainer qualifications and a uniform plan for staff training.

Explanation:

A critical position within the Processing Facility is defined as a position that affects the provision of service or product safety and quality. Personnel requirements are to be included in the Processing Facility QM Plan and should ensure that positions are identified and defined for those tasks that are critical to assuring product or service quality. Such positions would include technical processing and quality personnel. These requirements apply to all personnel, including those not directly employed by the Processing Facility but perform processing services.

Since these Standards as well as governmental laws and regulations and their interpretation change on a periodic basis, it is important to provide the opportunity for continuing education in this area to ensure staff is informed.

Initial qualifications generally include minimal educational requirements or formal training that is preferred but not required. Initial training documentation must include each procedure that a specific staff member will perform (as defined in the job description), and should clearly indicate that the staff member has been approved to perform each procedure or function.

Evidence:

The inspector should review training records to insure 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 confirm that such educational opportunities are available. The inspector should review procedures or policies describing the elements of staff training and continued competency as described in D4.3.

The inspector should review the records of one or more employees to ensure that all of the required elements are documented. Documentation of annual competency assessment and continuing education should be verified.

The inspector should trace examples of initials or identification codes to a source document that identifies the full name of the employee and the inclusive dates of employment.

The training plan should also define the minimal qualifications of individuals who can be designated as a trainer.

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.

Legal and regulatory context can be demonstrated by including initial training related to GTP, GMP, these Standards, and other relevant governmental laws and regulations. EU regulations contain some specific requirements for personnel training that are not specifically stated in these 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.

Initial competency and annual continued competency may be assessed by: 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.

Identification through records of the individual performing an activity provides a vital link in assuring that processing steps are performed by qualified and competent personnel, as required by regulations and these Standards. It is essential that there be a mechanism to associate initials or codes to individuals unless a full signature is used in the records.

STANDARD:

D4.4 The Quality Management Plan shall include, or summarize and reference, policies and procedures for development, approval, validation, implementation, review, revision, and archival of all critical processes, policies, and procedures.

Explanation:

Documents serve multiple purposes for the QM Program. Documents provide the structure needed for quality assurance through policies and procedures that control product collection, processing and infusion, ensure quality control using forms and worksheets, and substantiate QM activities with audit reports, outcomes analyses, training records, etc. The QM Plan needs to identify the documents critical to the Processing Facility and describe how they are conceived, generated, implemented, distributed, reviewed, and stored. The QM Plan must further describe how individual parts (including documents) fit together to constitute a process.

These Standards define a process as “A goal-directed, interrelated series of actions, events, or steps.” Although a process could be described in a single SOP (for example, product receipt into the processing facility), other processes may require multiple documents for its performance. Standard D4.4 requires that the QM Plan have methods for all aspects of process development and requires that in addition to the individual steps, the overall process itself must be controlled.

In previous versions of these Standards, this was referred to as protocol development. In these current Standards it is emphasized that protocols should be translated into written procedures that are readily available to staff in order to consistently manufacture reproducible quality products and to correctly put together the multiple pieces that constitute critical processes.

Archiving is specifically mentioned in this standard and is an important element of the QM Program. 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 policies, procedures, and forms to determine if an operational change is the cause.

Evidence:

The inspector should review documented evidence that policy processes and procedures have been written and verified to be accurate and effective and have been approved by the Processing Facility Director prior to implementation.

The inspector will look to see how the Processing Facility controls modifications of documents and whether retrospective review is possible.

Example(s):

For example, the process by which autologous HPC, Apheresis product collections are handled requires multiple procedures, 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. It would also describe the steps for communication between the Processing Facility, the physician, and the Collection Facility regarding target cell doses. The process document would describe how these pieces are put together to ensure that the desired number of HPCs are available for the patient.

This may be documented as part of product development and validation, or it may be based on staff review and comment with suggestions from this review being inserted prior to the distribution and implementation of the final document.

STANDARD:

D4.5 The Quality Management Plan shall include, or summarize and reference, a system for document control. The document control system shall include at a minimum the following elements:

Explanation:

This standard primarily addresses the need for a comprehensive document control system that covers all of the critical documents used by the Processing Facility. The document control system is intended to ensure that document versions are tracked, that they go through a formal review and approval process, and that approved documents cannot be modified without authorization. Certain critical documents must fall under this system as listed in the standard. The Processing Facility Director should determine any additional documents that should also fall under this system. There must be a listing of active critical documents. This list must include all critical documents that are currently in effect.

The Processing Facility must have an SOP outlining the method by which the Processing Facility creates, approves, implements, reviews, and updates its SOPs (the “SOP for SOPs”). As controlled documents, the process for creating and modifying SOPs must include a system for numbering and titling that allows for unambiguous identification of procedures. The numbering system should allow for identification of revisions of the procedure with the same title. The Processing Facility should be consistent in the design of policies, reports, worksheets, and forms. Like SOPs, these are also considered controlled documents and require a numbering and titling system.

The language in the SOP should be clear and allow an appropriately trained individual to achieve the goals of the procedure. The “SOP for SOPs” should be written in the Processing Facility’s standard SOP format.

The proposed change should be reviewed, analyzed for compliance, risk assessment and impact to existing processes, procedures, or policies. After careful review the change must be approved in the same manner as the original process, procedure, or policy. The change must be effectively communicated to all that are impacted prior to implementation of the change.

The actual terminology used in the document control system can be different from the verbiage in the Standards as long as the intent is met. For example, the Standards require an approval date for when key personnel approve a document, and an effective date for when all approvals have been obtained and the document is actually in use by at least one person. Some may call the effective date the “implementation date,” which is acceptable if it meets the definition of effective date.

Personnel are required to adhere to the approved SOPs in their manual. Although only review every two years is required, when conditions require that a procedure or practice be modified, SOP review and revision must occur in a timely fashion. This process must include a description of who may make changes and how these changes are reviewed, approved, documented and implemented by authorized personnel.

Evidence:

The inspector should confirm that the Processing Facilities process for change control is defined in a written policy or procedure. This process should be reviewed to assess if it is effective to

prevent unintended changes to processes, policies, or procedures. The inspector should confirm that documentation exists that these practices are followed.

The inspector should review the entire process by which one or more controlled documents are created, implemented, used, and retired to confirm that the process corresponds to that described in the QM Plan.

The inspector will look to see how the Processing Facility controls modifications of documents, whether retrospective review is possible, and whether previous policies and procedures can be identified.

The inspector should review the process in place for SOP revision. Documentation that staff have reviewed new and revised procedures and received appropriate training before the procedures are implemented should be reviewed by the inspector.

Example(s):

Electronic documents can be protected from inadvertent change by several methods, including using the security features of word processing or spreadsheet program software to lock specific areas, the whole document, or to prevent printing or have printed copies indicated as copies. Control over the location and number of SOP manuals and the photocopying of documents is another method. The intention is to make sure that only the currently approved document is available for use.

It is recommended that there be a specific signoff sheet for every policy and procedure 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:

D4.5.1 Listing of all active critical documents that shall adhere to the document control system requirements. Controlled documents shall include at a minimum:

D4.5.1.1 Policies.

D4.5.1.2 Standard Operating Procedures.

D4.5.1.3 Worksheets.

D4.5.1.4 Forms.

D4.5.1.5 Labels.

D4.5.2 A procedure for preparation, approval, implementation, review, revision, and archival of all policies and procedures.

D4.5.2.1 Archived policies and procedures, 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:

Archiving is specifically mentioned in this standard and is an important element of the QM Program. 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 policies, procedures, and forms to determine if an operational change is the cause. Procedures must be archived minimally for 10 years and the inclusive dates of use for each version documented. Institutional or governmental regulations may require a longer period of retention; if so, the longer period applies.

Evidence:

The inspector should review the SOP archival system, including local requirements.

Example(s):

The archived system may contain items such as date removed, version number, reason for removal, and person who performed removal.

STANDARD:

- D4.5.3 A standardized format for policies, procedures, worksheets, forms, and labels.*
- D4.5.4 Assignment of a numeric or alphanumeric identifier and title to each document and document version regulated within the system.*
- D4.5.5 A procedure for document approval, including the approval date, signature of approving individual(s), and the effective date.*
- D4.5.6 A system to ensure that controlled documents cannot undergo accidental or unauthorized modification.*
- D4.5.7 A system for document change control that includes a description of the change, the signature of approving individual(s), approval date(s), and effective date.*
- D4.5.8 A system for the retraction of obsolete documents to prevent unintended use.*
- D4.5.9 A system for record creation, assembly, review, storage, archival, and retrieval.*
- D4.6 The Quality Management Plan shall include, or summarize and reference, policies and procedures for establishment and maintenance of written agreements with third parties whose services impact the cellular therapy product.*
 - D4.6.1 Agreements shall include the responsibility of the facility performing any step in processing, testing, or storage to comply with applicable laws and regulations and these Standards.*

D4.6.2 Agreements shall be dated, reviewed, and renewed on a regular basis.

Explanation:

Most, but not all, Processing Facilities will have some of the activities or services covered by these 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 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 must be accredited by the World Marrow Donor Association (WMDA). If agreements exist, examples should be reviewed by the inspector for adherence to the Processing 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 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.

This may be accomplished by reviewing the facility's internal and external audit reports, performing onsite inspections for compliance or receiving period performance reports from the facility. There may be other alternatives but the contracting facility must ensure that their contracted services are meeting requirements.

STANDARD:

D4.7 The Quality Management Plan shall include, or summarize and reference, policies and procedures for documentation and review of cellular therapy product efficacy and/or outcome analysis, as appropriate, including at least:

D4.7.1 For HPC products intended for hematopoietic reconstitution, a process for documentation and review of time to engraftment following cellular therapy product administration.

D4.7.2 For other cellular therapy products, the criteria for product efficacy and/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, including adverse events and engraftment in the case of HPC products being used for hematopoietic reconstitution. When HPC products are being used for non homologous use (i.e., HPC-M for the treatment of cardiac failure) other criteria need to be defined and monitored. Acceptable criteria for each cellular therapy product should be developed by the Processing Facility in conjunction with the clinical team and this process defined by an SOP. Evaluation of patient outcome is required to ensure that the highest quality product has been manufactured and distributed. Any unexpected outcomes should be investigated and corrective action or process improvement implemented. The Processing 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 its mere collection. The analysis should include the average (or median) and observed ranges of engraftment for the various products and transplant procedures performed by the program. Product characteristics, especially CD34 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 infused after non-myeloablative treatment.

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. 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.

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):

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 patients 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 quality management meeting where facility personnel are in attendance.

STANDARD:

D4.8 The Quality Management Plan shall include, or summarize and reference, policies, procedures, and a timetable 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 procedures.

D4.8.1 Audits shall be conducted on a regular basis by an individual with sufficient expertise to identify problems, but who is not solely responsible for the process being audited.

D4.8.2 The results of audits shall be used to recognize problems, detect trends, identify improvement opportunities, and implement corrective actions when necessary.

D4.8.3 Audits shall include documentation that external facilities performing critical contracted services have met the requirements of the written agreements.

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 procedure and achieve specified endpoints. Compliance is verified by examination of objective evidence. Audits are conducted to ensure that the QM Plan 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 Processing Facility Director or designee should identify areas to be audited and should ensure that all aspects of the process are being audited with a reasonable audit frequency. The process by which the Processing Facility performs audits must be documented.

Standard D4.8.1 dictates that audits must be performed regularly. This means that the audit process should occur throughout the year with reporting of audit results, corrective action, and follow-up on a regular schedule.

To be effective, audits must be conducted by individuals with sufficient knowledge to identify problems and their probable cause, but should not be performed by the individual directly

responsible for the area being audited. While it is desirable that someone from outside of the Processing Facility conducts the audit, such individuals may not have the needed expertise.

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 ensure 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.

There should be evidence that audit reports are shared with the Processing Facility staff and the Processing Facility Director and Medical Director as appropriate and the Program Director, Collection Facility Director, and others with potential interest.

Evidence:

The inspector should review the audit process and example audits to determine that this is an ongoing process. Corrective actions or process improvement activities that are based on audit findings should be available in the QM records.

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.

The inspector may review audit schedules and results, but it is not the intent to use a facility's audits to identify deficiencies during an inspection.

Example(s):

Audit results should be used to identify trends. 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 expected 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, etc.).

Other examples of audits within the Processing Facility include:

- Adherence to policies and procedures (e.g., correct labeling procedures).
- Presence in the facility of written medical orders prior to processing and infusion 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.

STANDARD:

D4.9 The Quality Management Plan shall include, or summarize and reference, policies and procedures on 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 Release of the product, including identification of authorized individuals and criteria for product release.

D4.9.4 Investigation of cause.

D4.9.5 Notification of the recipient's physician, collection facility, and/or any other facility in receipt of the product, as applicable.

D4.9.6 Reporting to regulatory agencies if appropriate.

Explanation:

Standard D6.14 requires that the Processing Facility 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 infusion. Preliminary or final results should be available for cryopreserved products prior to infusion.

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 infused. Policies and procedures are required in all three areas of a cellular therapy program – clinical, collection, and processing - to deal with elements for which that area of the program is responsible. This standard lists the topics that must be addressed in policies and procedures, but does not dictate a single policy or procedure that must be followed.

Policies and procedures must be in place for the timely notification of the Collection Facility and clinical staff of the positive culture result, so that appropriate patient care can be delivered to the donor, and, if the product has already been infused, to the recipient. If the product has been shipped or transported to another Processing Facility, that facility must also be notified. For products found to have positive microbial cultures prior to infusion, procedures should describe notification of the responsible transplant physician, determination of who is authorized to decide whether or not a specific product with a positive culture result will be used, how that decision will be documented, how recipient notification will be handled, labeling of the product to be infused, and reporting of positive culture results to appropriate governmental agencies in accordance with applicable law.

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.

There should be a policy for disposition of a product that is found to be positive for microbial contamination prior to infusion that includes criteria when such products may be used, and, for the Clinical Program, how the recipient is to be notified and provide consent, for release, and notification of recipient and labeling if it were released. Labeling requirements defined should include requirements for the use of a biohazard label and warning statements.

The Processing Facility should have policies that cover timely notification of the transplant physician caring for the patient

Evidence:

The inspector may ask to see the processing record of a cellular therapy product that was found to be contaminated and review how the facility managed the process.

Policies and procedures 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 that might explain the positive result. Since a positive microbial culture is a biological product deviation, all of the requirements of D4.10 also apply.

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 Europe Union, all adverse events shall be reported to the relevant competent authority. In all locations, facilities must have policies that cover responsibility for reporting (see guidance for D4.10).

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

- Review of processing records for any indication of breach in sterile technique or other adverse event, particularly if extensive processing was required.
- Documentation of proper equipment cleaning, particularly for the biological safety cabinet.
- Review of environmental conditions for sources of possible contamination (BSC sterility testing, particle counts).
- Review of staff competency for possible trends.
- Follow up and review of findings from Collections area for possible breach in aseptic, donor sepsis or other issues.
- Follow up of the recipient for adverse reaction to infusion, infection by the contaminating organism, or other adverse event.
- Report to regulatory agencies as appropriate.

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 procedures for errors, accidents, adverse events, biological product deviations, variances, and complaints.

D4.10.1 Policies and procedures shall include methods for:

D4.10.1.1 Detection.

D4.10.1.2 Investigation.

D4.10.1.3 Evaluation.

D4.10.1.4 Documentation.

D4.10.1.5 Reporting.

D4.10.1.6 Corrective action.

D4.10.1.7 Follow-up for effectiveness of corrective action.

D4.10.2 Documentation of each adverse event associated with a cellular therapy product shall be reviewed in a timely manner by the Processing Facility Director and/or Processing Facility Medical Director, as appropriate.

D4.10.3 A written description of adverse events shall be made available to the recipient's physician and the collection facility, if appropriate.

D4.10.4 When applicable, adverse events shall be reported to appropriate regulatory agencies within the required timeframes.

D4.10.5 Deviations from Standard Operating Procedures shall be documented.

D4.10.5.1 Planned deviations shall be pre-approved by the Processing Facility Director or designee and if medically relevant, by the Processing Facility Medical Director or designee.

D4.10.5.2 Unplanned deviations and associated corrective actions shall be reviewed by the Processing Facility Director or designee, or Processing Facility Medical Director or designee, as appropriate.

D4.10.6 There shall be a defined process improvement plan that includes policies or procedures for the recognition and investigation of the cause of all issues that require corrective action.

D4.10.6.1 The implementation of corrective actions shall include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence.

D4.10.6.2 Follow-up activities shall be conducted to determine if the corrective actions were effective.

Explanation:

There must be a mechanism to report errors, accidents, adverse reactions, and complaints in a timely fashion to key individuals, including the Processing Facility Director, Processing Facility Medical Director, Clinical Program Director, and governmental agencies (as appropriate). The Processing Facility should define errors, accidents, deviations, adverse reactions, and complaints and describe when and how each is reported. See the definitions of each of these types of incidents in Part A Definitions.

It is especially important that there be a clear reporting mechanism by which the Processing Facility informs the Clinical Program how adverse reactions to product infusions are investigated. This includes adverse events which are likely a result of the product infusion such as transmission of a communicable disease directly resulting from infusion of the product. While the Clinical Program is responsible for reporting such adverse reactions to the Processing Facility, the facility must track these reactions to determine if a series of products distributed from the facility had the same result. It is important to maintain a channel of communication with the Clinical Program regarding adverse reactions both in the reporting of those reactions and in the follow-up and evaluation of them.

Deviations from SOPs may be planned or unplanned. Adverse reactions are deviations, and are always unplanned; however, unplanned deviations are not always associated with adverse events or reactions. Planned deviations occur when a specific change is made to a process or procedure without having validated that change in advance. It may involve a process step or a reagent or supply. Such planned deviations require advance approval.

QM involves ongoing assessment of the stability, reproducibility, and effectiveness of critical processes in order for there to be continual improvement of processing efficiency and quality as well as improved patient outcomes. QM assessment findings are compared to pre-established specifications. When pre-established specifications are not met, there must be an investigation to determine the cause. Based on this investigation, implementation of corrective or improvement strategies is undertaken and monitored with follow-up assessment to determine the effectiveness of the change.

Corrective actions should, at a minimum, address:

- Identification of the cellular therapy product affected and a description of its disposition, where relevant;
- The nature of the problem requiring corrective action;
- A description of the corrective action taken;
- The date(s) of implementation of the corrective action; and
- Follow-up of the effectiveness of the corrective action, where relevant.

Evidence:

The detection, investigation and reporting of adverse reactions should be defined in an SOP or policy that can be reviewed. Files of adverse reactions should be available containing evidence that adverse reactions are reviewed by the Processing Facility Director and reported as appropriate, to the Clinical Program Director, the Collection Facility, and appropriate governmental agencies.

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

Example(s);

It is recommended that programs also define, document, investigate, take corrective action, report, and track and trend less severe adverse events, such as fever during infusion, fluid overload, etc. This practice may lead to significant process improvements within the program.

Communication of adverse reaction 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.

An example of a deviation is using a reagent in processing that is similar but not identical to the reagent specified in the SOP. The final effect on the product and patient may be minimal, or more significant, depending on the process and the reagent. If that reagent is subsequently demonstrated to be comparable to the originally specified reagent, the effect on the product and patient may be negligible. Alternatively, if the reagent that was used is subsequently found to be contaminated or otherwise unsuitable, there may be significant consequences to the purity or viability of the cellular therapy product. Other examples may include an unexpected failure to engraft after transplantation, an unexplained less than minimal product dose post-production, or an unexpected adverse reaction. This deviation may be planned (for example, there is a shortage of the reagent and the Processing Facility Director approved use of an alternate reagent until the supply is sufficient to meet demand) or the deviation may be unplanned (for example, personnel used the incorrect reagent which was subsequently reviewed by the Processing Facility Director).

The FDA defines an adverse reaction as one involving the transmission of a communicable disease, 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.

They may also include unexpected reactions to the graft that are designated as possibly, probably, or definitely related. For suspected adverse reactions to infusion of products, the results of investigation and any follow-up activities must be documented. Adverse reactions meeting the FDA definition, to products regulated under GTP (allogeneic HPC, Apheresis and HPC, Cord Blood, TC-T) or GMP (products produced under IND or IDE) must be reported to FDA within their specified guidelines.

The EU 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.

A biological product deviation, as defined by the FDA, is an event that represents a deviation from applicable regulations or established specifications that relate to the prevention of communicable disease transmission or HCT/P 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 HCT/P contamination. Such products are released by the Processing Facility for use by Clinical Programs 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 infusion has occurred.

EU Directives 2006/17/EC and 2006/86/EC include equivalent requirements for non-conforming products. How the Processing Facility manages biological product deviations in general should

be addressed by the QM Plan or by other policies or procedures and must be documented. Common biological product deviations encountered involve products with a positive microbial culture (as described in the guidance for standard D4.8) and products from ineligible donors. Specific issues regarding products from ineligible donors are addressed in the guidance for Standard D6.3.

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 you receive that implies the product or service did not meet quality specifications, failed to function as expected, or resulted in an adverse event 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.

STANDARD:

D4.11 The Quality Management Plan shall include, or summarize and reference, policies and procedures for cellular therapy product tracking and tracing that allows tracking from the donor to the recipient or final disposition and tracing from the recipient or final disposition to the donor.

Explanation:

One of the most important audit trails in the Processing Facility allows for tracking and tracing of information about the cellular therapy product at all steps between the donor and the patient. Documentation in the processing record should include the proper product name, unique product identifier and content of the cellular therapy product, identification of the donor, allogeneic donor eligibility status, and the unique identity of the intended recipient. There should also be a means, direct or indirect, that will allow outcome information to be related back to 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 infused, destroyed, released, or used for research, remains in storage, or other disposition. The process for product tracking and tracing must be well defined in policies and procedures.

Evidence:

The inspector should review examples of final labeled products and determine if tracing and tracking from the donor selection through final product disposition and recipient identification is possible. All critical steps should identify who performed the step or action and when it was completed.

Example(s):

A Processing Facility may add a unique product identifier as long as tracking and tracing from the donor to the recipient is possible and as long as that tracking and tracing system complies with all applicable regulations and these Standards.

For example, an HPC apheresis product drawn by the collections area may assign their unique product identifier: KC 12345. The Processing Facility receives this product (KC 12345) and assigns it another unique product identifier according to the Processing Facility's system of identification. Under this system KC 12345 now becomes BM6789. This is acceptable as long

as each product identifier can be used successfully to track and trace the product to both the donor and recipient or other final disposition.

STANDARD:

D4.12 The Quality Management Plan shall include, or summarize and reference, policies and 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 procedure is required for addressing emergencies and disasters (see B5), the facility must have a plan for how to handle interruptions that do not rise to the disaster level. It is appreciated that 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.

Policies, procedures 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):

Previous editions of these Standards specifically required a plan for when electronic record systems cease to function, and this is one example of a situation that would interrupt Processing Facilities. Other examples include drug shortages, power outages, equipment failures, etc.

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 procedures for qualification of critical supplies, reagents, equipment, and facilities.

D4.13.1 Suppliers of critical supplies, reagents, services, and equipment shall be qualified by a method that ensures they are compliant with applicable laws and regulations and these Standards.

Explanation:

Quality can be maintained only if there is control over critical supplies, reagents, equipment, services, and the facility itself. Qualification is defined in these Standards as, “The establishment of confidence that equipment, supplies, and reagents function consistently within established limits.” 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 ensure their proper performance as defined by an SOP (see D5.1.15).

The QM Plan must include a process to qualify reagents and supplies to ensure 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.

Qualification of the suppliers of critical materials and services is essential for the qualification and control of those materials and services. The Processing Facility must have a system in place that ensures that vendors provide materials in a timely and consistent manner that meets the acceptance criteria defined by the facility seeking FACT or JACIE accreditation. Supplier qualification must also ensure that vendors are compliant with applicable governmental laws and regulations and that there is a system in place that is consistent with these Standards, such that they can demonstrate process control.

Suppliers of laboratory services, such as the Flow Cytometry Laboratory or the Microbiology Laboratory that provides product testing, must also be qualified.

Evidence:

The inspector should review documentation that, at a minimum, confirms that specifications for products and services have been defined by the facility, are compliant with regulations and these Standards, and the supplier is meeting these specifications.

Example(s):

For example, the addition of a new controlled rate freezer might require qualification of the freezing program if the new controlled rate freezer is the same make and model as the one currently in use. This would ensure that the freezing parameters meet the predetermined specifications.

There are several ways to qualify a vendor of supplies, reagents, and services. The most effective is for the facility 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, and
- A documented review of the suppliers' past performance history.

Suppliers with pre-existing service agreements preceding the implementation of this FACT–JACIE 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 Processing Facility to identify the cause of service failures and taken corrective actions in the past may serve as documentation of service provider qualification.

STANDARD:

D4.13.2 Reagents that are not the appropriate grade shall undergo qualification for the intended use.

Explanation:

This standard applies to situations where there are no suitable clinical or pharmaceutical grade reagents available for the processing that is being conducted or for reagents being used under approved research purposes. Reagents meeting these criteria shall be qualified. This may include:

- Use under IND, IDE, or other exceptions approved by the appropriate regulatory agency,
- Evidence of extensive experience with the reagent and data showing that no suitable, equivalent reagent of the appropriate grade can substitute, or
- Extensive literature supporting use of the reagent for the specified purpose and data showing that no suitable, equivalent reagent of the appropriate grade can substitute.

If a reagent is not of the appropriate grade, it should be of the highest grade (or purity) available and the Processing Facility must validate that the reagent is safe and effective for the specified purpose.

DMSO not labeled as a cryoprotectant of human cells for human administration requires lot-to-lot qualification. These products are essentially used off-label, and new lots must undergo functional qualification demonstrating that the new lot preserves viability of cells as well as the previous lot. Verification for sterility or endotoxin is not required if the COA states the DMSO is sterile and includes endotoxin determination as negative or below level of determination.

Evidence:

The inspector should review the qualification of the reagent and the validation of the reagent for its intended use.

Example(s):

Qualification of a new reagent used in processing (washing, freezing, or other product manipulation) can be achieved by review of the certificate of analysis and sterility. This document should list contents and/or concentration of the components of the reagent and if the reagent is sterile and safe for human use. Qualification of a supply or reagent means you look at the proof or prerequisites of that supply or reagent to ensure that it will fulfill specified requirements.

For lot-to-lot functional DMSO qualification, the Processing Facility may compare viable cell recovery post-thaw between the previous and current lots using CFU, viable CD34 by flow cytometry, or other validated assay for viable cell recovery.

STANDARD:

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

D4.14.1 Critical procedures to be validated or verified shall include at least the following: processing techniques, cryopreservation procedures, labeling, storage, and distribution.

D4.14.2 There shall be documentation of review and acceptance of validation studies by the appropriate individual from Quality Management.

D4.14.3 Changes to a process shall be verified or validated to ensure that they do not create an adverse impact anywhere in the operation.

D4.14.4 Procedures for manufacturing reagents in-house shall be validated.

Explanation:

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

Verification is the confirmation of the accuracy of something or that specified requirements have been fulfilled. Qualification is another term commonly used in the laboratory and is most similar to verification in that it is the part of the process that confirms functional performance.

Validations can be performed prospectively, concurrently, or retrospectively. Validations should be performed on critical processes, equipment, reagents, and supplies.

In the Processing Facility, the following must be validated or verified:

- Processing procedures (see D4.14.3 and D6.4). 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 (see D10.3). The introduction of a piece of equipment such as a controlled rate freezer of the same model as already present in the Processing Facility would generally require a verification study, whereas the introduction of 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 (see D4.14.4). 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 (or verify) each new lot of the reagent under more limited testing to ensure its function.
- Labels (see D7.2.3 and D7.2.12). 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 I). 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.

- Electronic records system, if applicable (see D12.2.6).

Validation of a new reagent involves actual testing and should be performed using mock products with known values. The validation should test the new reagent to ensure acceptable endpoints can be achieved while maintaining purity, potency and safety of the product processed. Examples of acceptable endpoints may include but are not limited to nucleated cell recovery, viability, sterility, and red cell reduction.

There should be a consistent format for conducting the studies, analyzing the data, drawing conclusions, and documenting the implementation of changes resulting from the investigation. Reports of these activities should be complete, legible, and organized for review. The design of the study should be adequate to determine if the new or revised process achieves the purpose for which it is intended.

The validation studies must include documented review by the QM Supervisor and/or other appropriate individuals from Quality Management.

The intended use of all reagents and supplies must be validated to meet specifications designed to prevent transmission of infectious disease and/or impairment of product function or integrity. Validation may be performed by the Processing Facility or the manufacturer. In the case of manufacturer validation, the certificate of analysis should be available in the facility.

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 to document that the reagent or supply used performs as expected and does not cause harm to the product or the recipient of the product. Supplies or reagents not approved for human clinical use may be used if:

- The supplies or reagents are specified in a procedure 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, or
- The procedure 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.

The intended use of reagents generated in-house for use in progenitor cell processing must be validated and each new lot of reagent must be verified (or qualified) for function.

Evidence:

The inspector should ask to see the SOPs for conducting validation and verification studies. The inspector should review a sampling of validation studies. The inspector should note poorly designed or inadequately performed validation studies during the review process.

Example(s):

A change of reagents used to make up the solution for cryopreservation of HPC(A) would need to be validated to ensure product 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.

STANDARD:

D5 POLICIES AND PROCEDURES

D5.1 The Processing Facility shall establish and maintain policies and/or 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:

The policies and/or procedures required in D4 pertain to the QM Program, whereas those required in this section are operational in nature. This standard requires that each Processing Facility have written policies and/or procedures that comprehensively address all aspects of the Processing 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 Processing Facility to create its document hierarchy how it sees fit. The facility is not required to have both a policy and procedure for each item, nor is a dedicated policy and/or procedure 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 procedures must comply with the document control requirements listed in D4.5. Review and approval of all policies and procedures 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 procedures in Standard D5.1 and the facility's SOP Manual.

The inspector will be provided a Table of Contents for the procedure manual with the pre-inspection material. This Table of Contents must include all policies and procedures required by these 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 procedures and other activities that can only be verified in person at the inspection site.

Example(s):

Policies and procedures 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.

STANDARD:

D5.1.1 Donor and recipient confidentiality.

D5.1.2 Product receipt.

- D5.1.3 Processing and process control.*
- D5.1.4 Prevention of mix-ups and cross-contamination.*
- D5.1.5 Red cell compatibility testing and processing of ABO-incompatible products to include a description of the indication for and processing methods to be used for red cell and plasma depletion.*
- D5.1.6 Cryopreservation and thawing.*
- D5.1.7 Labeling (including labeling of associated forms and samples).*
- D5.1.8 Product expiration dates.*
- D5.1.9 Product storage to include alternative storage if the primary storage device fails.*
- D5.1.10 Release and exceptional release.*
- D5.1.11 Cellular therapy product recall to include a description of responsibilities and actions to be taken, including notification of appropriate regulatory agencies.*
- D5.1.12 Transportation and shipping, including methods and conditions within the Processing Facility and to and from external facilities.*
- D5.1.13 Product disposal.*
- D5.1.14 Reagent and supply management.*
- D5.1.15 Equipment operation, maintenance, and monitoring, to include corrective actions in the event of failure.*
- D5.1.16 Cleaning and sanitation procedures to include identification of the individuals responsible for the activities.*
- D5.1.17 Environmental control to include a description of environmental monitoring plan.*
- D5.1.18 Hygiene and use of personal protective attire.*
- D5.1.19 Infection control, biosafety, and chemical and radiological safety.*
- D5.1.20 Facility management.*
- D5.1.21 Decontamination and disposal of medical and biohazard waste to include Processing Facility-specific requirements where these differ from institutional requirements.*
- D5.1.22 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 procedures are utilized, there must be a defined mechanism for review and approval. Standard D5.1.22 requires that the Processing 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 product is undergoing cryopreservation at the moment of the disaster or what to do if you need to move products. Examples of disasters include fires, hurricanes, floods, earthquakes, nuclear accidents, etc. In cases where institutional policies and procedures are inadequate to meet these Standards or where there are issues that are specific to the Processing Facility, the facility must develop its own policies and procedures.

Evidence:

If a Processing Facility is operated out of a transfusion service and shares certain procedures or policies with the transfusion service, then an index of the shared procedures and policies should also be submitted.

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 individual Clinical Programs:

<http://asbmt.affiniscape.com/associations/11741/files/EmergencyPreparednessGuidelines.pdf>.

STANDARD:

D5.2 The Processing Facility shall maintain a detailed Standard Operating Procedures Manual.

D5.2.1 The Standard Operating Procedures Manual shall include a listing of all current Standard Operating Procedures.

Explanation:

The SOP Manual is a compilation of policies and procedures containing written detailed instructions required to perform procedures. The purpose of the SOP Manual is to maintain the policies and procedures in an organized fashion so that all current documents can be found. Many Processing Facilities have adopted an electronic method of compiling its policies and procedures, which is acceptable. Hard-copy, bound manuals also meet the intent of the standard.

Evidence:

The SOP Manual should be organized in such a manner for the inspector to ascertain that the policies and procedures are comprehensive and define all aspects of the Processing Facility. The inspector should verify the procedure for development and review for all policies and procedures is being followed.

The inspector must verify that all elements of an SOP are present as defined in the "SOP for SOPs," and that there is consistency in format from one SOP to another. The inspector should also ensure that SOPs adhere to the requirements for controlled documents as specified in standard D4.5.

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 inspection for compliance.

Example(s):

A Processing Facility may choose to have one SOP Manual or divide policies and procedures 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 procedure 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 Processing Facility desires.

STANDARD:

D5.3 Standard Operating Procedures shall be sufficiently detailed and unambiguous to allow qualified technical staff to follow and complete the procedures successfully. Each individual procedure shall include:

D5.3.1 A clearly written description of the objectives.

D5.3.2 A description of equipment and supplies used.

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

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 literature, if applicable.

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

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

D5.3.9 A current version of orders, worksheets, reports, labels, and forms, where applicable.

Explanation:

This standard defines the minimum elements required in each SOP. Copies of current versions of worksheets, reports, labels, and forms, where applicable, must be present and may become a part of 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. Review of procedures should include review of the applicable worksheets, forms, and attachments.

The policies and procedures 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 procedures to actually describe the actions that are taken. The minimal elements described in D5.3 should be included on all SOPs; if one of the items is not applicable, this should be indicated with N/A.

FACT-JACIE Standards require documented review of each procedure 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, procedures or policies for reporting adverse reactions to product infusion or procedures 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.

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.

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.

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.

Determination of a mean \pm 1 or 2 standard deviations from such an analysis may be used to define an acceptable range.

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 procedures may be revised throughout the year.

STANDARD:

- D5.4 Copies of Standard Operating Procedures relevant to processes being performed shall be readily available to the facility staff.*
- D5.5 All personnel in the Processing Facility shall follow the Standard Operating Procedures related to their positions.*
- D5.6 Review and/or training by a staff member shall be documented before the staff member is allowed to perform new and revised policies and procedures.*

Explanation:

The written copy or electronic version (with provisions for hard copies as necessary) of the Processing Facility's policies and procedures 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 procedures into different SOP Manuals, facilities may choose to only have necessary procedures to perform specified processes at a workstation. However, all procedures that an employee must comply with must be readily available to him/her for reference when needed.

There must be only one source document created from which review occurs. Any copies of the SOP Manual in use 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 ensure access to the SOPs at all times, even if the network is not available. Policies, procedures, 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.

Before a staff member is allowed to perform new and revised policies and procedures, 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 procedure, but must document an individual's review and/or training before that person uses the revised policy or procedure.

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.

Example(s):

Sometimes a revision to a policy or procedure 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:**D6 PROCESS CONTROLS**

D6.1 There shall be a process for controlling and monitoring the manufacturing of cellular therapy products to ensure products meet predetermined release specifications.

Explanation:

D6 contains standards designed to control the processing of cellular therapy products. While all of the FACT-JACIE Standards are important for process control, the elements in this section are considered to be of primary importance to the safety and quality of the product.

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 or qualified processing procedures and the use of testing to monitor processing can greatly reduce the inherent

variability and result in high quality products. SOPs are required that describe each processing procedure and its associated process control (see D5.1.3).

Evidence:

Processing Facilities will be requested to provide SOP(s) describing the procedures to be followed during the manufacturing of cellular therapy products, including the release criteria.

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:

D6.1.1 The Processing Facility Director shall define tests and procedures for measuring and assaying cellular therapy products to ensure their safety, viability, and integrity and to document that products meet predetermined release specifications. Results of all such tests and procedures shall become part of the permanent record of the product processed.

Explanation:

The Processing Facility Director is responsible for defining release criteria for cellular therapy products distributed by the Processing 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 D5.1.10). All test results that are available at release must be present in the processing record. Certain tests on the product or the donor are required to be performed by these Standards, including:

- Communicable disease testing (allogeneic only)
- HLA typing (allogeneic only)
- 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 Processing 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 Processing Facility Director may not always be required for release from the Processing 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.

If testing is not performed after a given processing procedure, the Processing Facility must document that the procedure does not affect test result.

Example(s):

For cellular therapy products that are CD34-enriched for the purpose of removing mature T cells, testing of the final product must minimally include TNC (required for all processing that affects TNC), sterility testing (required for all products at infusion), 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:

D6.1.2 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, as applicable.

D6.1.2.1 There shall be a mechanism to identify the individual obtaining the sample, the date, the time (if appropriate), and the sample source.

D6.1.2.2 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):

It is recommended that test sample labels include the cellular therapy product unique identifier and the sample source (and if appropriate, the stage of processing), and that there 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:

D6.1.3 There shall be the establishment of appropriate and validated assays and test procedures for the evaluation of cellular therapy products.

D6.1.3.1 For all cellular therapy products, a total nucleated cell count and viability measurement shall be performed.

D6.1.3.2 For HPC products, a CD34 assay shall be performed.

D6.1.3.3 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 target cell population before and after the processing procedures.

D6.1.4 For tests required by these Standards performed within the Processing Facility:

D6.1.4.1 There shall be a process for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments.

D6.1.4.2 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.

D6.1.4.3 Where available, reference material shall be used each day of testing and shown to give results within the defined range established for that material.

D6.1.4.4 Function checks shall be performed for testing instruments, as appropriate, prior to testing donor, recipient, or cellular therapy product samples.

D6.1.4.5 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.

D6.1.5 Tests required by these Standards, not performed by the Processing Facility, shall be performed by a laboratory certified or accredited by the appropriate laboratory regulatory agency.

Explanation:

A limited number of assays are required by these Standards: 1) TNC, 2) viability, 3) CD34 testing after processing that is shown to affect HPC product CD34 content, 4) monitoring assays for target populations after enrichment or depletion, 5) post-processing microbial cultures

(D6.13), 6) ABO group and Rh typing from allogeneic donor blood; testing shall be available on two independently collected samples (D6.20), and 7) communicable disease testing within specified time limits before collection (D6.1.6). Additional tests and test intervals other than those required are to be determined by the Processing Facility and the SOP for a given processing procedure must indicate what tests are required and when during a procedure they are to be performed. The test results should be immediately available for review, preferably in the patient's file.

For the most part the test methods that are used for these assays are not specified by these Standards. Rather, it is up to the Processing Facility to determine what assays are appropriate and to ensure that they have been validated for the cellular therapy products that are being tested. Non-standard testing should be validated and should be performed using appropriate equipment, reagents, and controls.

Minimal tests required by these Standards include assessment of TNC count and cellular therapy product viability, but unlike earlier editions of these Standards, it is not specified when these assays are to be performed. Previously testing was required after collection, but such testing should also be performed at the end of processing if TNC or viability is affected by the processing performed. If a procedure requiring minimal manipulation has been validated to demonstrate that reproducible recovery of cells occurs, repeat cell counts or CD34 cell assessment post-processing are unnecessary.

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 patients whose engraftment appears to be delayed.

Post-thaw assessment of cellular therapy products that are directly thawed and infused 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 Processing 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.

Requirements of the 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 Processing Facility does not have to be formally certified or accredited, there must be a process in place to ensure that the results are accurate. Minimally the reagents used for testing should be confirmed to give the expected results using previously assayed control materials where those are available or compared to the previously used reagent lots. Instruments and test methods should include day of use positive controls and appropriate controls for instrumentation function must be performed. Suitable control materials may not be available for manual procedures commonly performed in Processing Facilities, such as manual cell counts of Trypan Blue viability assessments. In such cases, processing personnel are required to participate in proficiency testing programs (when available) for the procedures and/or tests that they perform. While separate accreditation for the tests performed by the facility may be available, it is not required by these Standards. However, performance of such testing should be consistent with the standards of other such accrediting bodies.

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:

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.

The inspector should perform a review of proficiency testing results, if available.

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.

Example(s):

When processing procedure validation demonstrates a loss of CD34 cells and/or a loss in total nucleated cells, for example, 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 infusion or cryopreservation.

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 ensure 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.

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.

STANDARD:

D6.1.6 Communicable disease testing required by these Standards shall be performed using test reagents or kits approved by the appropriate regulatory authority and performed in an appropriately registered laboratory that is accredited or licensed in accordance with applicable laws and regulations.

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.

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:

D6.1.7 Cellular therapy products that do not meet allogeneic donor eligibility requirements 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.

D6.1.8 Notification of the transplant physician of nonconforming cellular therapy products and approval for their release shall be documented.

D6.2 There shall be a written request from the recipient's physician before processing is initiated 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 infusion (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:

D6.3 For allogeneic cellular therapy products, information required by the Processing Facility prior to distribution of the product shall include:

D6.3.1 A statement of donor eligibility.

D6.3.2 For ineligible donors, the reason for their ineligibility.

D6.3.3 Documentation of urgent medical need and physician approval for use, if applicable.

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 not generally performed by the Processing Facility, but rather by the Clinical Program or Collection 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. See the guidance for D7.8 for additional information regarding product distribution from the facility.

With this edition of the Standards, communicable disease testing is not required for autologous donors in conjunction with cellular therapy 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.

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:

D6.4 For cryopreserved products received from another facility, the Processing Facility shall ensure availability of adequate storage space at the appropriate temperature.

D6.5 Processing procedures shall be validated in the Processing Facility and documented to result in acceptable target cell viability and recovery.

D6.5.1 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. This analysis may be best performed at the time of SOP review.

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. See the guidance for Standard D4.14 for a further discussion of procedure validation.

In some cases the Processing Facility may implement a processing procedure or process that has been validated by another facility and/or has been published. In such cases it may not be necessary to undergo a full validation study; rather the Processing 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 ensure these are being performed as required by these 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 these Standards and have remained unchanged, retrospective or concurrent validation is acceptable. Examples may include controlled rate freezing, cryopreservation using DMSO, automated cell washing, and buffy coat preparation and red blood cell depletion protocols.

STANDARD:

D6.5.2 The Processing Facility shall use validated methods for preparation of cellular therapy products for administration.

D6.5.2.1 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.

D6.5.2.2 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 Processing Facility to verify the processing procedure prior to performing the procedure on products intended for administration to a recipient.

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.

STANDARD:

D6.6 Critical control points and associated assays shall be identified and performed on each cellular therapy product as defined in Standard Operating Procedures.

Explanation:

As specified in D6.1.1, the Processing Facility Director is responsible for defining tests and procedures for measuring and assaying cellular therapy products to ensure 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, such as lot release criteria. 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:

D6.7 Methods for processing shall employ aseptic technique and cellular therapy products shall be processed in a manner that minimizes the risk of cross-contamination.

D6.7.1 Where processing of tissues and cells involves exposure to the environment, processing shall take place in an environment with specified air quality and cleanliness.

D6.7.2 The effectiveness of measures to avoid contamination and cross-contamination shall be verified and monitored.

Explanation:

The simultaneous presence of cellular therapy products from more than one donor in a Processing Facility is a frequent occurrence. Procedures must be in place to prevent the possibility of mix-ups (see D5.1.4) or cross-contamination of products in such circumstances. Procedures 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 infusion. 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 to ensure that there is no mix-up of information.

STANDARD:

D6.8 Equipment, supplies, and reagents used to process cellular therapy products shall be used in a manner that prevents product mix-ups, contamination, and cross-contamination, and that does not compromise product function and integrity.

D6.9 Supplies and reagents used in processing, testing, cryopreservation, and storage shall be controlled by a materials management system that includes requirements for:

D6.9.1 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.

D6.9.2 Records of receipt that shall include the supply or reagent type, quantity, manufacturer, lot number, date of receipt, acceptability, and, as applicable, the expiration date.

D6.9.3 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. 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:

D6.9.4 The 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 D4.13.2 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:

D6.9.4.1 Non-disposable supplies or instruments shall be cleaned and sterilized using a procedure verified to remove infectious agents.

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:

D6.9.5 The use of supplies and reagents in a manner consistent with instructions provided by the manufacturer.

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:

D6.9.6 A process to prevent the use of expired reagents and supplies.

Explanation:

There should be a mechanism to monitor the flow of supplies and reagents within the Processing Facility to prevent the use of outdated supplies and reagents. This system should also be able to identify the location of a given lot of a supply or reagent in the event that there is a manufacturing recall.

Evidence:

The inspector should evaluate the inventory control system to determine if it is adequate to prevent the use of outdated or damaged supplies and reagents.

Example(s):

A first 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:

D6.10 There shall be a system to uniquely identify and track all critical equipment used in the processing of cellular therapy products.

D6.10.1 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, Standard D6.10 requires that there be a system by which the critical equipment can be uniquely identified.

In parallel to the standard for supplies and reagents, 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.

STANDARD:

D6.11 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, disinfection, calibration, and maintenance at prescribed intervals.

D6.11.1 The equipment shall be inspected for cleanliness prior to each use and verified to be in compliance with the maintenance schedule daily 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 facility described intervals. It is also important to maintain a schedule of equipment cleaning, sanitation, and disinfection that is described by an SOP (see D5.1.16).

Evidence:

The inspector should verify that equipment is evaluated for cleanliness and that maintenance records have been reviewed for compliance prior to use on each day of use. The inspector should confirm by visual inspection that equipment can be easily accessed for cleaning, disinfection, and maintenance.

Example(s):

Inspection of equipment cleaning, sanitation, and disinfection may be after each use, on each day of use, or some other interval but the process must be designed to prevent microbial

contamination of cellular therapy products, as well as to prevent transmission of infectious disease and cross-contamination.

STANDARD:

D6.12 The equipment shall be standardized and calibrated on a regularly scheduled basis as described in Standard Operating Procedures and in accordance with the manufacturer's recommendations.

D6.12.1 All equipment with a critical measuring function shall be calibrated against a traceable standard, if available. Where no traceable standard is available, the basis for calibration shall be described and documented.

D6.12.2 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 during the period of uncertainty.

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 ensure that the critical parameters are maintained within acceptable limits at all times. There must be a schedule for equipment maintenance and quality control.

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 procedures should include limits for accuracy and precision.

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.

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 ensure that equipment is properly maintained and calibrated.

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 D5.1.15). 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.

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:

D6.13 There shall be a procedure that addresses the actions to take in the event of equipment malfunction or failure.

D6.14 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.

EUD 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 EUDs. Staff using such equipment must have appropriate training. For additional guidelines regarding this requirement, visit:

<http://ec.europa.eu/enterprise/newapproach/legislation/guide/>.

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, etc.) to ensure 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-slc.gov/dts/otpca/nrtl/index.html>.

STANDARD:

D6.15 The Processing Facility shall monitor and document microbial contamination of cellular therapy products after processing, as specified in Standard Operating Procedures.

D6.15.1 The results of microbial cultures shall be reviewed by the Processing Facility Director or designee in a timely manner.

D6.15.2 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 ensure 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 procedures 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 ensure 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 infused 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 procedures for the management of products with positive microbial culture results are required by standard D4.9. Contaminants should be identified to the level required to allow for antibiotic coverage appropriate to the organism(s) at the time of or following infusion of a known contaminated product.

Evidence:

The inspector should ask if any processing procedures are performed outside of a closed system and ask to review the sterility records for those procedures. The inspector should review sterility report results to 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. Likewise, the inspector should expect to see some action taken to determine the source of contamination.

The inspector should look for systems that allow immediate notification of the Processing Facility when a culture tests positive.

Example(s):

Measures of air quality such as particle counts and microbial colony counts are additional ways to verify the effectiveness of measures to minimize the risk of contamination and cross-contamination.

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.

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.

Following the EUD 2006/86/EC, it has been stated that when tissue and cells are exposed to the environment during processing, without a subsequent microbial inactivation process, an air quality with particle counts and microbial colony counts equivalent to those of Grade A as defined in the current European Guide to Good Manufacturing Practice (GMP), Annex 1 and Commission Directive 2003/94/EC is required with a background environment appropriate for the processing of the tissue/cell concerned but at least equivalent to GMP Grade D in terms of particles and microbial counts. A less stringent environment may be acceptable where it is not technically possible to carry out the required process in a Grade A environment (i.e., due to requirements for specific equipment in the processing area that is not fully compatible with Grade A). It must be demonstrated and documented that the chosen environment achieves the quality and safety required with the intended purpose, mode of application, and immune status of the recipient taken into account.

STANDARD:

D6.16 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.

D6.16.1 Records shall identify the person immediately responsible for each significant step, including dates and times of various steps, where appropriate.

D6.16.1.1 The Processing Facility shall maintain 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. These records shall include dates of employment.

D6.16.2 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. The inspector may observe a random sample of reagents in use to document that these are in-date and appropriately labeled.

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:

D6.17 Lot numbers, expiration dates, and manufacturers of critical reagents and supplies and identification of key equipment used in each procedure shall be documented.

Explanation:

Retention of records that identify the manufacturers and lot numbers of all reagents and supplies used for processing is critical for tracing purposes in the event of a problem, recall, or adverse event.

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.

Example(s):

The inventory control system may be manual or electronic. Ordering and stocking procedures to limit the number of different lots of reagents and supplies in the Processing Facility at a given time may be part of an inventory control program.

STANDARD:

D6.18 The Processing Facility Director or designee shall review the processing record for each cellular therapy product prior to release or distribution.

D6.18.1 The recipient's physician and the Processing Facility Medical Director shall be notified when the clinically relevant processing end-points are not met.

D6.18.2 Notification and appropriate remedial actions, if taken, shall be documented in the processing record.

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.

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:

D6.19 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 recipient of the cellular therapy product, and in compliance with applicable laws and regulations.

Explanation:

Recipients must sign consent forms for any graft manipulation beyond minimal as defined by these 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.”

STANDARD:

D6.20 For allogeneic cellular therapy products containing red blood cells at the time of administration:

D6.20.1 Results for ABO group and Rh type testing shall be available from two independently collected samples. Discrepancies shall be resolved and documented prior to issue of the cellular therapy product.

D6.20.2 Results for a red cell antibody screen 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.

If HPC, Cord Blood products are selected for transplantation, two independent ABO tests can only be performed when additional samples are available for testing.

These 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 D5.1.5). 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 infusion, 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 Processing Facility's responsibilities are and what should be done with the product in the case of an infusion reaction that is suspected to be the result of red blood cell antibodies.

Evidence:

The inspector will look for records of ABO and Rh typing results and antibody screening in the processing chart records.

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. Tests can also be performed on the product itself, although the plasma that would be available for red cell antibody screening would be diluted, potentially causing weak but significant antibodies to be missed.

STANDARD:

D6.21 One or more aliquots representing the cryopreserved cellular therapy product shall be stored.

D6.21.1 Aliquot(s) from cryopreserved cellular therapy products shall be stored under conditions that ensure a valid representation of the clinical product.

D6.21.2 For cryopreserved cellular therapy products with low volume and/or low cellular content when the storage of product aliquots is not feasible, a cryopreserved sample representing the final steps of processing shall be stored and available for future testing.

D6.21.3 Cryopreserved aliquots shall be retained according to institutional Standard Operating Procedures.

Explanation:

This standard requires that one or more aliquots of individual cryopreserved cellular therapy products be available in case further testing of the product is required. Aliquots 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 aliquots 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 infused 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 Processing Facility Director should verify that appropriate consent and/or IRB approval is in place before stored aliquots are used for research projects. Routine tests performed on aliquots for quality control purposes should be determined by the Processing Facility 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 or fresh cellular therapy products, storage of additional aliquots is not possible due to low volume and/or low cellular content of the final product. In such situations, a cell-free aliquot 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 an aliquot shall be determined by the Processing Facility Director.

The cellular therapy product aliquot(s) that are not used for testing must be stored according to institutional SOPs.

Evidence:

The inspector should request an inventory log for aliquots of cryopreserved cellular therapy products that are, or have been, stored.

Example(s):

It is preferred but not required that aliquots 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 aliquot(s) minimally 10 years after the final disposition (infusion, transfer, or discard) of the cellular therapy product or until the patient expires. While there may be scientific value in maintaining product aliquots longer, it is appreciated that cryopreservation storage space may be at a premium. The inspector should review the Processing Facility's policies and procedures for storage of archive samples.

STANDARD:**D7 CODING AND LABELING OF CELLULAR THERAPY PRODUCTS****D7.1 ISBT 128 CODING AND LABELING**

D7.1.1 Cellular therapy products shall be identified according to the proper name of the product, including appropriate modifiers and attributes, as defined in ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.

Explanation:

Product identification must use the product's proper name, attributes, and modifiers according to the standard terminology for cellular therapy products. This terminology can be found in the document titled, *ISBT 128 Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions* at

<http://iccbba.org/uploads/03/ea/03eade50519de4e5fd9c51a92db9a05a/standardterminology.pdf>

This required terminology is *ISBT 128*, 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 the 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, 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 work of CTCLAG can be found in the following publications:

- Ashford, P. et al: *Standards for the Terminology and Labeling of Cellular Therapy Products*. Transfusion 2007; 47:1319-27
- Ashford, P. et al: *ISBT 128 Implementation Plan for Cellular Therapy Products*. Transfusion 2007; 47:1312-8

The three main pieces of the standard terminology to unambiguously describe a product are class, modifiers, and attributes. Classes are broad descriptions of products (such as HPC, Apheresis), modifiers describe the next step in categorization (such as Cryopreserved), 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 optional characteristics 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 designed using common, well defined terms that are printed in eye-readable format on the label. 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 modifiers or attributes were included because of the 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. As an example of appropriate format, the appropriate product name for labeling purposes would be HPC, Apheresis, however, the acronym HPC,(A) would be an abbreviation acceptable in documents but not acceptable for labeling. 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 in the unique identification of products worldwide and in the use of common language, facilities should register with ICCBBA. This allows the creation of a unique facility identification code that becomes part of each product’s unique alphanumeric identifier. Facilities in or affiliated with hospitals may find that their Blood Bank has already registered and a unique facility code already exists. Stand-alone facilities can individually register and pay a nominal annual membership fee.

Evidence:

Inspectors should examine the labels on site and the labeling process and procedures to verify the appropriate use of *ISBT 128* terminology is in use with the regard to class, modifiers and attributes.

STANDARD:

D7.1.2 If the Processing Facility has not fully implemented ISBT 128 technology, an implementation plan for the usage of ISBT 128 coding and labeling shall be in place.

Explanation:

The use of *ISBT 128* for all cellular therapy products provides a uniform coding and labeling system worldwide. *ISBT 128* is an international standard for the transfer of information associated with human tissue transplantation, cellular therapy, and blood transfusion. It provides for a globally unique donation numbering system, internationally standardized product definitions, and standard data structures for bar coding and electronic data interchange.

In the previous version of the standards, *ISBT 128* terminology became mandatory. In a survey among cellular therapy facilities worldwide, it has been shown that although *ISBT 128* is being supported by FACT and JACIE accredited facilities, the transition towards full implementation of *ISBT 128* is not yet completed by most of them. In this version of the standards, an implementation plan of *ISBT 128* coding and labeling is mandatory, which has been supported by FACT and JACIE and numerous other organizations in the field for cellular therapy. On the ICCBBA website (<http://www.iccbba.org/subject-area/cellular-therapy>), the most recent versions of the terminology are published. Moreover, the advisory group published a paper to help centers to implement *ISBT 128*.

Evidence:

The cellular therapy coding and labeling advisory group of ICCBBA has published the detailed terminology and the use of these product codes need to be verified. An *ISBT 128* implementation plan describes the steps necessary to reach *ISBT 128* implementation within three years must be present.

Example(s):

ISBT 128 is the subject of a pending decision by the EU on a European Coding System. JACIE inspectors visiting facilities in EU member states should take into account the uncertainty this pending decision causes Marrow Collection Facilities in terms of regulations in this area.

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 and product samples.

Explanation:

The printing of labels can either be done by pre-printing sets of labels (D7.2.2) to be used during processing or by printing them “on demand” (D7.2.3). 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

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

The inspector should verify that labels are available for every type of product collected, with suitable modifications.

Evidence:

Label content (discussed below) will have been pre-reviewed by the FACT office or by JACIE inspectors. Example labels will be available to the inspector prior to the inspection visit. 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 ensure proper identification of products and product samples. The inspector should observe the location where labels are stored to verify that they are organized in a manner to prevent errors and there is evidence of inventory and version control applicable to labeling system.

The inspector should review all relevant labeling SOPs (see D5.1.7).

Example(s):

Examples of label lay-outs are available on the ICCBBA website. *ISBT 128* provides an example of a label that may be used by facilities. This label is in Chapter Five, Product Labeling, in the document titled *ISBT 128 for Cellular Therapy: An Introduction*, available at <http://www.iccbba.org/uploads/b9/9c/b99cd262a99a0b3590497807cf1ca4c2/CTintrobooklet.pdf>.

STANDARD:

D7.2.2 The labeling operation for pre-printed labels shall include, at a minimum, the following controls:

D7.2.2.1 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 ensure accuracy regarding identity, content, and conformity.

D7.2.2.2 Stocks of unused labels for different cellular therapy products shall be stored in a controlled manner to prevent errors.

D7.2.2.3 Stocks of obsolete labels shall be destroyed.

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, if applicable
- 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 label should be included in this comparison before release.

Furthermore, 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.

Changed labels should reflect version control and evidence of label inventory control.

Evidence:

The process should be reviewed by the inspector to ensure 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 ensure accuracy regarding identity, content, and conformity of labels to templates approved by the Processing Facility Director or designee.

Explanation:

These requirements also apply to labels that are printed “on demand.” “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 ensure 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 the hardware, software and interfaces are installed properly and that the computer systems are maintained and backed up appropriately and includes user access and security requirements.

- Operational qualification (OQ) which tests operating parameters of the system at the limits of the system and including process variables and test cases that include repetition to show system reliability under different conditions of use (typically including worse case).
- Performance qualification (PQ) includes test cases to demonstrate the system works as intended for use.

Evidence:

The validation of labels on demand and the complete process should be reviewed by the inspector to ensure 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.

D7.2.4.1 Representative obsolete labels shall be archived minimally for ten (10) years with inclusive dates of use or as defined by applicable laws and regulations.

Explanation:

The document control system used for these various elements and what constitutes a label version must be defined by the facility or Program. Any change in the label or label element that would change the interpretation of the label information 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.

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.

Evidence:

The label version control should be reviewed by the inspector to ensure 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. Procedures should address the timeframe for retention consistent with applicable laws and regulations.

Example(s):

Changes in the requirement for a uniform product proper name (i.e., from Hematopoietic Progenitor Cells-Apheresis to HPC, Apheresis) or changes in the wording of required statements or warning statements would require a version change to that base 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:

D7.2.5 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.

D7.2.7 The information entered on a container label shall be verified by at least two (2) 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. Details regarding validation of electronic record systems are found in D12.2.6.

No fewer than two people must ensure that manually entered information on the label is accurate. 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 transplantation, the procedure must include details on how to prevent errors. When transferring a cellular therapy product, labeling of new containers or aliquots shall meet the labeling requirements of these Standards, including documentation of verification of correct labeling information, whether by manual or automated methods.

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

Evidence:

The inspector should 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, as well as the date. For systems using computer-assisted label verification to ensure label accuracy (such as bar-code scanning), procedures and records should show how the automatic

verification works. If relabeling is being done, the relabeling procedure must be adequately described and the prevention of errors needs to be addressed.

Logs and forms contain documentation of staff and date of unit specific labeling information checks and validation documentation demonstrates computer-assisted label verification processes function as intended. Staff can describe or demonstrate process for labeling CT products, including transfer of product to new containers or aliquots.

STANDARD:

D7.2.8 Labeling elements required by applicable laws and regulations shall be present.

D7.2.9 All data fields on labels shall be completed.

D7.2.10 All labeling shall be clear, legible, and completed using ink that is indelible to all relevant agents.

D7.2.11 Labels affixed directly to a cellular therapy product bag shall be applied using appropriate materials as defined by the applicable regulatory authority.

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.

This standard does not apply to labels applied to a base label of a cellular therapy product bag.

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.

Explanation:

All labels need to fulfill regulatory requirements. All data fields on a label must be complete; fields for which information is not required must be filled as "NA."

Indelible ink must also be used to record any information entered manually on the label. To support label integrity, computer assisted labeling should include a check to ensure label stock is appropriately aligned in the printer regularly and when label stock is changed and ink is smear-proof. If labels are being used to label cryopreserved products, tests need to be done to validate the ink on the labels. Labels to be fixed on bags needs to be glued onto the bag in a

manner that doesn't affect the cellular therapy product. Labels must have been validated to ensure they remain legible under the conditions in which they are used. This is of particular importance for labels used on cryopreserved products and after thawing of the product in a water bath.

Evidence:

The validation of the labels and the choice of labels (glue) need to be checked by the inspector. Examples of completed labels must not contain blank spaces. "N/A" or "none" should be used as indicated. Use of specific labeling information or wording is required by some countries. Processes should include direction to address labeling requirements of the receiving country, if applicable.

Example(s):

The ICCBBA website, iccbba.org, lists vendors licensed to supply *ISBT 128* software to facilities, including labeling vendors. 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 using tie tags.

STANDARD:

D7.3 PRODUCT IDENTIFICATION

D7.3.1 Each cellular therapy product shall be assigned a unique numeric or alphanumeric identifier by which it will be possible to trace any product to its donor and to all records describing the handling and final disposition of the product.

D7.3.1.1 The cellular therapy product, concurrent plasma, and donor and product samples shall be labeled with the same identifier.

D7.3.1.2 If a single cellular collection 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, where the donor can be identified.

Each Processing Facility must have a procedure 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 both original donations.

Product and donor samples collected at the time of cell 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.

Evidence:

The Processing Facility must have a policy or SOP that clearly describes how product identifiers are assigned that addresses multiple bags from a single donation, products that are pooled for processing or infusion, and product samples. The inspector should verify the way the unique product identifier is assigned and maintained and verify that each is labeled with a unique product identifier separate from the donor 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 product label on each bag (such as Bag 1 of 2, 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.

STANDARD:

D7.3.2 The Processing Facility may designate an additional or supplementary unique numeric or alphanumeric identifier to the cellular product.

D7.3.2.1 Supplementary identifiers shall not obscure the original identifier.

D7.3.2.2 The facility associated with each identifier shall be noted on the label.

Explanation:

Collection Facilities are also required to assign products unique identifiers. In some cases the product identification system may be shared with the Processing Facility but that is not required. 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 supplemental unique identifier is replaced with another identifier, records must link the current unique identifier to the previous one.

Evidence:

If supplementary identifiers are being used, the inspector should inspect the way the identifier is fixed to the products and 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 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.

STANDARD:*D7.4 LABEL CONTENT*

D7.4.1 Each label shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

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:

The required label content as specified in Appendix I 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. Per the COI, 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.

Allogeneic donor eligibility determination is achieved both through infectious disease marker testing and through screening for high-risk behaviors and other potential exposure by use of a donor questionnaire. A biohazard label must be attached or affixed on any product from which a sample from the donor has tested positive for a communicable disease or when the donor

screening indicates a risk factor for relevant communicable disease or disease agents. The one exception is a donor that tests positive for syphilis using a non-treponemal donor screening test licensed, approved, or cleared by the appropriate authorities in accordance with manufacturers' instructions (such as RPR or VDRL) for which the donor tests negative using a specific treponemal confirmatory assay (such as an FTA-ABS). Only in this specific testing combination may a reactive screening test for syphilis be considered as false positive syphilis testing which does not require a biohazard label. Biohazard labeling is required by FACT-JACIE Standards and by cGTP regulations.

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 B6.4 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.

As interpreted by some institutions, the use of a biohazard symbol on a product label where it may be observed by non-medical staff may be considered in violation of applicable confidentiality laws and regulations. In these settings, the biohazard label may be attached using a tie tag in a manner that limits exposure to the casual observer, yet will provide this information to program personnel, as required.

Warning statements with or without a biohazard label are required to be affixed or attached to the product when product testing or screening is positive for infectious disease risk or is incomplete. The exact warning statement, or biohazard labels, required as part of the extended label as accompanying records/ documents differ for autologous and allogeneic products. For allogeneic donors where an eligibility determination is required, this is determined by:

1. If the donor eligibility determination has not been completed and if the donor has any identified increased risk or not, and
2. If the donor eligibility determination was completed and the donor was found to be "eligible" (not increased risk/hazard to the patient) or "ineligible" (testing or screening shows increased risk/hazard to the patient).

For products processed or designated for use in the U.S., the table in Appendix III details the circumstances under which these statements and warnings are required as part of the accompanying documentation and the product labels required for autologous, related and unrelated allogeneic donors and consistent with *the Circular of Information (COI), Table 2. "Biohazard and Warning Labels on Cellular Therapy Products Collected, Processed, and/or Administered in the United States."*

For autologous donors that have been tested or screened by medical history for communicable disease risk factors prior to product collection and found to be positive, the product must bear the same biohazard legend and warning statements as specified in Appendix I, with one exception. Since autologous recipients are not at risk of contracting a communicable disease from their own products, the statement "Warning: Advise patient of communicable disease risk" is not required on autologous product labels even if testing results are positive, although a biohazard label is required.

If the complete donor screening is not performed on an allogeneic or autologous donor these products must be labeled with the statement “Not Evaluated for Infectious Substances.” This statement must also be 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 period for HPC products and TC-T cell products (allogeneic and autologous products) as defined by applicable laws and regulations. In contrast, testing and screening within 30 days for TC-T cell products as well as HPC products are required under the EU Directive. Moreover, autologous as well as allogeneic cells must be evaluated for all the infectious disease markers, with the exception of HTLV, because that is only necessary for high-risk donor/patients. 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.

Labels at the completion of collection are the responsibility of the Collection Facility, so they are not specifically listed in the Processing Facility section. Processing facilities that supply these labels to the collection site should refer to Appendix I for the requirements and to the Collection Facility guidance for specific issues regarding collection labels.

Evidence:

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. 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 offices, as applicable.

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 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/uploadedFiles/COI-CT-2009.pdf>. Autologous product labels should be examined to ensure that “Not Evaluated for Infectious Substances” is present when the donor screening does not contain all of the elements listed in B6.4.3 through B6.4.7.

Inspector should examine labels to ensure that confidential donor information is not included in the label per national and local laws and regulations and that appropriate identities and addresses of 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 US, 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.

A donor is considered “ineligible” per FDA criteria if a donor has increased risk of relevant communicable disease agents or diseases as determined through infectious disease testing and/ or donor health history and screening. 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 requires a biohazard label and the statement “Warning: Advise Patient of Communicable Disease risks.”

The GTP regulations in the U.S. require neither screening nor testing for autologous donors, but if such testing is performed, the product must be labeled in accordance with the results.

In the European Union, the manufacturing of Advanced Therapy Medicinal Products (ATMP) also require the minimal IDM testing as for HPC –products and TC-T cells as described in the European Directive 2006/17/EC.

STANDARD:

D7.5 PARTIAL LABEL

D7.5.1 If the cellular therapy product container is capable of bearing only a partial label, the container shall have affixed, at a minimum, the unique numeric or alphanumeric identifier of the product, the proper name of the product, the appropriate product modifiers, and, if known, the name and identifier of the intended recipient.

D7.5.2 Minimally, the information required in D7.5.1 shall be present on the cellular therapy product during all stages of processing.

D7.5.3 Any container bearing a partial label shall be accompanied by the information required by the Cellular Therapy Product Labeling table in Appendix I. Such information shall be attached securely to the cellular therapy product on a tie tag or enclosed in a sealed package to accompany the product.

Explanation:

If the Processing Facility utilizes a partial label, the inspector must ensure 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 processing 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 modifiers and attributes should be applied to the label while it is undergoing

different stages of processing to ensure 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 facility procedures. An inspector can ask to follow a product through the processing steps at the facility or have staff explain to evaluate labeling compliance.

Example(s):

Additional information may be attached to the product via a tie tag, or included in accompanying documentation, as detailed in Appendix I.

STANDARD:

D7.6 LABELING AT COMPLETION OF PROCESSING

D7.6.1 At the end of processing, the label on the cellular therapy product container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

Explanation:

Refer to Appendix I for the label elements required at the completion of processing, prior to distribution. Note that while all of the listed information may be attached or affixed to the label, due to size limitations, some of the required information may be supplied in the accompanying product records. Much of this information will have to be affixed or attached before the product is distributed.

For all products, a numeric/alphanumeric donor identifier must be affixed to the label per D7.3.1. In the case of an autologous and first or second degree relative, the donor name (or other unique donor identifier such as the medical record number) must also be attached or affixed to the label.

The donor identifier must be distinguished from the product identifier, which is assigned for each collection day. See the guidance for D7.3.1 for a further discussion of product and donor identifiers.

The product proper name must include the modifiers and attributes appropriate for the processing that was performed. The name, modifier(s) and attributes must be affixed to the label together with the unique product identifier.

The date and time at the end of collection should be transferred to the product label (or in the accompanying records) after processing to allow the Processing Facility to make an accurate determination of the age of the product so as to apply to the label an appropriate expiration date and time. The expiration dates and times to use for a given product are not dictated by the FACT-JACIE Standards. Rather, these should be determined for each type of product based on the medical literature and/or on the Processing Facility's own experimental data and must be defined within an SOP (see D5.1.8).

Since the duration limits for storage of cryopreserved products has not been determined experimentally, frozen products are not required to include a specific expiration date. However, once thawed, an expiration date and time must be assigned.

The name and address of the Collection Facility should contain sufficient information to clearly identify the facility and to allow the facility to be contacted if the need arises. The Collection

Facility name and address should not be present on products obtained from unrelated donors so as to protect the donors' privacy; however, the name and address of the collection facility or registry must be part of the extended label. (see Standard D.7.3.3 and Appendix I)

The name, volume, or concentration of residual anticoagulant or other additives used during processing must be attached or affixed to the label, unless a partial label is used that does not support display of this information due to size. Such information may be clinically relevant to the recipient. For example, heparin in products containing some or all of the original plasma may cause bleeding; if the product is clearly labeled clinical precautions can be taken.

The Processing Facility address should be explicit enough to correctly identify the location and contact personnel if questions arise or an emergency occurs during transportation.

Products intended to restore hematopoiesis must have the statement "Do Not Irradiate" affixed or attached to the label after processing. This may be particularly important in Processing Facilities that operate within a blood center or transfusion service where blood products for transplant patients are routinely irradiated.

Products from allogeneic donors that contain red blood cells beyond a limit determined by the Processing Facility must include the results of ABO group and Rh type, either affixed or attached to the product or in the accompanying records. ABO and Rh may also be used to confirm product identity at the time the product is prepared for distribution to prevent transfusion reactions due to the presence of ABO incompatible red blood cells.

Evidence:

The inspector should look for evidence and justification of expiration dates and times on all products. This information should be present in Processing Facility SOPs and/or policies. The recommended storage temperature should include acceptable ranges, e.g., 2-8°C, 20-26°C, <= to -150°C, etc.

Example(s):

Labeled products should be examined to verify compliance with Appendix I and facility specific policies.

STANDARD:

D7.7 LABELING AT DISTRIBUTION

D7.7.1 At the time of distribution, the label on the cellular therapy product container shall bear the information in the Cellular Therapy Product Labeling table in Appendix I.

D7.7.2 The name and address of the facility that determines that the cellular therapy product meets release criteria and the name and address of the facility that makes the product available for distribution shall either appear on the product label or accompany the product at distribution.

Explanation:

The product label prior to distribution requires the same information as at the completion of processing, with the addition of "RBC compatibility testing results" (i.e., cross-match or antibody screening), if applicable. Each Processing Facility must determine which compatibility tests will be performed and under what circumstances. The circumstances under which RBC compatibility testing is to be performed and the process for the management of ABO

incompatible products must be defined by SOPs (see D5.1.5 and D6.19 and its associated guidance).

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 infusion as ABO incompatible. Under these circumstances there should be an SOP in the Clinical Program that explains and justifies the use of ABO incompatible HPCs 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.

The label at distribution should also contain the statement “Properly Identify Intended Recipient and Product” for all products, a statement warning against the use of leukoreduction filters (or conversely specifying the use of a filter that will not remove leukocytes), the statement “For Autologous Use Only” for all autologous products and the statement “For Use By Intended Recipient Only” for all recipients of allogeneic products. If a product is not intended for infusion it must bear the label “For Nonclinical Use Only.” The date of distribution must be in records accompanying the product at distribution (i.e., on the infusion form).

It is important for the staff of the Processing Facility to verify the accuracy of the donor and patient information and to ensure 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 review the labeling process. The inspector should verify that labeling during processing, at the completion of processing and at distribution contains all the information listed in Appendix I and contains appropriate biohazard and warning statements as specified in the 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 these Standards, it may be useful to include information on the cell types present in the product. For TC-T products in particular, the T cell content may be critical to the efficacy or safety of the product and should be confirmed with the physician order prior to infusion. Alternatively, this information may be in the accompanying records and should be verified by the processing and infusion staff at the time the product is distributed for infusion.

Cellular therapy products from unrelated donors may contain just a donor identification number supplied by the registry without identification of the collection center.

STANDARD:

D7.8 ACCOMPANYING DOCUMENTATION AT DISTRIBUTION

D7.8.1 Products collected in or designated for use in the U.S. shall have the elements in the Accompanying Documents at Distribution table in Appendix III accompany the cellular therapy product when it leaves the Processing Facility.

Explanation:

See Appendix III for explanations, evidence and examples for products collected in or designated to the U.S.

STANDARD:

D7.9 DOCUMENTATION IMMEDIATELY AFTER DISTRIBUTION

D7.9.1 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 ensure that patient notification is documented in the clinical record. Forms, logs or other documented records should clearly identify the staff involved in the notification process and timeframes involved.

Evidence:

Procedures and processes should define the circumstances of release of incompletely tested products and staff involved in and responsible for the need to release before allogeneic donor eligibility determination is complete, as well as the processes and documentation used to complete and inform the physician of the results in a timely manner. Inspectors should review the forms, logs or other documentation to ensure 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.

STANDARD:

D8 DISTRIBUTION

D8.1 PROCESSING, TRACKING, AND RELEASE CRITERIA

D8.1.1 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.

D8.1.1.1 Records shall demonstrate trackability from the donor to the recipient and traceability from the recipient to the donor.

D8.1.2 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.

D8.1.2.1 The Processing Facility Director or designee shall give specific authorization for release when the cellular therapy product does not meet technical release criteria.

D8.1.2.2 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.

D8.1.2.3 Documentation of agreement of the Processing Facility Medical Director or designee and the recipient's physician consent to use any non-conforming product shall be retained in the processing record.

D8.1.3 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.

D8.1.3.1 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:

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 infusion and release of the product to an outside facility for additional processing and/or infusion. In both cases, review of the product's processing and tracking records by the Processing Facility Director or designee is required to ensure that the product meets all predetermined criteria for release including those required by these Standards, the Processing Facility's own SOPs, and applicable regulations such as GTP. Documentation of specific areas of review must include:

- Allogeneic donor test results to ensure that the relevant communicable disease agent tests were performed within the required time span.
- Confirmation that testing was performed by an appropriately accredited laboratory.
- Confirmation that the unique product identifier on the label matches the identifier in the facility records and can be traced to the donor records. Tracking and tracing must be bi-directional from donor to recipient and from recipient to donor.
- Review of allogeneic donor medical screening summary records for high-risk behavior and medical evidence of communicable disease. (This could be a signed statement of donor eligibility).
- Review of the entire processing record for completeness, accuracy, and adherence to SOPs.

This review must be documented and the records maintained. If the review is not performed by the Processing Facility Director or Medical Director due to extenuating factors (e.g., late night, etc.) then an alternative method of review and release should be documented. In addition, this alternative method of review must be described in an SOP.

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.

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 ensure that the product is properly labeled, is intact, and is normal in appearance. The individuals may be members of the transplant or patient care team, or the Processing Facility staff.

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 ensure that the required documentation of Processing Facility Director, Processing Facility Medical Director, or designee approval and physician notification is present.

Example(s):

In addition to the elements requiring review listed above, additional release criteria may include CD34 cell content, T cell content, sterility results (for cryopreserved products) or other assay results and are up to the Processing Facility to define for given products or for given clinical protocols.

For failed release criteria that are technical or in some cases 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:

D8.2 DISTRIBUTION RECORDS

D8.2.1 The cellular therapy product processing records shall contain a written or printed record of product distribution including, at a minimum:

D8.2.1.1 The distribution date and time.

D8.2.1.2 Unique identifier of the intended recipient.

D8.2.1.3 The proper product name and identifier.

D8.2.1.4 Documentation of donor eligibility determination.

D8.2.1.5 Identification of the facility that distributed the product.

D8.2.2 The distribution record shall include documentation of:

D8.2.2.1 The identity of the individual who accepted the cellular therapy product.

D8.2.2.2 The date and time of receipt.

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 modifications to 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 infusion, the distribution records must also document receipt of the product by the medical staff responsible for infusion, including the date and time of receipt. Clinical standards in B7.3.2 additionally require documentation in the patient medical record of the unit identifier and a copy of the distribution record. This requirement along with the requirements in D7.7 and D8.2 may be met using a medical record approved "product infusion form," a copy of which can be maintained in the facility processing record. If the product is distributed to another 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.

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. SOP should state that the facility should keep signed product distribution and infusion record in processing record.

STANDARD:

D8.3 CIRCULAR OF INFORMATION

D8.3.1 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 as appropriate:

D8.3.1.1 The use of the cellular therapy product, indications, contraindications, side effects and hazards, dosage, and administration recommendations.

D8.3.1.2 Instructions for handling the cellular therapy product to minimize the risk of contamination or cross-contamination.

D8.3.1.3 Appropriate warnings related to the prevention of the transmission or spread of communicable diseases.

Explanation:

The frequency with which individuals are involved in infusion 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 facility 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 facility, but must include all cell types that are in use. The Processing 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 infusion although this is not required these Standards. The circular must be available to personnel at the sites where infusions 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 procedure 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 infusion.

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 D8.3 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://www.factwebsite.org/Standards_and_Resources/Resources.aspx.

Another method of circulating this information is via an SOP for infusion that describes all elements listed in D8.3.

STANDARD:***D8.4 RETURN OF CELLULAR THERAPY PRODUCTS FROM ISSUE***

D8.4.1 Cellular therapy products accepted for return shall meet the following criteria:

D8.4.1.1 The integrity of the primary container has not been compromised.

D8.4.1.2 The cellular therapy product has been maintained, subsequent to issue, at the specified temperature range during storage and shipping or transportation.

D8.4.2 If the criteria in Standards D8.4.1.1 and D8.4.1.2 have not been met, the Processing Facility shall not return the product to inventory unless the Processing Facility Director or designee gives specific authorization.

D8.4.3 The Processing Facility Director or designee shall consult with the recipient's physician regarding reissue or disposal of the returned product.

D8.4.4 Documentation of the events requiring return, the results of inspection upon return, and subsequent action taken to ensure product safety and viability shall be maintained in the Processing Facility records.

Explanation:

The return of any cellular therapy product issued for infusion is always a deviation from standard procedures, and requires a detailed report as to the cause and action taken by the Processing Facility to ensure product safety. 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 must meet the temperature requirements defined by the facility's SOP and the integrity of the unit must be intact (i.e., the infusion set should not have been inserted), to be eligible for subsequent reissue. Products that do not meet the criteria for reissue because they have been entered, stored at an inappropriate or unspecified temperature or have exceeded the specified expiration date and time cannot be reissued 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 transplant physician. Records for both the initial distribution and any subsequent distribution must be maintained in the 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 exception release SOP (see D5.1.10).

The FACT-JACIE Standards require a procedure for product recall (see D5.1.11), 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 infusion, such an event would be very rare. For laboratories that process products for multiple centers and distribute products in advance of the infusion day, such a situation may be more likely to occur. For all Processing Facilities, a process for product recall must be defined.

Evidence:

The inspector should verify the Processing Facility procedure 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 transplant is delayed.

EU standards require that this process include a description of the responsibilities and actions to be taken along with notification to the proper authority as required by law when a recall occurs.

STANDARD:**D9 STORAGE**

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, in consultation with the Clinical Program, shall establish policies for the duration and conditions of storage and indications for disposal.

D9.2.1.1 Patients, donors, and associated Clinical Programs should be informed about these policies before the cellular therapy product collection.

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

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 ensure that cellular therapy products are stored in a manner that maintains their integrity and potency and that ensures that products are not released prematurely before all release criteria have been met. Standard D2.1.2 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 may occur 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 ensure adequate viability and to decrease the risk of contamination. Processing procedures should specify the temperatures at which products are handled and processed prior to storage. Likewise, transport and shipping temperature both from the Collection Facility to the Processing Facility and at distribution from the Processing Facility must be defined.

The medical literature reports a variety of cryoprotectant agents used to store HPC products, as well as temperatures ranging from -80°C to liquid phase nitrogen (-196°C). The chosen storage temperature must be adequate for the preservation of the desired cell type, as documented either in the medical literature or the Processing Facility's own experience. When possible, storage of cryopreserved cellular therapy products at temperatures $\leq -150^{\circ}\text{C}$ is advisable. Methods to reduce the risk of contamination or cross-contamination (see D9.4.2) 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.

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 Processing Facility's established storage criteria for all relevant cellular therapy products and any related contracts or consents.

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.

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 Processing Facilities storing cellular therapy products shall quarantine each product until completion of the donor eligibility determination as required by applicable laws and regulations.

D9.4.3.1 All cellular therapy products with positive infectious disease test results for relevant communicable disease agents and/or positive microbial cultures shall be quarantined.

D9.4.3.2 Processes for storing cellular therapy products in quarantine shall be defined in Standard Operating Procedures.

D9.4.3.3 Quarantined cellular therapy products shall be easily distinguishable and stored in a manner that minimizes the risks of cross-contamination and inappropriate distribution.

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 patients following the infusion 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 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 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.

D9.5.2 There shall be a mechanism to ensure that levels of liquid nitrogen in liquid nitrogen freezers are consistently maintained to assure that cellular therapy products remain within the specified temperature range.

D9.6 ALARM SYSTEMS

D9.6.1 Storage devices for cellular therapy products or reagents for cellular therapy product processing shall have alarm systems that are continuously active.

D9.6.2 Alarm systems shall have audible signals or other effective notification methods.

D9.6.3 Alarm systems shall be checked periodically for function.

D9.6.4 If trained personnel are not always present in the immediate area of the storage device, a system shall be in place that alerts responsible personnel of alarm conditions on a 24-hour basis.

D9.6.5 Alarms shall be set to activate at a temperature or level of liquid nitrogen that will allow time to salvage products.

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

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

D9.6.6.2 Instructions shall outline procedures to follow to ensure that cellular therapy products are maintained at safe temperatures and the process for documentation of any corrective actions in order to maintain integrity of the products.

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

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 these Standards, the facility must have written procedures specifying actions to be taken in the case of cryopreservation failure.

The failure of mechanical or liquid nitrogen freezers can result in the loss of potentially irreplaceable cellular therapy products stored for future transplant. 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 ensure they are continuously active.

If temperatures fall outside of the established critical ranges, representative cellular therapy product samples, if available, should be tested to determine the effect of the abnormal conditions on product integrity and viability.

Back-up storage devices capable of maintaining cellular therapy products with an acceptable storage temperature range must be identified in advance in the event of mechanical failure of the storage device (e.g., rupture of liquid nitrogen storage tank) and instructions describing the actions to take must be in the form of an SOP (see D5.1.9). Records of temperatures during storage must be available, with notations made for action taken when temperatures fall outside of the designated range.

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 ensure levels of liquid do not fall below set limits between measurements. The objective is to ensure that products are continuously maintained at the target storage temperature. Validation studies may be especially important to ensure that the level limits that trigger alarms are suitable to allow sufficient time to rescue products before they reach temperatures that might compromise their viability and functionality.

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.

The inspector should review records of storage device alarm checks of function and triggering at the appropriate limits (temperature, liquid level, etc).

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:

D9.7 SECURITY

D9.7.1 The storage device shall be located in a secure area and accessible only to authorized personnel.

Explanation:

Cellular therapy products for infusion 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.

Example(s):

Security may include storage devices with locks, electromagnetic security capabilities, or an enclosed room with door locks.

STANDARD:

D9.8 INVENTORY CONTROL

D9.8.1 The Processing Facility shall use an inventory control system to document the availability and identity of critical reagents and supplies. This shall include:

- D9.8.1.1 A system to uniquely identify and track all critical reagents and supplies used to manufacture cellular therapy products.*
- D9.8.1.2 A system to identify each cellular therapy product for which each critical reagent or supply was used.*
- D9.8.1.3 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 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.

STANDARD:

D9.8.2 The Processing Facility shall use an inventory control system to identify the location of each cellular therapy product and associated sample aliquots. The inventory control system records shall include:

D9.8.2.1 Cellular therapy product proper name or specimen name.

D9.8.2.2 Cellular therapy product unique identifier.

D9.8.2.3 Recipient name or unique identifier.

D9.8.2.4 Storage device identifier.

D9.8.2.5 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.

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 ensure the integrity of the system is maintained.

Example(s):

The inventory control system may be in the form of an electronic database or may consist of log books or other manual systems.

STANDARD:*D10 TRANSPORTATION, SHIPPING, AND RECEIPT*

D10.1 Procedures shall be established and maintained for transportation, shipping, and receipt of cellular therapy products.

Explanation:

The Processing Facility must have procedures in place that describe the process of cellular therapy product receipt into the Processing Facility (see D5.1.2) and for product transport and shipping (see D5.1.12). SOPs addressing the topics should be current and staff should demonstrate familiarity with them and follow steps outlined. Records should document critical steps identified in the procedure and be traceable to the product and staff, including date and time where applicable.

Evidence:

The inspector should verify procedures exist to address the receipt process, including pre-established criteria of acceptance, documentation of receipt and inspection and the management of cellular therapy products that do not meet criteria. Transport and shipping procedures should define release criteria and documentation of release, including management of products that do not meet criteria. Quarantine should be addressed. Procedures should define how a product is packed for transport and/or shipment, using a validated process and container that has been shown to protect the integrity of the product during transit conditions.

STANDARD:

D10.2 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 and shall follow the applicable laws and regulations.

D10.2.1 The primary product container for non-frozen cellular therapy products shall be placed in a secondary container and sealed to prevent leakage.

D10.3 Cellular therapy products that require a temperature-controlled environment and that are transported or shipped over an extended period of time shall be transported or shipped in a container validated to maintain the appropriate temperature range.

D10.3.1 During transportation or shipping, the cellular therapy product temperature shall be maintained at the transport or shipping temperature specified by the receiving facility.

D10.4 Cellular therapy products that are shipped to another facility or transported on public roads shall be packaged in an outer container.

D10.4.1 Conditions shall be established and maintained to preserve the integrity and safety of cellular therapy products during transport or shipping.

- D10.4.2 The outer container shall conform to the applicable regulations regarding the mode of transportation or shipping.*
- D10.4.3 The outer container shall be made of material adequate to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling during transport or shipping.*
- D10.4.3.1 The temperature of shipping containers bearing cryopreserved cellular therapy products shall be continuously monitored during shipping.*
- D10.4.3.2 The shipping facility shall maintain a record of the temperature over the period of travel.*
- D10.4.4 The outer container shall be labeled as defined in the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II.*
- D10.4.5 There shall also be a document inside the outer container that includes all the information required on the outer container, in conformity with the Cellular Therapy Product Labels for Shipping and Transport on Public Roads table in Appendix II.*

Explanation:

The Processing Facility shall have written policies and procedures for the distribution of cellular therapy products to and from the Processing Facility. Such procedures may include transport or shipping from internal sites, such as from the Collection Facility to the Processing Facility and at release to internal clinical program sites or to external facilities. These procedures must ensure 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.

These procedures must ensure 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 usually requires the use an outer container that protects the product from adverse conditions encountered during transport (air pressure changes, rough handling, exposure to extremes of temperature, unexpected delays, etc), 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 and safely. 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.

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.

For cryopreserved cellular therapy products, a LN₂ vapor shipper (dry shipper) should be utilized. The vapor shipper must contain adequate absorbed LN₂ to maintain the temperature at least 48 hours beyond the expected time of arrival at the receiving facility and be “charged” for use following manufacturer’s instructions. When cryopreserved products are shipped to another facility and are not in control of Processing or receiving facility personnel, the temperature during shipment must be continuously monitored and that record must be maintained by the shipping facility. For cryopreserved products that are transported (hand carried) by knowledgeable personnel from the distribution or receiving facility, continuous monitoring is optional for short distances, based on validation data for the system in use. 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 ensure that the proper temperature was maintained. It is recommended that a copy of the data logger printout be shared with the receiving facility for their records; however, documentation from the shipping facility of the temperature conditions during transport would be acceptable.

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 ensure continued performance and verified or re-validated periodically per facility-defined procedures. Calibration and verification of function of data loggers per manufacturer’s recommendation is required.

Containers for distribution of cryopreserved and non-cryopreserved products that leave the 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.

Evidence:

The inspector must determine if the transport and shipping procedures 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 Processing Facility for adherence to these 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.

Example(s):

When heat sealers are used on the primary container(s), the tubing must be securely sealed to protect cellular therapy product integrity and prevent leakage (use of more than one seal to ensure integrity is maintained is recommended.) Review of transportation, shipping, receipt, and validation forms, checklists, or logs should address these standards. Heat sealing processes should ensure product integrity to prevent leakage.

Refrigerated cellular therapy products shall be insulated from cool packs 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.

STANDARD:

D10.4.6 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 II.

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 ensures that the product can be delivered in the event that the accompanying paperwork is lost or destroyed. To ensure anonymity of donors and recipients of unrelated transplants, neither the donor nor recipient name should 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.

Evidence:

The inspector should review transportation and shipping records and inspect outer containers to ensure that the elements in this section are met and documented.

Example(s):

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.

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:

D10.5 METHOD OF TRANSPORTATION AND SHIPPING

D10.5.1 The transit time shall be within time limits determined by the receiving and/or distributing facility to maintain cellular therapy product safety.

D10.5.2 If the intended recipient has received high-dose therapy, the cellular therapy product shall be transported by a qualified courier.

D10.5.3 There shall be plans for alternative means of transport or shipping in an emergency.

D10.5.4 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:

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. Alternative transportation and shipping plans in case the primary arrangement fails are required. 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.

STANDARD:

D10.6 RECEIPT

D10.6.1 Procedures shall be established and maintained for acceptance, rejection, and quarantine of cellular therapy products.

D10.6.2 The receipt of each cellular therapy product shall include inspection to verify the integrity of the product container, the appearance of the product, and appropriate labeling, and to evaluate for evidence of microbial contamination.

D10.6.3 There shall be procedures to verify that the cellular therapy product was appropriately transported or shipped.

D10.6.3.1 The receiving facility shall document the temperature of the outer container upon arrival.

D10.6.3.2 For cryopreserved cellular therapy products, receiving facility records shall include documentation of the outer container temperature during shipping.

D10.6.4 The receiving facility shall have readily available access to a summary of documents used to determine allogeneic donor suitability and eligibility.

D10.6.5 There shall be procedures to maintain cellular therapy products in quarantine until they have been determined to meet criteria for release from quarantine.

Explanation:

The cellular therapy product receipt SOP must minimally describe the criteria for product acceptance, rejection, and quarantine. Documentation of the receipt process must include the integrity of the primary product container and confirmation that the label information meets the requirements specified in Appendix I. There must also be a visual examination of the appearance of the cellular therapy product for evidence of microbial contamination (excess hemolysis or inappropriate cloudiness, or other unusual appearance). Any samples that accompany the product must be labeled 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 III.

A process to store cellular therapy products in quarantine until they have been determined to meet all predetermined release criteria must be in place. Management of the return of products must be addressed in procedures.

Evidence:

The inspector should review documentation of cellular therapy product receipt into the Processing Facility to ensure compliance with the facility's SOPs and these Standards, and should verify quarantine process is defined in procedures and physical or electronic systems are in place to support quarantine functions.

Example(s):

EU requirements for documents that should be available to the 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 procedure (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:

D10.7 TRANSPORTATION AND SHIPPING RECORDS

D10.7.1 Transportation and shipping records shall permit tracing of the cellular therapy product from one facility to another.

D10.7.2 Transportation and shipping records shall include:

D10.7.2.1 Date and time cellular therapy product was distributed.

D10.7.2.2 Date and time cellular therapy product was received.

D10.7.2.3 Identity of the transporting or shipping facility.

D10.7.2.4 Identity of the receiving facility.

D10.7.2.5 Identity of personnel responsible for cellular therapy product transportation or shipping and of personnel responsible for receiving the product.

D10.7.2.6 Identity of the courier.

D10.7.2.7 Documentation of any delay or problems incurred during transportation or shipping.

Explanation:

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 ask to review transportation and shipping records for cellular therapy products distributed between facilities for compliance with this section of the Standards.

STANDARD:

D11 DISPOSAL

D11.1 Disposal of cellular therapy products shall include the following requirements:

D11.1.1 A pre-collection written agreement between the storage facility and the designated recipient or the donor, as appropriate, defining the length of storage and the circumstances for disposal of cellular therapy products.

D11.1.2 The option to transfer the cellular therapy product to another facility if the designated recipient is still alive after the agreed upon storage interval.

D11.1.3 Documentation of designated recipient's death or no further need for the cellular therapy product before any product is discarded.

D11.1.4 Approval by the Processing Facility Medical Director or the recipient's physician for cellular therapy product discard or other disposition, and method of disposal.

D11.1.5 A method of disposal and decontamination that meets applicable laws and regulations for disposal of biohazardous materials and/or medical waste.

D11.2 If there is no pre-existing agreement describing conditions for cellular therapy product storage and/or discard or if the patient is lost to follow-up, the storage facility shall:

D11.2.1 Communicate with the designated recipient's physician about continuing need for storage of the cellular therapy product.

D11.2.2 Make a documented effort to notify the donor or designated recipient about product disposition, including disposal or transfer.

D11.3 The records for discarded or transferred cellular therapy products shall indicate the product was discarded or transferred, date of discard or transfer, disposition, and method of disposal or transfer.

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 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.

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, and 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 facility must offer the recipient an opportunity to move the product to another facility. 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.

Two of the biggest 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 patients are lost to 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.

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 facility is in compliance with standards of biohazard waste disposal.

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.

If the Medical Director of the storage facility approves of cellular therapy product disposal documentation, 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.

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 RECORDS

D12.1 GENERAL REQUIREMENTS

D12.1.1 A records management system shall be established and maintained to facilitate the review of records pertaining to a particular cellular therapy product prior to distribution and for follow-up evaluation or investigation.

D12.1.1.1 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.

D12.1.1.2 For cellular therapy products that are to be distributed for use at another institution, the receiving institution shall be informed of the tracking system and requirement for tracking the product in writing or electronic format at or before the time of product distribution.

D12.1.2 Records shall be maintained in such a way as to ensure their integrity and preservation.

D12.1.2.1 If records are maintained in more than one location, there shall be a system to ensure prompt identification, location, and retrieval of all records.

D12.1.2.2 Records shall be accurate, legible, and indelible.

D12.1.3 All records and communications between the collection, processing, and transplant facilities, and their recipients and donors, shall be regarded as privileged and confidential.

D12.1.3.1 Safeguards to assure this confidentiality shall be established and followed in compliance with applicable laws and regulations.

D12.1.4 Records required for donor eligibility determination shall be in English or translated into English when crossing international borders.

D12.1.5 Employee records shall be maintained in a confidential manner as required by applicable laws and regulations.

D12.1.6 Records shall be maintained in one or more forms that are retrievable.

D12.1.6.1 Equipment to make the records available and legible shall be readily accessible.

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 ensure 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 ensure prompt identification, location, and retrieval of all records. The methods for filing and transfer of records to archival storage should be specified in the SOP manual.

For records that have been translated into English, an accompanying statement of authenticity by the translator should be present.

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.

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.

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):

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.

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. 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.

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 D5.1.1).

If research records are stored independently of patient records, the same considerations regarding confidentiality apply.

STANDARD:

D12.2 ELECTRONIC RECORDS

D12.2.1 The Processing Facility shall establish and 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:

D12.2.1.1 In lieu of paper.

D12.2.1.2 To make decisions.

D12.2.1.3 To perform calculations.

D12.2.1.4 To create and/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 they are:

- used in lieu of 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, and/or
- 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 are listed in Standard D4.14.1 and 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 ensure 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.

STANDARD:

D12.2.2 For all critical electronic record systems, there shall be policies, procedures, and system elements to ensure the accuracy, integrity, identity, and confidentiality of all records.

D12.2.2.1 There shall be a means by which access to electronic records is limited to authorized individuals.

D12.2.2.2 There shall be protection of the records to enable their accurate and ready retrieval throughout the period of record retention.

D12.2.2.3 All critical electronic record systems shall ensure that all donor, cellular therapy product, and recipient identifiers are unique.

D12.2.3 For all critical electronic record systems, there shall be an alternative system for all electronic records that ensures 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.

D12.2.4 For all critical electronic record systems, there shall be written procedures for record entry, verification, and revision.

D12.2.4.1 A method shall be established or the system shall provide for review of data before final acceptance.

D12.2.4.2 A method shall be established or the system shall provide for the unambiguous identification of the individual responsible for each record entry.

Explanation:

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 procedures are revised and issues with the use of critical electronic record systems are identified.

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 ensure all data is verified to be correct and to maintain documentation of who has entered pieces of information.

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:

D12.2.5 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.

D12.2.6 For all critical electronic record systems, there shall be validated procedures for and documentation of:

D12.2.6.1 Systems development.

D12.2.6.2 Numerical designation of system versions, if applicable.

D12.2.6.3 Prospective validation of system, including hardware, software, and databases.

D12.2.6.4 Installation of the system.

D12.2.6.5 Training and continued competency of personnel in systems use.

D12.2.6.6 Monitoring of data integrity.

D12.2.6.7 Back-up of the electronic records system on a regular schedule.

D12.2.6.8 System maintenance and operations.

D12.2.7 All system modifications shall be authorized, documented, and validated prior to implementation.

Explanation:

This standard is not meant to require Processing Facilities to assume responsibility for hospital-wide data systems. Any data system that does exist within the scope of control of the facility is required to meet these standards.

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.

Each Processing Facility must determine in advance whether the staff will depend on an electronic record or a paper record system to perform a regulated activity. This determination should be documented for all records created and maintained by the facility.

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 ensure that problems are reported and resolved.
- Evidence that changes to records do not obscure previously entered information.
- Documentation that deleted electronic files have been converted to non-electronic media such as microfilm, microfiche, or paper in a manner that preserves the content and meaning of the record.

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.

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.

Evidence:

The inspector should determine the scope of electronic records used by the Processing Facility and any circumstances where the electronic record is used in lieu of a paper record.

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.

Example(s):

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 in lieu of 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 infusion. 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.

For example, 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, etc.) 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 in lieu of 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:

D12.3 RECORDS TO BE MAINTAINED

D12.3.1 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.

D12.3.2 Processing Facility records related to quality control, personnel training or competency, facility maintenance, facility management, 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, unless otherwise specified in these Standards.

D12.3.2.1 Facility maintenance records pertaining to facility cleaning and sanitation shall be retained for at least three (3) years. All other facility maintenance records shall be retained as in D12.3.2.

D12.3.3 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. The following records shall be maintained:

D12.3.3.1 Processing records.

D12.3.3.2 Compatibility test records.

D12.3.3.3 Cryopreservation records.

D12.3.3.4 Distribution records.

D12.3.3.5 Records of errors, accidents, adverse events, adverse reactions, and complaints.

D12.3.3.6 All quality management records.

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 referred to in D.4 Quality Management: 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 as detailed in D4.3: 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.
- Facility maintenance management and general facility issues including all items referred to in D2: dates and extent of renovations and new construction; dates and extent of repairs on mechanical systems; preventative maintenance on equipment; agreements and/or contracts with any facility served by the Processing Facility; sterilization records; disposition of supplies and reagents; and the outcome of any building and/or Processing

Facility inspections for safety and/or compliance with governmental and/or other agencies.

- Facility management records should include a list of responsible individuals with job titles and areas of oversight and resolution of facility problems.

General facility records include global policies for the institution of which the Processing 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 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.

Records related directly to processing, testing, storage, or release of cellular therapy products 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.

Specific records to be maintained are specified in D12.3 and include records of reagents, supplies, and equipment utilized in processing or storing that cellular therapy product. Transmission of infectious disease agents, adverse events in the recipient and/or product recall are events that generally result in an investigation necessitating tracing.

Evidence:

The inspector should look for evidence of 10-year retention of representative records from D12.3, 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 Processing 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-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 these 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.

In the U.S., NMDP requires that records from unrelated donor eligibility determination, and HPC(A) 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.

EU regulations on record retention relating to cellular therapy products stored or distributed by the Processing Facility specifically require records of donor identification, place of procurement, identity of the Processing Facility, product proper name, pool or split number (if applicable), expiry date, and tissue/cell status (i.e., quarantined, suitable for use, etc). Most, if not all, of this information should be available in the product's processing records.

STANDARD:

D12.4 RECORDS IN CASE OF DIVIDED RESPONSIBILITY

D12.4.1 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.

D12.4.2 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.

D12.4.3 There shall be a system to allow the Processing Facility access to information that tracks and traces all manufacturing steps performed by other facilities. This tracking and tracing system shall comply with D4.11.

D12.4.4 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 they concern the safety, purity, or potency of the cellular therapy product involved.

Explanation:

In the event that two or more facilities participate in the collection, processing, storage or administration of a cellular therapy product, the records of each participating facility must clearly indicate the extent of each facility's responsibility. The Processing Facility's records should include relevant contracts and agreements. 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 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.

The Processing Facility shall have an applicable SOP 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 in checking 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.

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CELLULAR THERAPY PRODUCT LABELING

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

Element ³	Partial label	Label at completion of collection	Label at completion of processing	Label at distribution for administration ²
Unique numeric or alphanumeric identifier	AF	AF	AF	AF
Proper name of product ¹	AF	AF	AF	AF
Product modifiers ¹	AF		AF	AF
Product attributes (manipulations) ¹			AC	AC
Recipient name and identifier (if applicable)	AF	AT	AT	AT
Identity and address of collection facility or donor registry		AT	AC	AC
Date, time collection ends, and (if applicable) time zone		AT	AC	AC
Approximate volume		AT	AT	AT
Name and volume or concentration of anticoagulant and other additives		AT	AT	AT
Donor identifier and (if applicable) name		AT	AT	AT
Recommended storage temperature range		AT	AT	AT
Biohazard and/or Warning Labels (as applicable, see CM7.4, C7.4, D7.4).		AT	AT	AT
If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES"				
Statement "WARNING: Advise Patient of Communicable Disease Risks"		AT	AT	AT
Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"		AT	AT	AT
Identity and address of processing and distribution facility(ies)			AC	AC
Statement "Do Not Irradiate"			AT	AT
Expiration Date (if applicable)			AT	AT
Expiration Time (if applicable)			AC	AT
ABO and Rh of donor (if applicable)			AC	AC
RBC compatibility testing results (if applicable)				AC
Statement "Properly Identify Intended Recipient and Product"				AT
Statement indicating that leukoreduction filters should not be used.				AT
Statement "FOR AUTOLOGOUS USE ONLY" (if applicable)		AT	AT	AT
Statement "For Use By Intended Recipient Only" (if for allogeneic recipient)				AT
Statement "For Nonclinical Use Only" (if applicable)				AT
Date of distribution				AC

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

¹Product proper names, modifiers, and attributes (manipulations) 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*.

²Products thawed at the bedside do not require a new label.

³Facilities registered with ICCBBA, Inc. 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.

APPENDIX II

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 and time, if appropriate	AC	AF
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, C7.4, D7.4).	AC	
If applicable: Statement "NOT EVALUATED FOR INFECTIOUS SUBSTANCES"	AC	
Statement "WARNING: Advise Patient of Communicable Disease Risks"	AC	
Statement "WARNING: Reactive Test Results for [name of disease agent or disease]"	AC	

AC= Accompany on a single document, AF=Affix

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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:

Documentation	Allogeneic Donors-Eligible	Allogeneic Donor-Ineligible ¹	Allogeneic Donor-Incomplete ¹
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 ²	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 ³	X	If applicable	If applicable
Statement noting the reason(s) for the determination of ineligibility		X	
Statement that the donor-eligibility determination has not been completed			X
Statement that the product must not be transplanted or infused until completion of the donor-eligibility determination, except under condition of urgent medical need			X
Listing of any required screening or testing that has not yet been completed			X
Results of donor screening that has been performed			X
Documentation that the physician using the cellular therapy product was notified of incomplete testing or screening			X
Instructions for product use to prevent the introduction, transmission, or spread of communicable diseases	X	X	X
Instructions for reporting serious adverse reactions or events to the distributing facility ⁴	X	X	X

¹ 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 must be shipped in quarantine. For products distributed prior to completion of donor eligibility, you must complete the determination and inform the physician of the results.

² Access (electronic or otherwise) to the source documents by the distributing facility and/or receiving facility is sufficient.

³ Includes laboratories certified under CLIA of 1988, as amended from time to time, those 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.

⁴ Access to the Clinical Program SOPs and forms could suffice when the distributing and clinical facilities are within the same building.

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 cellular therapy products from allogeneic donors are listed in Appendix III above.

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 donor eligibility has been documented (see 21 CFR 1271.55).

Consistent with the GTP, FACT-JACIE Standards allow for products obtained from ineligible allogeneic donors to be distributed for infusion provided that there is documented medical need that the product be used despite the risks to the recipient. Use of products from an ineligible allogeneic donor requires documented approval of the Processing Facility Medical Director that includes the reason that the donor was ineligible, and documentation that the physician administering the product has been notified of all testing and screening results. Standard B6.4.12 also requires that the donor and recipient of a product from an ineligible donor provide documented informed consent before the product is distributed by the Processing Facility for use.

Cellular therapy products that are needed for infusion before all required donor screening and testing are complete may also be distributed provided that the distribution documents (such as the product infusion form) includes a statement that eligibility determination is not complete, the results of the screening and testing that has been completed is provided, there is a list of required testing or screening that has not been completed, and there is documentation that the physician was notified of the incomplete testing or screening. Per FDA requirements, when shipped with incomplete eligibility that is not intended for immediate infusion due to urgent medical need, the product should be shipped in quarantine and include a statement that the product must not be transplanted or infused until completion of the donor-eligibility determination. Allogeneic donor eligibility must be completed during or after use of the product under urgent medical need, and the recipient’s physician must be notified of the result of the determination.

It should be the Processing Facility Medical Director in concert with the attending physician, rather than the Processing Facility personnel, who determine if a request for product release prior to completion of testing is warranted. Such a situation would likely fall under the category of a non-conforming product and would require exceptional release and Processing Facility Medical Director agreement (See D8.1.2.3).

With this edition of these Standards, communicable disease testing is not required for autologous donors 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.

At the time of distribution, the cellular therapy product must be accompanied by a document that contains instructions for administration that include methods to prevent the introduction, transmission, or spread of communicable disease and reporting serious adverse events and reactions.

In the U.S., products that are regulated under the FDA 312 regulations must be labeled with the statement “Caution: New drug limited by federal law for investigational use.” HPC, Apheresis products from unrelated donors collected 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.

Once regulated cellular therapy products have reached the stage of licensure, the label or accompanying records must include the statement “Rx Only” indicating that the product may only be distributed by a prescription from the physician. In addition, a U.S. License Number will be issued by the FDA and will be included in the product labeling of a licensed product. The physician order form required by these Standards may serve as the prescription. As of this writing, guidance for cord blood unit licensure has been released from FDA and cord blood banks will be distributing licensed cord blood units during the timeframe that these Standards are in effect. In addition to these labeling requirements, other applicable regulations for licensed products must be followed.

Evidence:

The inspector should review the records of one or more products issued from an ineligible donor or prior to the completion of testing to determine if this process is performed according to D7.9.1. The inspector should review the labeling of products from NMDP-facilitated transplants to ensure this statement is used on the product or in the accompanying record (the infusion form or distribution record) issued with the product. The inspector should review the systems in place that assure the Processing Facility has access to source data for the information that must be provided at distribution.

Once licensed products are approved, the inspector should ensure that they are distributed with the required statement and license number on the label or in the accompanying records.

Example(s):

It is permissible to have hard copies of each item physically accompany the product. That may be appropriate in some cases, as when a product leaves the Collection Facility and is transported to another institution for processing, storage, and/or infusion.

A “Circular of Information for the Use of Cellular Therapy Products” document (prepared jointly by the AABB, American Association of Tissue Banks, American Red Cross, American Society for Blood and Marrow Transplantation, American Society for Apheresis, America’s Blood Centers, Foundation for the Accreditation of Cellular Therapy, ICCBBA, International Society for Cellular Therapy, JACIE, and National Marrow Donor Program) should accompany the product or be made available to the staff responsible for administering the product at the Clinical Program (available at <http://www.factwebsite.org/uploadedFiles/COI-CT-2009.pdf>).

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CHANGES TO FIFTH EDITION ACCREDITATION MANUAL

The table below outlines the changes made to the *FACT-JACIE Cellular Therapy Accreditation Manual* with each version of the fifth edition of this Manual.¹

Version Number ²	Standard	Change
5.1	B2.4.6	Addition of clarifying guidance information.
5.1	B3.3.4	Addition of clarifying guidance information.
5.1	B3.4.3.3	Pre-transplant patient evaluation, including assessment of appropriate patient eligibility <u>suitability</u> and HPC adequacy with respect to collection. <i>(for clarity)</i>
5.1	B4.10.5	Deviations from the following key Standard Operating Procedures, B5.1.1, B5.1.6 5 , and B5.1.7 6 , shall be documented. <i>(for clarity)</i>
5.1	B6.4.2	A red cell antibody screen shall be performed on allogeneic donors and allogeneic recipients.
5.1	B6.4.10	Addition of clarifying guidance information.
5.1	B7.4	Addition of clarifying guidance information.
5.1	D2.1.4	Deletion of minimum acceptable level of oxygen concentration.
5.1	D6.1.2.2	Addition of clarifying guidance information.
5.1	D6.1.7	Cellular therapy products that do not meet release or <u>allogeneic</u> donor eligibility requirements 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.
5.1	D6.1.7.1 <u>D6.1.8</u>	Notification of the transplant physician of nonconforming cellular therapy products and approval for their release shall be documented. <i>(for clarity)</i>
5.1	D10.4.6	Deletion of requirements already included in Appendix II.
5.1	Multiple	Clarification that donor eligibility refers to only allogeneic donor eligibility throughout the manual.
5.2	CM6.3.10	A red cell antibody screen shall be performed on allogeneic donors and allogeneic recipients.
5.2	C6.4.2	A red cell antibody screen shall be performed on allogeneic donors and allogeneic recipients.
5.3	D4.13.2	Addition of clarifying guidance information.
5.3	Appendix III	Deletion of requirements for accompanying documentation for autologous cellular therapy products.
5.3	Multiple	Updated references to Appendix IV.

¹ This appendix does not include minor numbering or reorganization changes that were a result of the substantive changes listed above.

² The effective date of version 5.1 is November 30, 2012.
The effective date of version 5.2 is November 30, 2012.
The effective date of version 5.3 is September 20, 2013.

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ACKNOWLEDGEMENTS

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